

Guideline for Physicians Working in California Opioid Treatment Programs

Editor: Deborah K. Stephenson, MD, MPH
for the CSAM Committee on Treatment of Opioid Dependence

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California Society of Addiction Medicine

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PREAMBLE

This monograph was developed by the Committee on Treatment of Opioid Dependence 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. It was prepared and distributed first in 1998 and updated once in 2004. This 2008 edition incorporates current information.

OTP is the term used by Federal and California regulating agencies to refer to clinics that are specially licensed to provide opioid pharmacotherapy for addiction treatment. OTPs are commonly known as methadone clinics. Both the Federal and state governments regulate OTPs. Federal regulations are found in 42 CFR Part 8, and California's regulations are found in Chapter 4, Division 4, Title 9 of the California Code. This document will reference these regulations, but it is not designed to summarize all of them. Rather, this monograph is meant to serve as a reference offering 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.

Federal regulations require that OTPs be accredited by an agency approved by the Center for Substance Abuse Treatment (CSAT.) In California, in 2008, 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 a separate issue. This monograph's focus is on the medical piece.

This monograph was circulated for review to interested parties, including representatives of these organizations and agencies:

- Center for Substance Abuse Treatment
- American Association on the Treatment of Opioid Dependence
- California Organization of Methadone Providers
- American Society of Addiction Medicine Sub-Work-Group on Opioid Agonist Treatment
- California Department of Alcohol and Drug Programs

The Committee considered all comments received and made additions and/or changes based on the information submitted in the comments.

Guidelines discussing clinical practice are subject to periodic review and revision to incorporate new developments. The CSAM Committee plans to review this document periodically to determine if revisions may be appropriate. If the document is revised, it will be circulated for comment and published with a new date. The latest revision is always available from the CSAM website: www.csam-asam.org

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INTRODUCTION

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 in a largely indigent population with limited access to health care. The past experiences of opioid dependent patients in medical settings often result in mistrust, and even hostility, toward mainstream medical providers, which discourages them from seeking even the limited care available.

Characteristically, addicted patients receive high-cost crisis care in Emergency Departments and hospitals. After discharge, there is little to no follow-up. 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 heroin and opioid addiction and providing treatment or referrals to address these problems. The OTP physician is also in a position to positively impact the public health of the community by screening for and treating communicable disease and offering other preventive health services.

As of September 2008, there are two medications available and approved for use in opioid maintenance treatment: methadone and sublingual formulations of buprenorphine. This document focuses primarily on treatment with methadone and includes a brief review of treatment with buprenorphine in Appendix B.

The benefits of MMT extend beyond pharmacologic ones.

Methadone maintenance treatment (MMT) in the United States is regulated, comprehensive treatment which requires observed dosing, random urine drug testing and participation in counseling. It offers major pharmacologic benefits, such as the alleviation of the symptoms of physical withdrawal, the reduction or elimination of opioid craving and partial or complete blockade of the euphoric effects of outside opioids. All of these benefits help to support patients' efforts to achieve and maintain abstinence. However the benefits of MMT extend beyond pharmacologic ones. Medical and counseling interventions help patients to reduce needle sharing and unprotected/risky sexual behaviors associated with drug use. Retention in treatment allows medical and psychosocial issues to be addressed. MMT allows patients to receive consistent and ongoing counseling to support the lifestyle changes necessary to progress in recovery. It is helpful for OTP personnel to have a basic understanding of 12 Step programs and of all elements of recovery to assist patients toward long-term goals. Ultimately, long term goals include improved family stability, decreased hospital admissions, regular medical and dental care, decreased criminal activity and incarceration, and vocational rehabilitation. Achieving these goals benefits society as well as the individual patient.

OUR OBJECTIVE

This document is intended to assist OTP physicians in understanding their role and responsibilities in treatment, including those areas governed by California or federal regulation. It describes the role of the physician in an opioid treatment program and the clinical judgment involved in the development of an appropriate treatment plan for the delivery of patient care. It describes responsibilities that should be carried out by the physician or the physician's designee. It does not describe a standard of care. It does not prescribe 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.

Section on

DIAGNOSIS OF OPIOID DEPENDENCE

Opioid Treatment Programs are designed to treat patients who are opioid dependent. Criteria for making the diagnosis of opioid dependence are found in The Diagnostic and Statistical Manual, Fourth Edition Text Revision (DSM-IV-TR) under Substance Related Disorders in three related diagnostic categories:

1. The “generic” diagnosis of substance use and substance dependence disorders
2. Clinical syndromes related to intoxication and withdrawal: substance-induced disorders, and
3. Drug-induced psychiatric disorders: substance-induced mental disorders

Both substance use disorder and substance dependence are characterized by a group of behavioral, cognitive and physiological symptoms occurring within a specific time frame (12 months). DSM-IV distinguishes “dependence” from “abuse.” **Dependence is characterized by compulsive drug seeking and use with loss of the ability to control the drug use despite adverse consequences, whether or not physical manifestations of tolerance or withdrawal occur.** DSM criteria for dependence include physical dependence, but also include other behaviors, notably continued use despite adverse consequences. To be diagnosed with dependence, a patient must meet 3 or more criteria within the same 12 months. This definition is distinguished from usage in general medical settings, where the designation “opioid dependence” often refers only to physical dependence (tolerance, withdrawal). These two uses of the word “dependence” may be confusing.

In general medicine, physical dependence and continued use despite adverse consequences is often diagnosed as “addiction.” In regulations pertaining to treatment of opioid dependence, “dependence” is generally used with its DSM connotation. **Abuse is characterized by repeated drug use under hazardous conditions and/or use despite harmful consequences.** The diagnosis of abuse can be made only if the patient has never met the criteria for dependence. The salient features of the DSM-IV-TR diagnostic criteria for substance dependence and substance abuse are listed in Table I.

Patients who meet the DSM diagnosis of *Opioid Abuse* but do not meet the DSM diagnosis of *Dependence* are not eligible for opioid agonist treatment. For each patient who requests admission to treatment, the physician should determine whether opioid dependence is present and document that the patient meets diagnostic criteria by recording the patient’s history, physical examination findings and laboratory test results. Once the formal diagnosis of opioid dependence (addiction) is made, the physician should determine the suitability of the patient for treatment in an opioid treatment program. The physician should then determine whether the patient

is a candidate for opioid detoxification or opioid maintenance treatment. The ASAM Patient Placement Criteria (Mee-Lee et al. 2001) for opioid detoxification and opioid maintenance treatment may be a helpful resource.

There are specific federal and California regulations concerning eligibility for opioid agonist treatment. These regulations will be summarized later in this monograph; see Table 2. Federal regulations concerning admission criteria are found in 42 CFR Part 8; California regulations are in Title 9, Section 10270 (Criteria for Patient Selection). <http://ccr.oal.ca.gov> California state and federal regulations concerning admission criteria differ, with California regulations generally being more stringent. California's Department of Alcohol and Drug Programs has indicated that the next revision of the California Code of Regulations Title 9 will make it more similar to federal regulations.

In summary, the role of the OTP physician in the diagnosis of opioid dependence is to determine whether patients seeking admission to methadone treatment meet the diagnostic criteria for opioid dependence as defined in DSM-IV-TR.

Table 1 ~ DSM-IV-TR Criteria for Substance Dependence and Substance Use

| <p style="text-align: center;">Dependence</p> <p style="text-align: center;">(3 or more in a 12-month period)</p> | <p style="text-align: center;">Abuse</p> <p style="text-align: center;">(1 or more in a 12-month period)</p> <p style="text-align: center;">Symptoms must never have met criteria for substance dependence for this class of substance.</p> |
|---|---|
| <p>A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:</p> <ul style="list-style-type: none"> • Tolerance (marked increase in amount; marked decrease in effect) • Characteristic withdrawal symptoms; substance taken to relieve withdrawal • Substance taken in larger amount and for longer period than intended • Persistent desire or repeated unsuccessful attempt to quit • Much time/activity to obtain, use, recover • Important social, occupational, or recreational activities given up or reduced • Use continues despite knowledge of adverse consequences (e.g., failure to fulfill role obligation, use when physically hazardous) | <p>A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring at any time in the same 12-month period:</p> <ul style="list-style-type: none"> • Recurrent use resulting in failure to fulfill major role obligation at work, home or school • Recurrent use in physically hazardous situations • Recurrent substance related legal problems • Continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by substance |

Section on

CRITERIA FOR ADMISSION TO METHADONE MAINTENANCE TREATMENT

Federal and California admission criteria are summarized in Table 2. Current federal regulations require that patients meet the diagnostic criteria for opioid dependence and have documentation of at least a one-year history of opioid addiction to qualify for admission to methadone maintenance treatment (MMT.) California regulations require current physical dependence, a two-year documented addiction history and documentation of at least two failed attempts at detoxification. Waivers are needed for situations in which the physician determines that admission to MMT is indicated for a patient who does not meet these criteria. OTPs can apply for a permanent program-wide waiver that allows for admission to MMT of intravenous drug-using patients who meet the federal regulations without meeting California's two-year plus two-detoxification failure requirement. Most programs already have a permanent California waiver to allow admission of patients with a one-year history of addiction. Often a failed detoxification provides the necessary documentation of the duration of opioid dependence.

Beginning treatment as early as possible reduces the likelihood of HIV and HCV infection and transmission.

If a program-wide waiver is not in place, a physician can apply for an exception (or waiver) for an individual patient when withholding treatment constitutes a life or health-endangering situation. 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 injection drug users will acquire HCV antibodies within a year of beginning injection drug use. (Garfein et al. 1996) Sharing snorting paraphernalia also increases the risk of blood borne infection.

Regulations require that patients enter opioid maintenance treatment voluntarily. When determining whether a patient is suitable for MMT, the physician should assess the risks and benefits of starting methadone. Factors for the patient and OTP physician to consider are the physical dependence-maintaining properties of the medication, the mandatory observed dosing in clinic, the counseling requirements, the long-term nature of the treatment, the exposure to a large number of addicted persons congregated at the clinic, the restriction on travel and the requirement for random urine drug testing or toxicology screening. The physician should assure that there is documentation that the patient was informed and has consented to treatment.

For patients under eighteen years of age, federal regulations require documented parental consent before the patient begins treatment with pharmacotherapy. 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 twelve months prior to admission to MMT. In California, pre-approval by the Department of Alcohol and Drug Programs (ADP) Narcotic Treatment Program Licensing Branch is also required.

(Anyone aged 12 or older may consent for psychosocial treatment of addiction in California.)

There are patients who are not currently physically dependent, but who have a history of opioid dependence and whose current situation puts them at high risk of relapse. The physician should carefully evaluate and consider these patients for admission to MMT to prevent relapse. Prior to admission the physician must carefully review federal and California regulations and obtain exception waiver(s) if necessary.

Federal and California regulations do make specific provision for the admission of certain patients who meet the criteria for opioid dependence but are not currently physically dependent. These exceptions are summarized in Table 3. Federal and California regulations differ. Federal regulations (42CFR8.12.e.3) specify the following exceptions to the general requirement that the patient be “currently addicted to an opioid drug:”

- patients released from a penal institution, within 6 months of release
- pregnant patients
- former MMT patients, within 2 years of discharge.

California’s regulations (Title 9, Section 10270, D5, A and B.) are more restrictive than federal regulations but do allow the following two exceptions to the requirement for physical dependence at intake:

- 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.
- 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.

■ **Note** No exception is mentioned in Title 9 to the requirement of physical dependence for pregnant women. A California exception may be requested on a case-by-case basis.

Table 2 ~ Admission Criteria: Federal vs. California

| | Meet DSM Criteria for Dependence | Current Physical Dependence | Duration of Dependence | Failed Detoxification Attempts | Treatment Voluntary |
|--|----------------------------------|-----------------------------|---|---|---------------------|
| Federal Regulations | Required | Not required | One year | Only required for minors | Required |
| California Regulations | Required | Required | Two years | Required; must document failure of two or more attempts | Required |
| With "Two + Two" Programmatic Exception from California | Required | Required | All or most of the past year – defined as six months plus one day | Not required | Required |

Table 3 ~ Exceptions to Requirement for Current Physical Dependence at the Time of Admission: Federal vs. California

| | Incarcerated Patients | Pregnant Patients | Former MMT Patients |
|-------------------------------|---|--|---|
| Federal Regulations | If admitted within six months of release | If document past history of addiction and current risk of relapse | If admitted within two years of discharge from MMT |
| California Regulations | If admitted within one month of release, AND if incarcerated for at least one month, AND if eligible for admission to MMT when incarcerated | Requires current physical dependence and past history of opioid dependence | If admitted within 6 months of discharge from an MMT episode of at least 6 months, AND if voluntarily discharged. |

The physician should balance the risks and benefits of medication-assisted treatment against the risk of non-treatment or other forms of addiction treatment, especially in cases where there is a medical indication for treatment but uncertainty about the length of time of addiction or when documentation of the patient's history is not readily available. In such cases in California, the physician should apply for prior approval from the Narcotic Treatment Licensing Branch. (ADP Form 8045. See Appendix D)

The benefit of treatment is directly proportionate to the length of treatment and the adequacy of the maintenance dose.

MMT must be viewed as a long-term treatment commitment that will include medication and psychosocial intervention. Opioid abuse puts patients at risk of multiple medical problems, including accidental overdose. 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 abuse or relapse to opioid abuse, 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. However, participation in MMT is voluntary, so patients must be free to choose the length of time they will remain in MMT.

MMT is suitable for patients with a history of opiate dependence of sufficient severity and length for whom detoxification has not succeeded or can not reasonably be expected to succeed and who is willing and able to commit to the long term, physical dependence-sustaining nature of pharmacologic treatment and the encumbrances of opioid maintenance treatment.

In countries outside the US, methadone maintenance treatment is offered in office-based settings, at the discretion of individual physicians. In the United States, office based opioid treatment (OBOT) is available on a pilot basis in San Francisco, but is not routinely available outside of a small number of pilot programs. See Appendix C.

Patients who do not meet the criteria for MMT as described above may be considered for methadone detoxification. In addition, there are patients who are eligible for MMT, but request detoxification treatment instead. See Appendix A regarding methadone detoxification.

In summary, the role of the OTP physician in selecting a patient for methadone maintenance treatment:

- **To verify history of opioid dependence** to ensure that the patient has a documented history of opioid dependence of sufficient severity and duration.
- **To verify current opioid dependence** to ensure that the patient is currently opioid dependent or meets Federal and California exception criteria.
- **To consider alternatives to MMT** to establish and document that previous attempts at withdrawal have not been successful and that maintenance treatment is the appropriate treatment option.
- **To consider contraindications:** to ensure that there are no medical, psychological or cognitive contraindications to MMT.
- **To obtain informed consent:** to answer patients' questions regarding MMT, to advise patients regarding the risks and benefits of methadone treatment, and to obtain informed consent for treatment.
- **To obtain federal/California exceptions when needed:** to apply for federal and/or California admission waivers if MMT is medically indicated and the patient does not meet regulatory requirements.

Section on

INITIAL HISTORY AND PHYSICAL EXAM

The primary purpose of the physician's admission assessment is to confirm and document current opioid dependence and to determine whether the patient is fit for methadone treatment through a comprehensive history and physical examination and appropriate laboratory tests. Appendix D provides an example of a form for recording the intake history and physical examination.

At admission, most of the patients are uncomfortable due to symptoms of opiate withdrawal, guilt and shame associated with the lack of control over drug use, and past experiences in medical settings. A caring, respectful and non-judgmental manner helps to establish a therapeutic relationship with the patient and makes it more likely that the patient will disclose important information about his or her substance abuse history.

Severity of withdrawal does not necessarily indicate high tolerance, and does not reliably establish need for a high maintenance dose.

Since opioid addiction is the patient's presenting complaint, often the assessment begins with the opioid history including the age at initiation of use, age when first opioid dependent, route(s) of administration, prior treatment episodes (type and outcome), periods of sustained abstinence, current pattern of use (frequency, quantity and duration of the current period of use), and current symptoms of withdrawal.

It should be noted that symptoms and signs of opiate withdrawal are subject to the effects of environment (less intense in controlled settings) and dependent on the amount and timing of the last use prior to evaluation. Severity of withdrawal does not necessarily correlate with high tolerance, and does not reliably establish need for a high maintenance dose. The earliest manifestations of opioid withdrawal are often subjective. Table 4 shows anticipatory, early, and fully developed symptoms and signs of opiate withdrawal. The physician should expect to see at least early signs of withdrawal. The Clinical Institute Narcotic Assessment (CINA) Scale (Table 5) measures 11 signs and symptoms commonly seen in patients during narcotic withdrawal. This can help to gauge the severity of the symptoms and to monitor changes in the clinical status over time. The Clinical Opiate Withdrawal Scale (COWS) (Table 6) can be used to document the presence of and to quantify the severity of opioid withdrawal.

Table 4 ~ Medical Syndromes Associated with Opioid Use: Anticipatory, Early, and Fully Developed Symptoms and Signs of Opiate Withdrawal

| Syndrome (Onset and Duration) | Characteristics |
|---|--|
| Opiate intoxication | Conscious, sedated, “nodding” Mood normal to euphoric Pinpoint pupils History of recent opiate use |
| Acute overdose | Unconscious Pinpoint pupils Slow, shallow respirations |
| Opiate withdrawal: Anticipatory* (3-4 hours after last use) | Fear of withdrawal Anxiety Drug seeking behavior |
| Early (8-10 hours after last use) | Anxiety Restlessness Yawning Nausea Sweating Nasal stuffiness Rhinorhea Lacrimation Dilated pupils Stomach cramps Drug-seeking behavior |
| Fully developed (1-3 days after last use) | Severe anxiety Tremor Restlessness Piloerection** Vomiting, diarrhea Muscle spasm*** Muscle pain Increased blood pressure; tachycardia Fever, chills Impulse-driven drug-seeking behavior |
| Protracted abstinence (Indefinite duration) | Hypotension Bradycardia Insomnia Loss of energy, appetite Opiate cravings |

* 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.”

Table 5 ~ The Clinical Institute Narcotic Assessment (CINA) Scale for Withdrawal Symptoms

Adapted from Peachey and Lei 1988. Reprinted with permission from Blackwell Publishing, Ltd.

| PARAMETERS | POINTS | FINDINGS |
|--|----------------|--|
| Parameters Based on Questions and Observation: | | |
| 1. Abdominal Changes: <i>Do you have any pains in your abdomen?</i> | 0 | No abdominal complaints; normal bowel sounds |
| | 1 | Reports waves of crampy abdominal pain |
| | 2 | Crampy abdominal pain; diarrhea; active bowel sounds |
| 2. Changes In Temperature: <i>Do you feel hot or cold?</i> | 0 | None reported |
| | 1 | Reports feeling cold; hands cold and clammy to touch |
| | 2 | Uncontrolled shivering |
| 3. Nausea And Vomiting: <i>Do you feel sick to your stomach?</i> <i>Have you vomited?</i> | 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 |
| 4. Muscle Aches: <i>Do you have any muscle cramps?</i> | 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 |
| Parameters Based on Observation Alone: | | |
| 5. Goose Flesh | 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 |
| 6. Nasal Congestion | 0 | No nasal congestion or sniffing |
| | 1 | Frequent sniffing |
| | 2 | Constant sniffing watery discharge |
| 7. Restlessness | 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 |
| 8. Tremor | 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 |
| 9. Lacrimation | 0 | None |
| | 1 | Eyes watering; tears at corners of eyes |
| | 2 | Profuse tearing from eyes over face |
| 10. Sweating | 0 | No sweat visible |
| | 1 | Barely perceptible sweating; palms moist |
| | 2 | Beads of sweat obvious on forehead |
| | 3 | Drenching sweats over face and chest |
| 11. Yawning | 0 | None |
| | 1 | Frequent yawning |
| | 2 | Constant uncontrolled yawning |
| TOTAL SCORE: Date: _____ Time: _____ | SUMMARY | Percent of maximal withdrawal symptoms: = (total score/31) x 100% = ____/31 x 100% = ____% |
| Patient Name: | | Number of Absent Signs and Symptoms: ____ out of 11 Number of Maximal Signs and Symptoms ____ out of 11 |
| | | Minimum score = 0, Maximum score = 31. The higher the score, the more severe the withdrawal syndrome. |

Table 6 ~ Clinical Opiate Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient's signs or symptom. 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/minute 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: <i>over last ½ hour</i> 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: <i>observation of outstretched hands</i> 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching |
| Restlessness: <i>Observation during assessment</i> 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: <i>Observation during assessment</i> 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: <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i> 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: <i>Not accounted for by cold symptoms or allergies</i> 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

The assessment continues by exploring the patient's use of other substances. Obtaining a complete substance abuse history will allow the physician 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 overall addiction problems, not just the opioid one. Other substances to explore include stimulants (methamphetamine, cocaine, nicotine), sedatives (barbiturates, benzodiazepine, alcohol, muscle relaxants/OTC sleep preparations), marijuana, PCP, designer drugs (ecstasy, and others) other OTC or prescription medications taken inappropriately. (See the Section on Co-morbid Polysubstance Use.)

The California Department of Justice maintains a record of the controlled substance prescriptions filled for individual patients and will provide a report of California prescriptions for a particular patient at the request of the treating physician. The report will include California prescriptions filled in the preceding 6 months or longer. Although consent from the patient is not required to obtain the report, information in the report is governed by confidentiality rules. Physicians may request this information only for patients in their care. Physicians will be asked to enter their DEA number on the form. Appendix D provides further information. The report request form can be downloaded from the website of the California Attorney General: <http://caag.state.ca.us/bne/pdfs/BNE1176.pdf>.

A brief social history should be reviewed by the physician. Review of the patient's current living and transportation arrangements as well as past and present involvement with criminal justice will help to elucidate the severity of addiction and to identify barriers to daily dosing.

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 methadone treatment. Specific questions regarding painful conditions, chronic or acute, and past and current management may reveal prescription drug problems and/or the need to coordinate care for pain management. Some needle-related conditions might require urgent care (see the Section on Concurrent Medical Conditions.)

Questions regarding past hospitalizations, accidents/injuries, surgeries and medications being taken help to bring to light conditions the patient does not immediately remember or volunteer. Screening for symptoms of communicable disease is an important component of this section of the interview. The most commonly encountered communicable diseases are TB, hepatitis, sexually transmitted diseases and HIV. Many patients are due for a tetanus booster. It is very helpful, and sometimes essential, that patients sign an authorization for release of information to all treating physicians to allow coordination.

Many opioid dependent patients have untreated mental health problems, most commonly major depression, anxiety and bi-polar 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, and the family history will allow triage and follow-up as appropriate. It is helpful, and sometimes essential, to coordinate with any physician providing mental

Federal regulations govern the confidentiality of patient information when the patient is in treatment; a general form for release of information is not adequate.

health care. The patient must sign an authorization for release of information prior to communication. Federal regulations governing the confidentiality of patient information when the patient is in treatment for addiction are found in 42 CFR Part 2.

■ **NOTE** A general form for release of information form is not adequate. See Table 7 for the specific requirements. See Appendix D for a sample release form that meets the federal requirements.

Table 7 ~ Specific Requirements for Written Authorization for Release of Information Forms Under 42 CFR Part 2

Under these regulations, disclosure must include these elements:

1. The specific name or general designation of the program or person permitted to make the disclosure
2. The name or title of the individual or the name of the organization to which disclosure is to be made
3. The name of the patient
4. The purpose of the disclosure
5. How much and what kind of information is to be disclosed
6. The signature of the patient and, when required for a patient who is a minor, the signature of a person authorized to sign under 42CFR § 2.14; or, when required for a patient who is incompetent or deceased, the signature of a person authorized to sign under 42CFR § 2.15 in lieu of the patient
7. The date on which the release is signed
8. A statement that the release 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
9. The date, event, or condition upon which the release will expire if not revoked before. This date, event, or condition must insure that the consent will last no longer than reasonably necessary to serve the purpose for which it is given

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

- Vital signs
- HEENT
- Neck (including thyroid)
- Chest (including heart, lungs and breasts)
- Abdomen
- Skin
- Extremities
- Neurological screening

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 and the patient consents.

The physical examination provides an opportunity to observe for signs of opioid withdrawal (see Table 4). The presence of signs of withdrawal establishes the diagnosis of physical dependence. California regulations require that the physician document the presence of physical dependence on opioids prior to admission to methadone treatment. **The patient should be in at least mild withdrawal prior to the first dose of methadone.** (Exceptions to this requirement are listed in the Section on Criteria for Admission.)

Laboratory evaluation should be individualized, but hepatitis serology, liver function tests, and HIV screening 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.

Addiction affects every aspect of a patient's life, and addiction treatment is holistic in its approach. The eventual care includes attention to the disruption in family and friendship networks and personal growth of the patient. The initial history and physical exam provides the opportunity to collect information necessary for development of the treatment plan and to build a rapport with the patient that can make a positive contribution to the patient's chances of succeeding in treatment.

In summary, the role of the OTP physician in conducting the initial history and physical examination:

- **To document the patient’s drug history,** including opioids and other drugs of abuse.
- **To identify patients needing medical detoxification** from alcohol, benzodiazepine or other sedatives and to determine where and when this is to be accomplished.
- **To identify acute medical conditions,** including mental health issues, and to determine how, when and where they will be addressed.
- **To screen for communicable disease** and address as appropriate.
- **To document the presence or absence of opioid withdrawal** by physical exam.
- **To assess the patient’s suitability** for participation in an outpatient program requiring daily attendance.

Section on

DETERMINING AND ADJUSTING THE DOSE

Once the patient has been found medically fit and appropriate for opiate agonist therapy, the physician is responsible for determining the initial dose of medication and all subsequent adjustments.

Two medications may be used in OTPs: methadone and the sublingual forms of buprenorphine (Suboxone® and Subutex®). The body of this document focuses on methadone; buprenorphine is reviewed in AppendixB.

Methadone: Description and Properties

Methadone is a synthetic opioid drug taken by mouth. It is available in liquid or tablet form. In California, OTPs are required to use the liquid formulation. An exception request may be submitted if there are special circumstances making liquid methadone problematic. However, CSAT, as of September 2008, is considering discontinuing methadone tablets.

The bioavailability of methadone varies from patient to patient. Methadone acts as a full agonist at the mu receptor. This drug's long half-life, (average 24-36 hours), has rendered it a very useful drug for the treatment of opioid dependence. In most cases, methadone can be used on a once a day basis with safety and efficacy. However, the rate of metabolism is genetically determined and varies widely, meaning that some patients will require more frequent dosing to remain asymptomatic between doses.

Methadone's onset of action is 30-60 minutes. The peak effect of any one dose is achieved in two to four hours. Tissue stores build up over time, and steady state will not be achieved for 5-7 days. This gradual buildup of tissue stores is part of methadone's effectiveness through long-term suppression of withdrawal and craving. **This buildup of tissue levels produces daily increases in the medication's impact on the patient in the first week of treatment,** so patients should be carefully assessed daily during this crucial time. Documented daily assessment of the response to the previous day's dose is a guide to determination of subsequent doses. Careful observation and regular evaluation are imperative until steady state has been achieved.

The pharmacological properties of methadone make it a very effective medication for the treatment of opioid dependence. However, the long half-life means that any given dose of methadone will produce a higher blood level each day for the first 5-7 days of ingestion. There is a very real risk of overdose during the induction period if the starting dose of methadone is too high or if the dose is increased too quickly. Because of cardiac events and respiratory deaths during induction, a black box warning was added to the methadone label on November 27, 2006. (See Section on Adverse Events.) Conversion of pain patients to methadone from treatment with other opioid agonists 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.

There is a very real risk of overdose during the induction period if the starting dose of methadone is too high or if the dose is increased too quickly.

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 approximately one week.

It is essential that a complete list of prescribed, OTC and herbal preparations be obtained and reviewed prior to starting methadone treatment.

Induction: The Initial Dose and Establishing Tissue Stores Safely

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

- Knowledge of California and federal regulations that limit the size of the initial dose.
- Knowledge of methadone's pharmacology, the individual patient's characteristics, and the patient's current medications.
- The patient's current level of opioid dependence (tolerance). Note that there is no direct way to measure tolerance. The presence of withdrawal confirms the diagnosis of physical dependence; however the severity of withdrawal does not establish the level of tolerance. **In other words, severe withdrawal at intake does not necessitate a higher starting dose.**

Factors to consider when assessing a patient's level of tolerance:

- The quantity of drug used daily. Patients using $\frac{1}{4}$ gram of heroin or less are apt to have a low level of tolerance.
- The route of use. Heroin is less efficiently absorbed when it is snorted or smoked than when it is injected intravenously.
- Recent use of naltrexone or buprenorphine. Recent use of an opioid antagonist or partial agonist significantly reduces opioid tolerance.

There is no direct way to measure tolerance. The severity of withdrawal at intake is not a measure of the level of tolerance.

When the patient has been using prescription opioids, use of an opioid equi-analgesic dose table is not recommended.

- The type of opioid being used. Patients using low potency opioids such as codeine or hydrocodone may have low tolerance. Patients using high potency opioids such as oxycodone may have high tolerance.
- Time elapsed since last period of daily opioid use. Patients who have been recently released from an institutional stay, such as incarceration, hospitalization or residential treatment in the absence of opioids will have low tolerance.
- History of opium smoking. These patients may have very high or very low levels of tolerance depending on how much opium they are smoking in a day.
- Observed vs. unobserved dosing. Caution must be exercised when inducing patients who have been prescribed methadone or other long acting opioids in a pain setting. There is no way to confirm that the patient is taking the dose as prescribed. If the patient is selling some or most of the medication, his/her tolerance will be lower than otherwise anticipated.

Selecting a starting dose is particularly challenging when the patient has been using prescription opioids. Use of an opioid equi-analgesic dose table is not recommended. The conversion table gives the dose of various opioids that will have the same effect as a given 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 may be too high when given as a daily dose.

If there is any question as to the level of the patient’s tolerance or the patient is likely to have a low tolerance level, an initial dose of 5 - 15 mgs maybe safely given, and follow-up doses may be provided every 3 to 5 hours as clinically indicated. Indeed, this may be 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, but 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.

The next few days are critical. Patients are uncomfortable; it may be hard for them to avoid using heroin or other opioids, and they are at risk for overdosing if they do.

Although “start low and go slow” reflects safety concerns in early methadone treatment, most heroin addicted patients in the United States ultimately require daily doses between 80 and 120 mg to achieve stability. Daily doses may be lower for patients addicted to prescription opioids or opium. A very conservative approach to induction, which automatically requires patients to wait 5 days between dose adjustments, **can delay relief to the point that patients will continue to use, putting them at risk of overdose and delaying stabilization.**

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 will allow the physician to address the patient's discomfort. If the patient did not experience complete suppression of withdrawal within 3-4 hours of dosing on the preceding day, it is safe and reasonable to increase the dose by 5-10 mg. However, if the patient did experience complete suppression of withdrawal 3-4 hours after dosing on the preceding day, but symptoms re-emerged before 24 hours, any increase in the dose should be delayed for another day or two, while observing the patient, to allow for the accumulation of the stores, with the expectation that the dose will cover a little longer each day.

Patients in whom the first dose suppresses withdrawal completely for a full 24 hours may experience sedation as tissue stores accumulate. Symptoms of overmedication include sleepiness, sedation or unusual feelings of excess energy with or without euphoria. **Patients need to be aware that symptoms of overmedication must be reported 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.** Asking patients about symptoms daily during the first five days of induction is an important safeguard.

Patients should be advised that suppression of severe physical withdrawal is usually accomplished after the first day or two, complete suppression after over a week or two, concluding the first phase of treatment induction.

The goal is to achieve methadone levels that will prevent craving and withdrawal as quickly as can be done safely. **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 dose changes should be clearly documented in the patient's record.

The first dose should NOT be expected to fully suppress withdrawal nor to fully eliminate craving and is probably too high if it does so.

In maintenance treatment, once steady state has been achieved, the proper dose of methadone or buprenorphine should accomplish the following clinical objectives:

- Control of physical signs and symptoms of opioid withdrawal.
- Control of opioid craving (e.g., intrusive thoughts and dreams of usage, urges to use.)
- Blockade of the usual "high" or euphoric effects of opioids.
- Avoidance of sedative side effects.
- Minimization of other side effects, such as sweating, constipation, decreased libido.
- The first dose should NOT be expected to fully suppress withdrawal nor to fully eliminate craving, and it is probably too high if it does so.

Stabilizing on a Therapeutic Dose

A dose that completely suppresses physical withdrawal may or may not be a therapeutic dose. A therapeutic dose will also take away the urge to use or unwanted thoughts about using (cravings). In order to reach stabilization, some patients need a blocking dose, which is a dose that will prevent opioids

At a steady state, a therapeutic dose suppresses withdrawal and reduces craving (biological more than conditioned) for the entire time between doses without sedation.

of abuse from binding to opioid receptors and causing feelings of euphoria. A therapeutic dose provides suppression of withdrawal and reduces craving for the entire interval between doses without sedation. A therapeutic dose will also help to control cravings. **There are two types of cravings – biological and conditioned. Biological cravings** are the result of decreased opioids in the brain. Methadone is very effective at suppressing biological cravings. **Conditioned cravings** occur with exposure to persons, places or things associated with using. Methadone is less effective at suppressing conditioned cravings.

Outcomes are better when a therapeutic dose is achieved, so frequent check-ins with the patient about dose adequacy are important early in treatment, during stabilization. In some OTPs, the counselors are specifically trained to interview the patient about symptoms of withdrawal, cravings and adequacy of dose and to pass on information to clinical staff when patients are symptomatic. This integration of care –involving the counselor, dispensing nurse, and clinician working together to assure that the patient stabilizes on a therapeutic dose – supports the patient’s compliance in treatment.

The physician, working closely with a well-trained staff, must always be mindful of the patient’s potential for concomitant use of illicit drugs, alcohol, and/or prescribed 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.

There are prescription medications that can raise or lower the methadone plasma level. See also the paragraphs regarding methadone drug-interactions under the heading “Re-evaluating the dose in the event that the clinical picture changes.” In the Section on Determining and Adjusting the Dose. There are several websites with information that may be helpful:

- <http://drug-interactions.com>
This website includes Cytochrome P450 Drug Interactions Tables by D.A. Flockhart from the Indiana University School of Medicine and is updated periodically.
- <http://www.urmc.rochester.edu/urmc/AAPCC/tables.html>
This website includes Cytochrome P450 Reference Tables Adapted From: E.L. Michalets Pharmacotherapy 1998;18(1):84-112.
- http://www.atforum.com/SiteRoot/pages/addiction_resources/Drug_Interactions.pdf
This website is sponsored by an educational grant from Mallinckrodt, manufacturers of methadone, and lists medications that affect methadone plasma levels and increase or decrease methadone effects.

Patients must be informed that interactions with other medications can be serious, so they need to alert their prescribing physicians that they are taking methadone. Patients should be encouraged to ask the pharmacist about the possibility of interaction with methadone before starting any new medication.

In general, it takes 4 – 5 half-lives (~ 5 days) to reach steady state. After an initial buildup, dosage adjustments of 5 – 10 mgs every 3 – 5 days are usually adequate. For example, a symptom-triggered protocol can be used which gives 5 mgs for drug craving or up to 10 mg for physical symptoms (i.e., runny nose, cramps, etc.) Essentially, each clinician must use his or her clinical judgment based on the unique characteristics of the individual patient. During this early period of stabilization, 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” (suppressed withdrawal) for the full 24 hours. A new dose that completely suppresses withdrawal 2 - 4 hours after it is taken, that is, 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. This is because of the build-up of tissue stores.

This initial stabilization period is one of the hardest to manage, clinically, because patients are fearful of being sick, and they are tempted to supplement their dose with outside opiates to alleviate the symptoms. The physician should inform patients that the methadone dose is expected to allow them to stop heroin use completely and should caution them against on-going use of heroin, explaining that using heroin on top of the methadone increases their tolerance and makes it more difficult to achieve a stable dose. The physician should also encourage patients to avoid people, places and situations where opiates are available because such situations can intensify craving and trigger symptoms of withdrawal.

Utilizing 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 abstinence may take longer and may necessitate doses in the 80 - 120 mg range (or higher) as clinically indicated. In California, the 180 mg dose cap was removed from the Health and Safety Code in 2002. While doses above this level are not the norm, sometimes they are necessary and appropriate. California regulations require physicians to justify doses above 100 mg in the patient’s record.

Every effort should be made to individualize the patient’s dose. The objective is to achieve a stable maintenance dose that allows the patient to conduct activities of daily life without sedation or withdrawal. Some patients continue to report symptoms of withdrawal between doses, but also report sedation a few hours after dosing. Patients may report this 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. Observation of the patient prior to dosing and again ~ 4 hours after dosing allows clinical confirmation.

Methadone Blood Levels

Plasma levels of methadone (i.e., trough and peak levels) can be utilized as an adjunct to clinical evaluation, to evaluate the safety and adequacy of a patient’s dose. It should be noted that methadone is an enantiomer and only the R isomer is active for the treatment of opioid dependence. 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) Center for Substance Abuse Treatment 2005); the correlation was much stronger in patients with no drug abuse when compared with patients who were using. As with all lab data, the entire clinical picture must be considered. Some clinicians obtain methadone quantitative blood levels when a patient's dose exceeds 100mg per day.

Obtaining and Interpreting Blood Levels

Methadone blood levels are generally obtained when a patient has reached steady state that is after 5-7 consecutive daily doses of the same amount. 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 is usually asked to remain at the clinic while waiting for the peak to be drawn to preclude other methadone ingestion in the interim.

Blood levels should not replace good clinical judgment, but they can provide a point of reference. There is no standard therapeutic blood level; blood levels vary from patient to patient. Payte notes that adequate trough levels in the highly tolerant opioid dependent patient are in the 400 to 600ng/ml range. Other patients may stabilize with trough levels of 100 to 200ng/ml. Payte and colleagues note that absolute numbers in evaluating trough levels are less useful than a comparison between peak and trough levels (Payte & Zweben 1998). The peak level is generally less than twice the trough level in a patient with a normal methadone metabolic rate. Comparing a patient's peak and trough levels can give the clinician a sense of a patient's rate of methadone metabolism. A peak level that is more than twice the trough level suggests a rapid metabolic rate of methadone.

Some patients cannot be stabilized on one dose per day.

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 variation as symptoms of withdrawal. Split dosing usually requires that the patient be given a daily take home dose. The physician must weigh the risk of diversion against the benefit to the patient. In cases where the patient has not been in treatment long enough (270 days) for the regulations to allow seven take-homes per week, a waiver from CSAT is needed prior to initiating split dosing. (<http://www.dpt.samhsa.gov/>) In addition, the patient must meet the other California and federal regulatory criteria in the Section on Take Home Medications.

Split doses are recommended in pregnancy. See the Section on Treatment of Pregnant Women. Split dosing may be helpful for patients with pain because patients report some analgesic effect for about four hours after dosing.

Example

A patient who usually comes in to dose at 7 am is observed to take 120mg of methadone for seven days at the dispensing window.

On the eighth day the patient goes to the lab, has the trough level drawn, then proceeds to the dosing window and takes the usual dose of 120mg. At 10 am the patient returns to the lab and has the second level drawn. The patient is given an appointment for the following week to meet with the physician and review the results. If the 10am level is more than twice the 7 am level and the patient is

stable enough to handle a daily take-home bottle of methadone, the patient and physician may agree to try splitting the dose. The patient will take 60 mg at 7 a.m. and an additional 60 mg at 7 p.m. After 5-7 days, the physician may adjust the amount and timing of morning and evening doses if necessary.

Re-evaluating the Dose in the Event That the Clinical Picture Changes

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, 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, changing the dose may solve the problem. 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.

Other times, the patient may be experiencing symptoms that feel like withdrawal but are not dose-related. Patients have a tendency to attribute new symptoms or discomforts to a problem with the methadone dose, but, when the clinical picture changes, the physician needs to reassess the patient to determine whether the methadone dose should be adjusted or other interventions recommended. Input from nursing and counseling staff may be helpful; it may be necessary to meet with the patient.

Some of the More Common Reasons for Destabilization

Relapse

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. In this situation, efforts to encourage abstinence by medical and counseling staff are indicated. If the short-acting opioid of abuse is still producing euphoria, a methadone dose increase to block this effect may be offered. A methadone dose increase may also help to suppress drug cravings. Coordination with prescribing physicians to limit the number of short-acting opioids obtained by prescription may also be helpful. (See the Section on Chronic Pain.)

Sedative Drug Use

Use of some sedating drugs such as alcohol and benzodiazepine may require methadone dose reductions to counter over-sedation. 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. If the patient is using or abusing a prescribed medication,

coordination with the prescribing physician will be necessary. Withholding or reducing the methadone dose may help prevent over-sedation, but will not solve this difficult problem. (See the Section on Management of Co-Morbid Poly Substance Use.) Continued abuse of non-opioid substances should be addressed vigorously in counseling sessions, and should not necessarily lead to discharge from treatment.

Non-specific stress

Non-specific stress can result in patients experiencing withdrawal symptoms. Addicted patients may suffer from deficits in the stress response system. In the event of a 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 initially indicated.

Drug Interactions

There are a host of medications that have the potential to interact with methadone. New medication or changes in the dose of an existing medication may precipitate sedation or withdrawal. However, the clinical response to co-administration varies widely from patient to patient and from drug to drug. Many drugs that could potentially increase or decrease the methadone blood level do not result in clinically significant symptoms. A potential methadone-drug interaction is not an absolute contraindication to co-administration. Careful clinical monitoring is necessary, so that the methadone dose may be adjusted if an interaction causes clinically significant symptoms.

There are some medications that frequently precipitate withdrawal. These include medications such as anti-convulsants (carbamazepine, phenytoin, etc.,) some antibiotics (rifampin) 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 earlier in the document 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, and others) 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 and may increase plasma methadone levels..

Medications used to treat HIV infections may affect methadone and buprenorphine. See Tables 11, 12, 13 on page 69. Underlying medical conditions, such as cirrhosis, pregnancy, chronic pain and psychiatric disorders, must be considered when assessing dose adjustments and safety.

Several websites with information concerning cytochrome P450 drug interactions are listed below:

- <http://drug-interactions.com>

This website includes Cytochrome P450 Drug Interactions Tables by D.A. Flockhart from the Indiana University School of Medicine; it is updated periodically.

- <http://www.urmc.rochester.edu/urmc/AAPCC/tables.html>

This website includes Cytochrome P450 Reference Tables Adapted From: E.L. Michalets Pharmacotherapy 1998;18(1):84-112.

- http://www.atforum.com/SiteRoot/pages/addiction_resources/Drug_Interactions.pdf

This website is sponsored by an educational grant from Mallinckrodt, manufacturers of methadone, and lists medications that affect methadone plasma levels and increase or decrease methadone effects.

Consultation with a pharmacist for information on drug interactions is recommended for new medications.

Medical and Psychiatric Conditions

Intercurrent medical or psychiatric conditions can sometimes explain new onset of withdrawal in a previously stable patient. Some such conditions may actually 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 may feel like withdrawal; patients need reassurance and suggestions for symptomatic relief. 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.

Insomnia

In the case of insomnia it may be hard to tell whether the dose should go up, down or stay the same. Stimulant use should be ruled out first. 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 may help distinguish the proper clinical choice in these cases.

Pregnancy

Pregnancy may significantly lower methadone blood levels in some patients, particularly in the first and third trimester; the initiation of prescription anti-convulsants or rifampin may also drastically decrease methadone blood levels. These situations do not respond to the incremental dose increases described above, patients may need a divided or split dose to re-stabilize. Split dosing is discussed earlier in the document in the Section on Determining and Adjusting the Dose.

To review, some of the more common reasons for a change in the clinical picture include:

- Relapse
- Stress
- Increase or decrease in exposure to “triggers”
- New medication
- Change in the dose of a medication
- Medical conditions
- Psychiatric symptoms
- Insomnia
- Pregnancy

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.

In summary, the role of the OTP physician with regard to the methadone dose:

- **To select a safe starting dose** based upon the patient’s addiction and medical history, taking into consideration the patient’s opioid status at presentation as well as use of other substances/medication(s) and medical conditions likely to impact methadone’s effects.
- **To adjust each patient’s methadone dose during induction** based upon his/her response to prior doses, particularly at the time of the peak methadone blood level.
- **To expedite stabilization** to ensure that patients reach a therapeutic methadone dose as quickly as is safely possible.
- **To re-evaluate as needed** to assess patients who report withdrawal, cravings or sedation after initial stabilization and to determine and address the likely cause(s), adjusting the methadone dose when appropriate.
- **To keep in mind methadone-drug interactions** and to counsel patients and clinic staff about the potential for methadone-drug interactions, monitor patients for such interactions and intervene as necessary to maintain patient comfort, stability and safety.

Section on

ADVERSE REACTIONS

When properly used for the treatment of opioid withdrawal, 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 November 27, 2006.

Methadone Black Box Warning

WARNING

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

In addition, cases of QTc interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks.

Adverse (i.e., unwanted or unfavorable) reactions have been described in the methadone label and are summarized in Table 8. Many of the listed effects are general opioid effects and would be expected to lessen when switching from a short-acting opioid (heroin) to a long acting opioid (methadone.) One notable exception is constipation; it is worse with long-acting opioids and does not resolve over time.

Table 8 ~ Adverse Reactions as Listed in the 2006 Methadone Label

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

The most frequently observed adverse reactions in methadone maintenance patients are sweating, constipation, sedation 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 whether methadone plays a role in the weight gain.

The most frequently observed adverse reactions are sweating, constipation, sedation and decreased libido. Tolerance to sweating and constipation is not likely to occur.

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 if stabilization persists. 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 or coma. 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. Emergency transport to a hospital in this situation is mandatory. A dramatic reaction to naloxone injection should be anticipated in any methadone patient, so treatment should be started with low doses of naloxone, watching for vomiting, aspiration and agitation. 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.

Tolerance to sweating and constipation is not likely to occur, but can be managed clinically using anticholinergics for sweating. Methscopolamine 2.5 mg tid may be used as a 'drying' agent in cases of severe sweating, but is not useful if patients have high blood pressure or urinary retention. Stool softeners or osmotic cathartics may be used for constipation. Decreased libido in men is also common, but treatable. 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 is less severe than with heroin. Methadone-related erectile dysfunction in males can be successfully treated with phosphodiesterase type 5 inhibitors, such as sildenafil (Viagra®), tadalafil (Cialis®) or vardenafil (Levitra®). Edema of the extremities is not uncommon and although 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.

Cardiac Considerations in the Context of MMT

Manufacturers' package inserts have always included possible cardiac-related side effects such as bradycardia, palpitations, faintness and syncope. In November of 2006, a black box warning was added which notes "QTc interval prolongation and serious arrhythmia (torsades de pointes) 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 corrected QTc interval (QTc) means prolonged cardiac ventricular repolarization, which can increase the risk of the occurrence of torsade de pointes (TdP). The definition of prolonged QTc interval varies. Women have longer QTc intervals than men by about 20 milliseconds (msec). Some sources indicate that for men a QTc > 430 msec is considered prolonged and for women a QTc > 450 msec. However, all sources agree that a QTc of 500 msec or more is prolonged. The risk of torsades de pointe usually begins at a QTc interval of about 500 msec and increases exponentially thereafter (Shah 2004).

Cardiologists vary in their recommendation as to when to avoid or discontinue methadone treatment from a QTc > 480 msec to a QTc > 550 msec.

Cases of prolonged QTc interval and TdP have been associated with a number of factors including family history, patient history of heart disease (especially CAD or CHF), congenital long QT syndrome, use of medication(s) that prolong the QTc, electrolyte instability (especially decreased potassium and magnesium), use of cardiotoxic drugs (cocaine, alcohol, etc), or signs/symptoms suggesting cardiac disease or arrhythmia.

A number of studies have been published in recent years elucidating the effect of methadone on the QTc interval. Two recent studies have examined adverse outcomes amongst patients on methadone; one studied syncope, the other sudden death. A summary of the studies appears in Table 9. All of these studies used a corrected QT interval (QTc).

Table 9 ~ Summary of Studies on the Effect of Methadone on the QTc Interval

The mechanism for methadone's effect on the QTc interval was studied by (Katchman et al. 2002). Methadone blocks the HERG gene, resulting in a blockage of the HERG K⁺ ion channel. This is a reversible effect (see Ehret below). It is the current dose of methadone that effects the QTc interval, not the duration of methadone treatment.

Martell conducted a study of heroin-dependent adults to compare the QTc interval before induction and 2 months later. (Martell et al. 2003) Small increases in QTc interval (mean of 10.8 milliseconds) were observed after stabilization on MMT at usual therapeutic doses of 30 to 150 mg; there is a greater increase in the QTc interval in men on MMT than in women. These increases were not clinically significant. An increase in the QTc interval of >40 milliseconds is generally considered to be clinically concerning.

A follow-up study was done by (Martell et al. 2005), which assessed QTc intervals prior to induction and 6 and 12 months after induction. They found that the 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. They also found that there was a positive correlation between serum methadone level and magnitude of QTc interval change. Studies by (Kornick et al. 2003) and (Krantz et al. 2003) also found a positive correlation between daily methadone dose and QTc prolongation.

It is interesting to note that (Maremmani et al. 2005) and (Peles et al. 2006) 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.

Ehret (Ehret et al. 2006) studied patients with a history of intravenous drug use 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 torsade de pointes. 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. The authors found that 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.

Fanoë (Fanoë et al. 2007) 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. They found a significant association between the methadone dose and the QTc in both genders. They found increasing incidence of syncope with higher doses of methadone and higher odds for reporting syncope with longer QTc intervals. They noted that opioid abuse decreased as methadone dose increased, making it unlikely that the increased syncope in the methadone patients on higher doses was due to opioid abuse. 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 (Chugh et al. 2008) conducted a prospective evaluation 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. Patients using recreational drugs or with any history of drug overdose were excluded from either group. 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. The author concludes that this lower prevalence of cardiac disease in the patients on methadone suggests that there may be an association between methadone and sudden cardiac death, but notes that one cannot rule out the possibility that some of the methadone patients died due to suppression of breathing, especially while asleep.

There is a case report by (Krantz, Garcia & Mehler 2005) Krantz et al in 2005 about a 42-year-old patient who experienced torsade de pointes while on 450 mg of methadone per day. The methadone was stopped and the patient given oral morphine. The patient was tapered off the oral morphine and induced with buprenorphine reaching a maintenance dose of 32 mg/day. No clinically significant QTc prolongation was observed during induction or at 1 and 2 month follow-up. Further studies are needed to determine whether buprenorphine may be a safe alternative for methadone in patients with opioid dependence who develop torsade de pointes. If this is the case, it will bring up many issues. Buprenorphine is more expensive and therefore not as readily available for most patients.

Cardiac Risk Monitoring Plan

Patient screening and monitoring, and patient education, are critical components of cardiac risk monitoring.

In response to the literature indicating that methadone can cause QTc prolongation and the known cases of TdP in patients on methadone maintenance, many OTPs are developing protocols to address this concern. Careful patient screening and monitoring as well as patient education are critical components. OTP physicians are screening at admission and periodically for conditions that may increase a patient's risk including individual and/or family history of cardiac disease and/or structural defects, use of other QTc prolonging medications, or conditions increasing the possibility of serum electrolyte fluctuation.

For patients identified as being at increased risk, the OTP physician may coordinate care with the patient's primary care provider (PCP) or cardiologist and discuss the advisability of pre- and post- induction ECGs and monitoring serum electrolytes. ECGs may also be recommended if the patient has a new cardiac diagnosis, begins taking another medication that prolongs the QTc interval or experiences a dramatic change in the serum methadone level or has symptoms suggestive of cardiac arrhythmia.

The OTP physician's discussion of the risks and benefits of methadone treatment prior to admission provides an opportunity for patients to be informed about the effects of methadone on the QTc interval and the associated risk of arrhythmia if the QTc interval is markedly prolonged. Patients may be reassured that in most people the increase in the length of the QTc interval is not clinically significant. Patients should also be informed that the risk is increased if they or a family member has certain heart conditions or if they other medications that prolong the QTc interval while they are on methadone. Patients should be cautioned to promptly report episodes of syncope, near syncope or seizure, to inform the clinic of new medical diagnoses and to register prescribed medications. Treatment alternatives, such as buprenorphine, may be considered if warranted after evaluating the risks/benefits of methadone treatment for a particular patient.

For a complete and well-referenced summary see the Addiction Treatment Forum web site at www.ATForum.com.

Endocrine Issues

Research and clinical evidence suggests 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 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 et al. 2005).

Female patients

The gonadal function problems experienced by women maintained on methadone or other opioids include luteal and follicular phase disruptions (Santen et al. 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.

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.

In summary, the role of the OTP physician with regard to potential adverse reactions associated with methadone treatment:

- **To inform patients of risks associated with methadone treatment** including ongoing physical dependence, risks of cardiac and respiratory suppression with potential for death if taken in excess of the prescribed dose or in combination with other sedatives (prescription drugs, illicit drugs or alcohol), the possibility of decreased gonadal function, the potential for cardiotoxicity and possible side effects.
- **To identify patients at increased risk of adverse reactions**, particularly cardiac or respiratory, and to develop a plan for managing risk.
- **To counsel at-risk patients regarding treatment options**, including sublingual buprenorphine and residential programs, and to intervene when clinically indicated.
- **To coordinate care** for at-risk patients with other treating physicians.

Section on

MANAGING MAINTENANCE TREATMENT

After admission to MMT and after stabilization of the patient's methadone dose, physicians provide ongoing medical oversight to 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. Psychosocial treatment is a vital component of MMT. The efficacy of MMT for the treatment of opioid dependence has been well established. Two NIDA funded studies in 1983 (Cooper et al. 1983) confirmed that opioid dependent patients did better on MMT than without treatment. Illicit drug use and crime decreased while rates of employment increased among those on MMT. Studies in the 1990s (McLellan et al. 1993) (Shepard & McKay 1996) showed that MMT plus weekly group and referrals was as effective as MMT plus a 25 hr/week day program in term of outcomes at three and six months. For both groups, drug use decreased significantly as did drug-related problems and HIV risk behaviors.

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.

Take-Home Eligibility

OTP physicians review requests for take home medication, exception take out and regular step take-outs. See the Section on Take Home Privileges.

Toxicology Testing

OTP physicians review the orders for toxicology testing in order to be sure the tests for the relevant drugs of abuse are included, and the frequency of testing is adequate. Review drug-screening results to assure accurate interpretation of the information and respond if medical evaluation is needed. The OTP physician needs to develop expertise in this area.

Medical Follow-up

OTP physicians encourage and support the patient in following up on new referrals and with seeing his/her regular physician for chronic conditions.

Prescription Medications

OTP physicians review and track the patient's prescription medications, intervening with the patient if use appears problematic and coordinating with prescribing physicians when necessary and possible. In the event that a medication interacts with methadone to the detriment of the patient or poses a risk of abuse, it may be necessary to discuss possible alternatives. Coordination with another physician requires the patient's consent. Some patients are reluctant to divulge their addiction treatment to physicians outside the OTP.

Advocacy

In our health care system, there are times when patients on MMT are denied medical treatments that are necessary and appropriate because of a lack of information or due to prejudice about methadone. A common misconception is that patients on MMT do not require pain medication to manage acute traumatic, dental or post-operative pain. Another is that patients on MMT are not apt to benefit from treatment for hepatitis C. Frequently patients on MMT are pressured to taper off methadone in order to qualify for treatment for hepatitis. Patients involved with the criminal justice system may be assigned to a probation officer that does not approve of methadone treatment. The OTP physician is in a position to intervene in many such situations, preventing unnecessary suffering.

Hospitalization and Incarceration

OTP physicians coordinate with medical staff at hospitals or jail medical units as necessary. The OTP physician may need to alert the jail medical unit or the hospital physician that a patient has a history of benzodiazepine or alcohol dependence and may be at risk for emergence of withdrawal or that a patient has a mental health condition that may destabilize if methadone is withdrawn or psychotropic medications abruptly discontinued. The OTP physician should be available for consultation by outside physicians regarding methadone dose determination and pain management, and such.

In summary, the role of the OTP physician in the ongoing management of methadone maintenance treatment:

- **To review each patient's treatment plan** every 90 days to ensure that it meets regulatory criteria and to addresses current recovery, medical and social needs.
- **To provide medical counsel** as needed and to ensure that the patient is receiving addiction-related counseling at the program.
- **To evaluate and adjust the patient's methadone dosage** to support him/her in achieving and maintaining abstinence while minimizing side effects and ensuring safety.
- **To evaluate patients who appear sick or intoxicated when they present for dosing** to determine whether they may be safely dosed, whether the dose should be adjusted and whether they need acute medical attention.
- **To make decisions concerning patients' eligibility for take-home doses.**
- **To review and interpret drug screen results** when necessary; to ensure patients are being tested for the relevant substances.
- **To review patients' prescription medications,** intervening with the patient and/or prescribing physician when there is a concern.
- **To advocate for patients** in medical and criminal justice situations to ensure they receive appropriate medical treatment (especially for pain) and are not penalized for being on MMT.
- **To coordinate with outside medical staff** in hospitals or jail medical units as needed to ensure ongoing treatment of opioid dependence and to alert staff in the event that a patient is at risk of emergence of withdrawal from non-opioid sedatives or psychiatric destabilization if psychotropic medications are abruptly discontinued; to provide consultation when needed.

Section on

MANAGEMENT OF CO-MORBID POLYSUBSTANCE USE

While there are patients who are using only opioids when admitted to MMT, polysubstance use is a common problem in the opioid-dependent population. There are patients who quit using all drugs upon admission to MMT, but many do not. Increasing the methadone dose will often stabilize patients who are using only illicit opioids. However, when patients are using non-opioid drugs, other interventions will be needed to help the patient achieve abstinence. The physician and/or other clinical staff members should meet with the patient to determine whether there are un-addressed medical issues, such as pain, insomnia, psychiatric illness or physical dependence on a non-opioid drug which may be contributing to the ongoing use. The counselor should work with the patient to determine the social and lifestyle issues interfering with the patient's ability to achieve abstinence. The treatment team should work with the patient to address identified issues by increasing participation in counseling and groups at the program. The patient must be cautioned about the risk of driving or operating heavy machinery while under the influence of illicit drugs and/or medications in combination with methadone. See Appendix D for a sample Concurrent Medication Driving Agreement form. Transfer to a more intense level of care, such as day treatment, or residential treatment, may be needed.

Methamphetamine and Cocaine

Signs and symptoms of stimulant intoxication include euphoria, paranoia, anxiety, agitation, irritability, and suicidal states. Signs and symptoms of stimulant withdrawal include anxiety, depression, fatigue, and possibly increased risk of suicidality. This withdrawal or "crash" period may last three to five days and may contribute to clinic absences. Patients may feel they are "not addicted" because the withdrawal is less obvious than opioid withdrawal symptoms, although craving is severe. Patients may present with sedation if they come to clinic while crashing. Patients may complain of symptoms of opioid withdrawal secondary to their stimulant use.

It is important to recognize cocaine or methamphetamine abuse as early as possible. The initial history, physical, and UA screen will usually identify a stimulant-abusing patient, and the initial treatment plan should address this problem as a treatment issue. Medical and psychiatric conditions should be explored as possible influences on stimulant use. Proper evaluations may require some period of abstinence from stimulant use. This may require stimulant-specific program interventions, such as mandated treatment in groups that focus specifically on stimulant use. Evaluation and treatment of psychosis and paranoia should not be delayed because of ongoing use.

Ongoing stimulant abuse is an indication that the patient is unstable and in need of a higher intensity of care. When possible, the patient should remain on MMT while in a more intensive outpatient or residential treatment setting. If residential treatment is not possible, it is reasonable to continue to work with

stimulant-abusing patients, addressing such abuse aggressively in counseling and only discharging the patient if methadone treatment or patient/clinic safety is compromised, such as with excessive absences from the clinic, volatile behavior in the clinic or failure to seek medical care for an imminently life-threatening condition. Discharge should be avoided unless concerns about the patient's safety make it impossible to continue treatment.

Alcohol

Alcohol use/abuse/dependence is not only a common problem among opioid dependent patients but also contributes to the high mortality rate in this population. Hepatitis C infection is almost universal among heroin-injecting patients, and the combination of active hepatitis C and alcohol abuse will accelerate the progression to cirrhosis and liver failure.

Alcohol abuse impacts methadone in two other substantial ways. Acute use, especially when 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. An alcohol history should be part of the initial admission evaluation; standardized screening instruments, such as the CAGE or AUDIT may be used. Alcohol breathalyzers can be used to identify patients who are unable to control their drinking. Breathalyzer testing may help to clarify a patient's drinking pattern, daily versus weekend or holiday binges. Some patients are able to titrate their alcohol consumption to avoid a positive breath test when they come to clinic to dose. Urine alcohol screens may be helpful in this situation, as the urine will remain positive longer than the breathalyzer test.

Safety to dose assessments may be needed for patients using alcohol.

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 (e.g., 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. A more common approach is to withhold the dose if the patient appears under the influence (UTI) or has a breathalyzer $>.04$. Intoxicated patients should relinquish their car keys and arrange other transportation home. Patients with a positive breathalyzer test $< .04$ may be given a partial dose (e.g., half) provided they do not appear under the influence. When the breathalyzer test is $< .02$, it may be reasonable to continue the regular dose. Other practitioners use different thresholds. 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. The patient must be cautioned about the risk of driving or operating heavy machinery while under the influence of alcohol; this risk will be increased when alcohol is used in combination with methadone. See Appendix D for a sample Concurrent Medication Driving Agreement form. Frequent follow-ups may be offered in order to provide brief interventions (see CSAT Tip 34, “Brief Interventions and Brief Therapies for Substance Abuse”) and possibly pharmacotherapy. (Center for Substance Abuse Treatment 1999).

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. The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) may be used to evaluate patients at risk of withdrawal after abrupt cessation of alcohol use. The CIWA-Ar includes ten categories of symptoms/signs which are scored based on severity. The maximum score is 67. Patients with scores <10 do not usually require medication. A copy of the CIWA-Ar is included in Appendix D. Some programs offer outpatient detoxification from alcohol with phenobarbital or benzodiazepine. Patients whose past history includes severe alcohol withdrawal (sometimes termed “DTs,”) such as seizures, or patients who are medically fragile or pregnant require hospitalization for detoxification from alcohol use. (ASAM *Principles of Addiction Medicine*) (2004) 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 per day. It is safe to start treatment with disulfiram when there is no detectible level of alcohol in the blood. A breathalyzer is useful and more convenient than a blood draw. Patients should be given information about inadvertent alcohol ingestion in mouthwash, marinades, etc and sign a consent that explains the potential violent 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. It is explained more fully in Chapter 6 of the textbook, *Methadone Treatment for Opioid Dependence*. (Stitzer 1999) The chapter title is “Other substance use disorders in methadone treatment: prevalence, consequences, detection and management.”

Acamprosate (Campral®) is another pharmacotherapeutic agent that has been approved by the FDA for the treatment of alcohol addiction. The usual dose is 666 mg three times daily. Treatment is delayed until the patient is abstinent from alcohol and neither experiencing nor at risk for alcohol withdrawal. The purpose is to assist the patient to maintain abstinence. There are no known drug interactions, but “the efficacy in promoting abstinence from alcohol in polysubstance abusers has not been adequately assessed.” (PDR 2005) The results of the large, 3 year, multi-site COMBINE (Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence) Study were published in *JAMA* in May of 2006 (Anton et al. 2006) and were disappointing in that the researchers found no effect on drinking with the medication acamprosate alone and no added benefit with naltrexone and acamprosate. The study compared the efficacy of medical management plus either naltrexone or acamprosate or naltrexone and acamprosate or placebo(s) with or without a combined behavioral intervention (CBI). The study found the best drinking outcomes for patients who received medical management with naltrexone, CBI or both. It must be noted that patients abusing drugs other than alcohol were not included: opioid dependent patients with alcohol dependence were excluded, so the applicability of the results to the OTP population is unknown (Anton et al. 2006).

Benzodiazepines

Abuse of benzodiazepines, particularly clonazepam (Klonopin®) and alprazolam (Xanax®), is common amongst opioid addicted patients. A methadone clinic in the Sacramento area reports a prevalence of 6% and a clinic in the San Francisco Bay Area reports a prevalence of 24%. Currently OTPs are not required by federal or California regulation to screen for benzodiazepines. However CSAT may require that a particular patient be routinely screened for benzodiazepines as a condition of approval for an exception take-out request.

From a safety perspective, benzodiazepine use is particularly problematic because benzodiazepines produce synergistic sedative effects with opioids such as methadone. The patient must be cautioned about the risk of driving or operating heavy machinery while under the influence of benzodiazepines; this risk will be increased when used in combination with methadone. See Appendix D for a sample Concurrent Medication Driving Agreement form.

Patients may use a benzodiazepine to suppress the agitation produced by stimulant abuse or to potentiate an opioid high. Some patients say that they use benzodiazepines because “it makes the methadone feel like heroin.” Abuse of this class of drugs is often implicated in polysubstance overdose deaths. Due to the frequency of abuse and patients’ inconsistent reporting at admission, it may be worthwhile to add benzodiazepines to the admission drug screen and to subsequent screens in patients whose history is suggestive or who screen positive at admission.

■ **Note** Testing for clonazepam (Klonopin®) and lorazepam (Ativan®) requires special assays; routine benzodiazepine screens may not detect them.

Patients may obtain benzodiazepines illicitly or by prescription from a physician. The OTP physician may need to meet with a patient who is taking

Abuse of benzodiazepine is often implicated in polysubstance overdose deaths.

a prescription benzodiazepine to discuss the risk of overdose, abuse and dependence and to explore the possibility of alternative treatments. The patient should be asked to sign a release allowing the OTP physician to communicate with the prescribing physician. See sample letter in Appendix D. Because of the potential for overdose when a benzodiazepine is mixed with another/other sedatives, the prescribing physician should be aware that the patient is on methadone maintenance treatment. Careful tracking of prescription records and urine screening tests provide information that can alert both the OTP physician and the prescribing physician to prescription abuse.

Withdrawal from long-term use of a benzodiazepine can be challenging. It tends to be a slow process, and symptoms may emerge which require treatment with ancillary medications. Patients may require residential care to comply with the supervised withdrawal. Protocols exist which can provide safe reduction and cessation of the drug if clinically warranted. Coordination with the patient's mental health and/or primary care provider is essential.

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 methadone maintenance, so the patient should be asked to sign a release allowing communication and coordination with the prescribing physician. Routine drug screenings do not identify carisoprodol; special testing is required to detect it.

Patients who present for dosing and who appear to be 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 his/her car keys and arrange other transportation home.

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.

Nicotine

The majority of patients in methadone treatment smoke cigarettes; NIDA estimates a prevalence of 85-95%. Most patients report smoking more when they are using illicit drugs. Unfortunately, methadone has been found to increase smoking satisfaction and to produce a dose-related increase in the number of cigarettes smoked and the number of puffs per smoking session (Chait & Griffiths 1984). As in the general population of smokers, most opioid addicted patients started in their teens. 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. Pharmacotherapy with bupropion (Zyban®), nicotine patches/lozenges/gum/inhalers, varenicline (Chantix®) may be very helpful, particularly for patients who are heavy smokers.

Varenicline is the newest medication available. A partial agonist at the nicotinic acetylcholine receptor in the brain, this medication binds to nicotine receptors producing some activation and preventing nicotine from binding. As a result, varenicline prevents withdrawal and eliminates the reinforcing property of cigarettes.

In November of 2007, the FDA issued the first alert about the possibility of serious neuropsychiatric symptoms associated with Chantix® use. Then in May of 2008, the FDA issued the following **recommendations and considerations for healthcare professionals**.

FDA has made specific recommendations regarding Chantix®.

- Healthcare providers should **monitor all patients taking Chantix® for symptoms of serious neuropsychiatric symptoms**. Symptoms include changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior. These symptoms have sometimes occurred in patients without pre-existing psychiatric illness and have worsened in some patients with pre-existing psychiatric illness treated with Chantix. In most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of Chantix therapy.
- **Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder, may experience worsening of their pre-existing psychiatric illness while taking Chantix.** Patients with serious psychiatric illness did not participate in the pre-marketing studies of Chantix. The safety and efficacy of Chantix in these patients has not been established.
- While Chantix has demonstrated clear evidence of efficacy, it is important to consider these safety concerns and alert patients about these risks.

The FDA also recommended that physicians who prescribe Chantix® should discuss with their patients, patients' families, and caregiver the following:

- **Tell the doctor about any history of psychiatric illness prior to starting Chantix®.** Patients taking Chantix have experienced worsening of current psychiatric illness, even if it is currently under controls, and the reoccurrence of previous psychiatric illness.
- **Be alert to changes in mood and behavior.** Symptoms include strange thoughts or behaviors, depressed mood, and thinking about or attempting suicide.
- **Immediately report changes** in mood and behavior to the doctor.
- Vivid, unusual, or strange dreams may occur while taking Chantix.

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 the patient launches the attempt to quit. Those already on antidepressants may require a dose adjustment once they quit.

In summary, the role of the OTP physician in evaluating and responding to concurrent polysubstance abuse:

- **To evaluate patients who appear to be under the influence.**
- **To monitor the safety of dually addicted patients.** This includes ensuring that patients are being screened by urine toxicology and breathalyzer at the appropriate frequency, meeting with patients when needed and counseling them regarding the medical risks associated with ongoing use.
- **To identify patients who require medical detoxification.**
- **To identify patients who would benefit from pharmacotherapy for the treatment of alcohol or nicotine dependence.** Medications such as disulfiram or acamprosate may be dispensed at the methadone window; participation in 12 Step recovery groups in the community may be encouraged. Prescribing nicotine replacement, Zyban® or Chantix particularly in conjunction with onsite smoking cessation classes will increase the likelihood of smoking cessation.
- **To coordinate with other medical providers,** particularly physicians prescribing medications with abuse potential. The OTP physician may offer to share urine toxicology results and to arrange for dispensing of medications at the methadone window when it will support a patient's compliance with medication regimen or taper. (The patient's written authorization is required.)
- **To discontinue methadone treatment if it becomes unsafe for the patient to continue.** The OTP physician must assess patients who are missing multiple doses or who are at significant risk of overdose to determine whether it is safe to continue methadone maintenance treatment.

Section on

CO-OCCURRING PSYCHIATRIC CONDITIONS

Numerous studies have documented the high incidence of psychiatric disorders in opioid addicted populations – disorders that often preceded the substance abuse.

It is important to diagnose and treat psychotic, mood, and anxiety disorders (Axis I disorders) because of the significant degree of impairment and discomfort associated with them and because when symptoms remain untreated, substance use is likely to continue. Mood disturbances may be a sign of withdrawal and may respond to dose adjustments; in some patients, even a small dose increase may be effective. If mood problems disappear at peak blood levels and recur at trough, this is suggestive of withdrawal-mediated mood disturbance, perhaps related to the rate of drop in the blood level. (Dyer et al. 2001)

It is also important to be alert for personality disorders (Axis II) because they are fairly common in opioid addicted patients. However, care must be taken and undue haste avoided in the diagnosis of Axis II disorders because an Axis II disorder is a label that carries additional stigma for an already stigmatized patient and is a diagnosis with a poor prognosis. Behaviors associated with active addiction should not be confused with antisocial personality disorder. Some behaviors that are associated with drug abuse, such as stealing or lying, may disappear after the addiction comes under control. Professionals unfamiliar with addiction are especially likely to miss important distinctions.

The frequent overlap between psychiatric illness and substance abuse disorders demands specific efforts at integrating services.

The OTP physician should be especially aware of the high incidence of physical and sexual abuse and post-traumatic stress disorder among opioid dependent patients. The frequent overlap between psychiatric illness and substance abuse disorders demands specific efforts at integrating services. These two disorders share many characteristics, yet historically, different funding mechanisms have created a system in which it is very difficult to provide appropriate and coordinated care for both conditions. Lack of cross training of substance abuse and mental health service providers further interferes with patients' getting the benefits of complementary care. The physician in an OTP must provide staff education and guidance to facilitate the treatment of co-occurring disorders.

Axis I Disorders

There are three service delivery models for managing co-occurring substance abuse and mental illness: integrated, parallel, and sequential. In an **integrated model**, the same staff provides both substance abuse and mental health services, usually in the same facility, increasing the likelihood of compliance with a consistent treatment plan. In a **parallel model**, different agencies provide treatment simultaneously but independently, resulting in difficulties with coordination of care and sharing of information. The parallel model is likely the most common one. The **sequential model** withholds one treatment,

usually mental health care, until the addiction, which is considered the primary problem, is addressed. This model may avoid unnecessary treatment when drug-related psychiatric symptoms clear rapidly. However, severe psychiatric symptoms, such as suicidal depressions, psychotic or bi-polar disorders, and severe anxiety disorders, must be evaluated and treated psychiatrically even if they are drug-related. In cases of severe mental illness, sequential treatment, which provides no mental health care until the patient is in recovery from substance abuse, is impractical and unethical.

It is the OTP's responsibility to screen for mental health disorders and to develop a treatment plan to address identified problems. If the patient already has access to ongoing mental health care, the OTP physician may need to establish a liaison with the therapist and/or psychiatrist to allow coordination of care and to ensure that the mental health providers are aware of the patient's history of substance abuse and participation in treatment for opioid addiction. Active substance use is not a contraindication to the use of anti-psychotics, mood stabilizers, antidepressants, or even judicious use of anti-anxiety agents. Appropriate psychiatric treatment can be critical to the patient's ability to participate in a recovery plan. Dispensing psychiatric medications at the methadone clinic may improve compliance and control misuse. The OTP may store non-opioid medication for the patient and assist the patient to take it on a regular schedule by observing him/her take it while at the dosing window. It is advisable to obtain a written consent from the patient to allow the dispensary to hold and dispense the medication. (See Appendix D for a sample form: Patient Request for Clinic to Hold and Dispense Medications.) Some DEA and California auditors have recommended a written release in such situations.

OTP physicians should develop the expertise to diagnose and treat uncomplicated Axis I disorders such as dysthymia, major depression, and anxiety spectrum disease. If time does not permit or if the psychiatric condition is severe, the physician should refer to a psychiatrist. The OTP physician should help establish a supportive mental health referral source for OTP patients. Supportive linkages are especially important in programs with limited or no psychiatric resources.

Personality Disorders

The incidence of personality disorders, in particular antisocial personality disorder (APD), is reported to be high in patients with addiction, and the diagnosis of personality disorders in this population is fraught with pitfalls. The diagnosis of a personality disorder is less reliable than the diagnosis of an Axis I disorder. This may be especially true when the patient is a substance user with co-occurring mental illness. To complicate matters further, these patients often have traits from more than one personality disorder. Historically, a common problem has been the use of this diagnosis as a statement of dislike of the patient, harkening back to an outdated moral model of addiction as 'character flaw.'

Opioid-addicted patients may present with traits clustering in the anti-social, borderline, and histrionic group (cluster B disorders), the passive, dependent, avoidant group (cluster C), and paranoid and schizotypal group (cluster A). It is not always clear if these character traits are primary or secondary

to the substance abuse. Much anti-social behavior associated with heroin addiction is a direct result of its illegality and the need to associate with the deviant element that controls the illegal drug trade. Some argue that behavior associated with APD, such as lying and stealing, is part of the patient's addiction making the Axis II diagnosis redundant because the same behavior can be explained by the Axis I diagnosis of drug dependence. Addiction treatment specialists have observed that patients with drug dependence can and frequently do experience and express remorse for their antisocial behavior and that such behavior may clear completely when the addiction is treated.

Regardless of the source or underlying diagnosis, aberrant behavior is frequently seen in the OTP, and addressing the drug use alone may not be sufficient to eliminate anti-social or aberrant behaviors. **These behaviors are best addressed by a well-defined structure of treatment, with clear rules of behavior and clear consequences for undesired behavior.** Structure creates safety for the patient in early treatment and during periods of instability. It is also important to address the anti-social or criminal thinking habits in counseling.

Whatever role personality disorders play in addiction, their role is neither exclusive nor essential, and the good news is that personality disordered patients can respond well to methadone treatment. Some of these patients will require specific psychiatric treatment programs to address problematic behaviors.

In summary, the role of the OTP physician in regard to co-morbid psychiatric conditions:

- **To screen for mental health issues** at intake, at annual medical reviews and upon request of patients or staff.
- **To treat or refer for treatment** when medication is indicated.
- **To coordinate care with mental health providers**, to ensure that prescribing physicians are aware that the patient is opioid-dependent and is taking methadone, and to arrange for psychiatric medications to be dispensed at the methadone window when appropriate.
- **To educate clinic staff** regarding co-occurring mental health disorders.

Section on

CONCURRENT MEDICAL CONDITIONS

The opioid-addiction-related medical co-morbidities seen in OTP patients are rarely directly due to the opioid. Instead, they are most often due to the method of ingestion or to involvement in high-risk activities related to obtaining the drug. The medical co-morbidities associated with non-opioid drugs of abuse are frequently directly related to the drug. Patients abusing alcohol may develop cirrhosis, dementia or GI bleeding. Patients abusing stimulants may have myocardial infarct or stroke. Patients smoking cigarettes may develop chronic lung disease or cardiovascular disease. These drug-related co-morbidities may be evident at intake or may emerge over the course of treatment, particularly in patients who continue to use. The sedating and analgesic properties of the abused opioid may partially mask urgent medical conditions. Some opioids (methadone and l-alpha-acetylmethadol (LAAM)) may be associated with cardiac arrhythmia including torsade de pointes. (EMEA (European Agency for the Evaluation of Medicinal Products) Human Medicines Evaluation Unit 2000; Krantz et al. 2003) Abstinent patients often continue to require care for addiction-related chronic medical problems.

Urgent Conditions

Abscess and Cellulitis

Needle-related skin infection may form an abscess that needs to be incised and drained. Neglected skin infections may spread to surrounding tissues producing cellulitis and requiring aggressive antibiotic treatment.

Necrotizing Fasciitis

Necrotizing fasciitis is a special case of needle-related (usually, but not always streptococcus group A) infection in which infection spreads horizontally under the superficial layers of the skin. It may present as areas that are painful beyond what would be expected given the clinical appearance of the skin. The clinician might misinterpret a patient's report of severe pain as drug-seeking behavior, especially in a new patient who is in withdrawal. Necrotizing fasciitis has the potential to progress rapidly to severe destruction of tissue and to death (Karch & Stephens 2000). Prompt intravenous antibiotics and debridement may be life saving (Smolyakov et al. 2002).

Botulism

The neurotoxin produced by anaerobic growth of clostridium botulinum produces descending paralysis. An early symptom of botulism, sometimes called 'bobbing head' may be misinterpreted by the clinician as opioid intoxication. Patients may also present with complaints of double vision, other vision changes, and difficulty speaking or swallowing. During the 1990s, cases of botulism began to appear in heroin users who injected Mexican 'black tar' heroin, and the epidemiology suggests that the toxin is present in the heroin itself (Anderson, Sharma & Feeney 1997; Jensen et al. 1998; McGarrity 2002; Werner et al. 2000). Treatment requires administration of an antitoxin, usually

several vials, followed by debridement of any identifiable site of infection. Respiratory paralysis may result if botulism is not treated promptly. When a patient with botulism does not respond to treatment, the possibility of “body packing” (a reservoir of heroin hidden in a body cavity) should be considered.

Infectious Endocarditis

Injection drug abusers with a murmur should be evaluated for endocarditis, especially if they have a fever.

Trauma

The OTP physician may encounter patients who have been in accidents or fights and are reluctant to seek medical care elsewhere. Even pain from severe injuries may be partially masked by drugs of abuse.

Conditions Affecting the Public Health

STDs

Syphilis serology is a mandatory part of OTP admission blood work. Screening for HIV, hepatitis B and C allows the OTP to identify, treat and/or prevent life-threatening disease. Although not all OTPs are set up to perform complete genital examination on site, drug abuse may be associated with frequent anonymous sexual encounters, so other STDs should be considered, particularly in patients experiencing symptoms of dysuria, dyspareunia, genital discharge, or having abnormal medical urinalysis at intake. Perhaps the advent of urine testing for chlamydia and gonorrhea will provide easier access to diagnosis and treatment for some OTP patients.

Methicillin Resistant Staphylococcus Aureus (MRSA)

Infection with MRSA is resistant to all currently available β -lactam antibiotics, including penicillins and cephalosporins. First seen in the 1960s, the prevalence has increased dramatically, particularly in skin and soft tissue infections. MRSA causes as many as 20% of Staphylococcus aureus infections in injection drug users. Patients who have a history of a prior MRSA infection, a history of endocarditis or a history of hospitalization in the preceding 12 months are at increased risk of MRSA infection.

As MRSA has become more common, there are an increasing number of community-acquired infections. MRSA is transmitted most frequently by direct skin-to-skin contact. With exposure, persons of all ages, including infants and children, are at risk. This means that institutional settings, including residential treatment programs, must have policies and procedures in place for infection control. The key is to keep infected skin/soft tissue appropriately bandaged and uninfected broken skin clean and covered. Good handwashing is critical. The CDC website is an excellent source of information.

Although necrotic skin lesions are a common presentation, no clinical features clearly distinguish MRSA from Methicillin-susceptible *S. aureus*. Information about local antibiotic-resistance patterns may be helpful in assessing the likelihood of MRSA. Incision and drainage is required for purulent skin and soft tissue infections. Oral or IV antibiotics may be indicated as well, particularly for larger infections, infections located on the head and neck and/or the presence of systemic symptoms (Daum 2007).

Injection drug users are considered to be at high risk for tuberculosis.

Tuberculosis

OTPs are mandated to screen for TB because injection drug users are considered to be at high risk for tuberculosis. For this reason, all staff and patients should have periodic screening by PPD skin testing, unless they have a history of a prior positive PPD. Patients and staff with a past positive are screened by symptom review and chest X-ray. A chest X-ray is obtained at the time of conversion and repeated if a person develops symptoms or is at risk because of a known exposure. Some clinics require a repeat chest X-ray with each new admission to methadone treatment or at regular intervals, such as every five years.

In the event of documented positive PPD skin test or of documented conversion from a negative to a positive skin test and a normal chest X-ray, prophylaxis with isoniazid (INH) is recommended for nine months for any adult, regardless of age. If a patient cannot comply with nine months, a shorter course (six months) may be beneficial. Alternative regimens are available. Directly Observed Therapy (DOT) is recommended if medication is to be administered on a twice/weekly schedule, rather than daily. (CDC Website: Division of Tuberculosis Elimination (DBTE): Interactive Core Curriculum Chapter 5 “Treatment of Latent Tuberculosis Infection; Treatment: Regimens for Specific Situations.”) The OTP provides an ideal opportunity for directly observed therapy. INH can be toxic to the liver, so a protocol should be used for symptom screening and laboratory testing if indicated. Baseline and routine laboratory monitoring is recommended for patients who have or are at risk for a liver disorder. (MMWR 6/9/2000). (American Thoracic Society 2000).

TB is spread by respiratory droplets when patients cough, speak, sing or laugh. OTP staff should be instructed to be alert to coughing patients. The patient may be handed and asked to wear a mask and/or to sit in an open, well-ventilated area, such as a large waiting room or outside. Coughing patients should be promptly interviewed regarding the common symptoms of TB (fever, night sweats, chronic cough and/or unexplained weight loss). Patients who are symptomatic require prompt screening by CXR. Some clinics dose high-risk patients outside the clinic and delay participation in counseling and groups until the patient is cleared. This precaution has become more important over the last 10 years or so as the population of methadone patients has become older and more medically fragile.

In addition to the PPD skin test, there is another test called the QuantiFERON®-TB Gold Test (QFT-G) that is available in some communities in California. The QFT-G is a whole blood test that can be used to aid diagnosis of mycobacterium TB infection including latent TB infection (LTBI) and TB disease. Further information is available from the fact sheet on the CDC website: <http://www.cdc.gov/tb/pubs/tbfactsheets/QFT.htm>

Chronic Medical Conditions

Lung Disease

Many OTP patients are cigarette smokers and are at risk for various lung problems. Some OTP patients already have smoke-related lung disease and may have frequent hospital admissions due to respiratory failure or with pneumonitis. Some patients are dependent on steroids or oxygen to control their lung disease. Methadone and high doses of other opioids can potentially

to suppress respiration. Although tolerance to respiratory depression is expected during methadone maintenance, hospital physicians may temporarily decrease the methadone dose in patients hospitalized because of acute exacerbation of underlying lung disease. Asthma is not uncommon. Patients may not seek medical care even when experiencing frequent, severe shortness of breath and/or wheezing. Treatment for cigarette smoking and nicotine dependence should be offered in OTPs. This may include counseling and nicotine replacement therapy. For those who fail these interventions, newer treatments including bupropion (Zyban®) or varenicline (Chantix®) may be options.

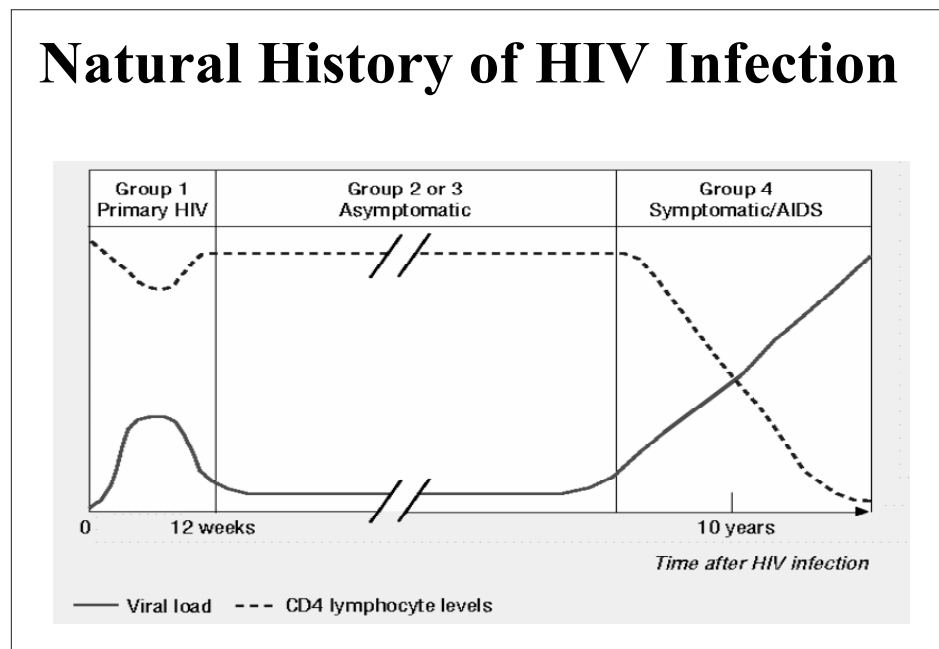
HIV

Needle-related HIV may be seen in up to 25 percent of OTP patients, with some regional variation in incidence. The OTP clinician's support of the HIV-positive patient will depend on the stage of the illness.

Testing for HIV

Since the advent of effective treatment in the mid-1990s, persons who are HIV positive and don't know it are the highest risk subgroup among HIV positive persons. Testing should be encouraged and offered on-site if possible. Some counties have outreach teams that might be willing to come to the OTP and perform anonymous testing by oral swab. Pre- and post-test counseling is required for HIV testing.

Table 10 ~ Natural History of HIV Infection



Primary HIV Infection

In the first 12 weeks after exposure to the virus, the acute sero-conversion or primary HIV infection may present as fever, malaise and adenopathy. This syndrome is seen infrequently because of its short duration. Patients who are experiencing daily opioid withdrawal may not differentiate the symptoms of primary HIV infection from withdrawal.

Latent Phase

After seroconversion, there may be a long symptom-free period. The focus of care is to support ongoing monitoring and self-care.

Treatment

Onset of symptoms, drop in CD4 count and/or rise in viral load are the usual indications for instituting treatment. Treatment is usually long-term triple therapy, with three drugs chosen from among the five classes of available antivirals. This long-term treatment is called Highly Active Antiretroviral Treatment (HAART). OTP clinicians may be helpful in encouraging compliance with these difficult regimens. Discontinuation of antiviral medications usually results in resistance to them, so efforts are made to reduce or treat side effects and to train patients to take medications consistently as prescribed. The OTP may offer observed dosing at the dispensing window. Some of the antivirals share and/or alter cytochrome P450 3A4 metabolism which is the primary CYP enzyme responsible for methadone metabolism, so there is the potential for interaction between antiretroviral medications and methadone. Drug-drug interactions could result in increased or decreased levels of the antiretroviral or the methadone. Tables 11, 12 and 13 list the known drug interactions between antiretroviral medications and methadone. While many interactions have been identified, not all are of clinical significance, and the clinical impact of drug-drug interactions can vary significantly from one person to the next. When anti-retroviral treatment is begun, patients need to be informed of this potential and encouraged to report any adverse symptoms they experience. Patients should be monitored for emergence of sedation/opioid withdrawal and efficacy/side effects of antiretrovirals. Doses of methadone or antiretroviral should be adjusted as needed in response to a particular patient's reaction. More interactions may become apparent as new combinations and higher doses of medications are used.

Known Interactions Between Antiretroviral Medications and Methadone

AZT levels are increased, and toxicity has been (rarely) observed, requiring a dose adjustment in some patients. Levels of didanosine (the tablet formulation) and stavudine are decreased, which could result in subtherapeutic concentrations putting a patient at risk of developing viral resistance. At this point, no methadone maintained patients with HIV disease should receive ddI tablets; rather they should receive the enteric-coated capsule. Methadone levels are decreased with nevirapine, efavirenz and with a lopinavir/ritonavir combination; patients on these antivirals may need an increased methadone dose to suppress symptoms of withdrawal. Both efavirenz and nevirapine are potent inducers of methadone metabolism. It may be necessary to increase methadone dose more rapidly than usual clinical practice. For example, for patients on methadone who are on either of these antiretroviral medications and who complain of the onset of opiate withdrawal, methadone dose may need to be increased by 5-10 mg every 2-3 days until withdrawal symptoms

abate. Dose increases of 50 percent have been required by some patients (McCance-Katz et al. 2002).

Tables 11, 12 and 13 list known drug interactions between antiretrovirals and methadone or buprenorphine. Nineteen antiretrovirals are listed; interactions have not been studied for seven, studies are underway for four and no information is provided for one. Of the seven remaining medications, only one clinically significant interaction has been identified: atazanavir alone or in combination with ritonavir significantly increases the levels of buprenorphine and norbuprenorphine; sedation may occur.

An excellent reference for HIV medication interactions for methadone and buprenorphine can be found in a Supplement to Clinical Infectious Disease entitled, "Buprenorphine and HIV Primary Care: New Opportunities for Integrated Treatment." (McCance-Katz et al. 2006; McCance-Katz et al. 2006)

Table 11 ~ Identified Drug Interactions Between Antiretroviral Medications and Methadone or Buprenorphine – Nucleoside Reverse Transcriptase Inhibitors

| NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS | | |
|---|---|---|
| HIV Medication | Interaction with Methadone | Interaction with Buprenorphine |
| Zidovudine (AZT) | ↑ AZT AUC by 40%, AZT toxicity observed requiring dose adjustment in several participants, no effect on methadone levels (McCance-Katz et al. 1998) | Non-clinically significant ↓ AZT concentrations ; no need to adjust AZT dose (McCance-Katz et al. 2001) |
| Didanosine (ddI) tablet | ↓ ddI AUC by 63%, no effect on methadone levels (Rainey et al. 2002) | Not studied |
| Didanosine (ddI) enteric-coated | No significant effect of methadone on ddI (this formulation should be used in patients with HIV/AIDS and who are methadone maintained (Friedland et al. 2002) | No clinically significant interaction |
| Zalcitabine (ddC) | None | Not studied |
| Lamivudine (3TC) | None | No effect of lamivudine on buprenorphine concentrations |
| Lamivudine/zidovudine | None (Rainey 2002) | Not studied |
| Stavudine (d4T) | ↓ d4T AUC by 25% (Rainey 2002) | Not studied |
| Abacavir (ABC) | ↑ Methadone clearance, but no withdrawal, no clinically significant effect on ABC concentrations (Sellers et al. 1999) | Not studied |
| Tenofovir | No significant interaction | No significant interaction |

Table 12 ~ Identified Drug Interactions Between Antiretroviral Medications and Methadone or Buprenorphine – NON-Nucleoside Reverse Transcriptase Inhibitors

| NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS | | |
|---|--|---|
| HIV Medication | Interaction with Methadone | Interaction with Buprenorphine |
| Nevirapine | Withdrawal symptoms, need for increased methadone dose (Altice, Friedland & Cooney 1999) 40% decrease in methadone (Stocker et al. 2004) | Under study |
| Delavirdine (DLV) | ↑ Methadone levels without toxicity (McCance-Katz et al. 2006), no effect on DLV | ↑ BUP concentrations without toxicity, no effect on DLV (McCance-Katz et al. 2006). |
| Efavirenz (EFV) | ↓ Methadone levels, withdrawal symptoms, ↑ methadone dose necessary (up to 50%) (Clarke et al. 2001; McCance-Katz et al. 2002) | ↓ BUP levels, no withdrawal, no dose change needed, no effect on EFV levels (McCance-Katz et al. 2006). |

Table 13 ~ Identified Drug Interactions Between Antiretroviral Medications and Methadone or Buprenorphine – Protease Inhibitors

| PROTEASE INHIBITORS | | |
|--|---|---|
| HIV Medication | Interaction with Methadone | Interaction with Buprenorphine |
| Nelfinavir (NLF) | ↓ Methadone levels, but no withdrawal symptoms observed (McCance-Katz et al. 2004) increased NLF, decreased M8 metabolite, no clinically significant change in NLF exposure | No effect on BUP (McCance-Katz et al. 2006) no significant effect of BUP on NLF |
| Indinavir | Not studied | Not studied |
| Ritonavir (RTV) | ↑ Methadone levels, not clinically significant (McCance-Katz et al. 2003) | ↑ BUP levels, not clinically significant, no effect of BUP on RTV (McCance-Katz et al. 2006) |
| Saquinavir | ↓ Methadone levels (S enantiomer), no withdrawal (Gerber et al. 2001) | Not studied |
| Amprenavir | ↓ methadone, no withdrawal | Under study |
| Lopinavir/ritonavir (L/R) | ↓ methadone, withdrawal may occur, methadone may need to be increased (McCance-Katz et al. 2003) | No significant effect on BUP, no effect of BUP on L/R (McCance-Katz et al. 2006) |
| Atazanavir (ATZ) or Atazanavir/ritonavir (ATV/r) | No effect of ATZ on methadone, no effect of methadone on ATZ (Friedland et al. 2005) | Significant increase in BUP and norbuprenorphine; sedation may occur (McCance-Katz et al. 2007); clinical observation of sedation and cognitive impairment with ATV/r (Bruce et al. 2006) |

Opportunistic Infections

If stabilization fails and HIV disease progresses, the patient's immunity to infection gradually disappears. Medications to prevent pneumocystis carinii, toxoplasmosis, and mycobacterium avium may be instituted.

End of Life Care

Worsening AIDS may include loss of vision, neuropathy, dementia, loss of balance with frequent falls, weakness, weight loss, etc. At this time, patients who have historically done well at the OTP and have take-home privileges may be at increased risk of losing their medication or making mistakes in their ingestion of take-home methadone. At the same time, disability may make it impossible to stand at the window or to come to clinic daily. A careful assessment of the home situation, the patient's condition and the availability of hospice or home nursing care is essential. Medical exception take-homes may be indicated or the prescribing of methadone may be transferred from the OTP to a hospice physician(s).

Hepatitis

Injection drug use is associated with a higher incidence of hepatitis B and C. Those who are susceptible to hepatitis B (HBV) should be encouraged to undergo immunization. Patients with hepatitis C virus (HCV) are at higher risk of an adverse outcome if they contract hepatitis A, so vaccination for hepatitis A is recommended as well, particularly for patients who travel to areas, such as Mexico, where hepatitis is endemic.

HCV prevalence in interavenous drug users (IDUs) is 60 to 90 percent in the OTP. As with HIV, the OTP clinician's intervention depends on the extent of disease. See Table 15 – Hepatitis C Evaluation Flow Sheet.

Table 14 ~ Hepatitis B Serologies

Hepatitis B serologic testing is used to determine whether a patient is susceptible to infection with or protection from hepatitis B. Below is a list of commonly used serologic “markers” and a table showing the interpretation of combinations of markers. **Patients positive for hepatitis B surface antigen (HBsA) are infected. Patients positive for hepatitis B surface antibody (anti-HB) are immune.**

Commonly Used Serologic Markers

| | |
|--------------|---|
| HBsAg | Hepatitis B surface antigen |
| Anti-HBs | Hepatitis B surface antibody |
| | |
| HBcAg | Hepatitis B core antigen |
| Anti-HBc | Hepatitis B core antibody |
| IgM anti-HBc | IgM antibody to hepatitis B core antibody |
| IgG anti-HBc | IgG antibody to hepatitis B core antibody |

Interpretation of combinations of serologic markers

| | | |
|--------------|----------|--|
| HBsAg | Negative | Susceptible |
| Anti-HBc | Negative | |
| Anti-HBs | Negative | |
| HBsAg | Negative | Immune due to natural infection |
| Anti-HBc | Positive | |
| Anti-HBs | Positive | |
| HBsAg | Negative | Immune due to hepatitis B vaccination |
| Anti-HBc | Negative | |
| Anti-HBs | Positive | |
| HBsAg | Positive | Acutely infected |
| Anti-HBc | Positive | |
| IgM anti-HBc | Positive | |
| Anti-HBs | Negative | |
| HBsAg | Positive | Chronically infected |
| Anti-HBc | Positive | |
| IgM anti-HBc | Negative | |
| Anti-HBs | Negative | |
| HBsAg | Negative | Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection |
| Anti-HBc | Positive | |
| Anti-HBs | Negative | |

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part 1: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

www.cdc.gov/hepatitis

Testing for Hepatitis C

Since only one in five patients infected with HCV has acute symptoms, most HCV infections will be diagnosed by screening patients who are at risk. Testing for hepatitis C has two phases. The first phase is a blood test that screens for the presence of HCV antibody. A positive Anti-HCVAb indicates exposure to the virus. This test is relatively inexpensive and is frequently offered as a finger stick by county agencies. If this first phase test is positive, the more expensive Phase 2 test for viral RNA and type is performed to see if exposure has resulted in ongoing infection. If untreated, a minority of those with ongoing infection will develop cirrhosis. The evaluation of patients with ongoing infection is complex and may involve periodic liver enzyme testing and liver biopsy. Patients are frequently confused about their status and need counseling about their HCV status.

Alcohol use accelerates HCV liver disease, so **one of the primary goals in liver disease management is the detection and prevention of alcohol use.** Patients should be given medical counsel about the risk of alcohol use. Periodic breath, saliva, or urine testing for alcohol should be performed. Aggressive intervention is recommended for patients who continue to drink alcohol. Because of the risk of hepatotoxicity with disulfiram or naltrexone (and opioid treated patients should not be prescribed naltrexone), there are limited pharmacotherapy options for alcoholism in those with HCV. One consideration is acamprosate which FDA has approved for the treatment of alcohol dependence.

Acamprosate is renally cleared and so is not expected to further compromise the liver. Unfortunately its effectiveness has been fairly limited in U.S. trials. However, given limited options, this medication may be useful. Failing such interventions, referral to a higher level of care may be necessary.

Treatment for Hepatitis C

Ribavirin ingested twice daily and pegylated interferon, injected weekly is the current treatment of choice for HCV yielding up to 60 percent sustained viral suppression after treatment. Length of treatment depends on viral genotype, with most IDUs needing a year of this treatment. The side effects of interferon include a flu-like syndrome, or the more serious problems of depression and anemia. The OTP physician will be monitoring the patient for these effects. Small increases in the methadone dose are sometimes required during treatment. Even when treatment does not result in sustained viral response, disease progression is delayed significantly.

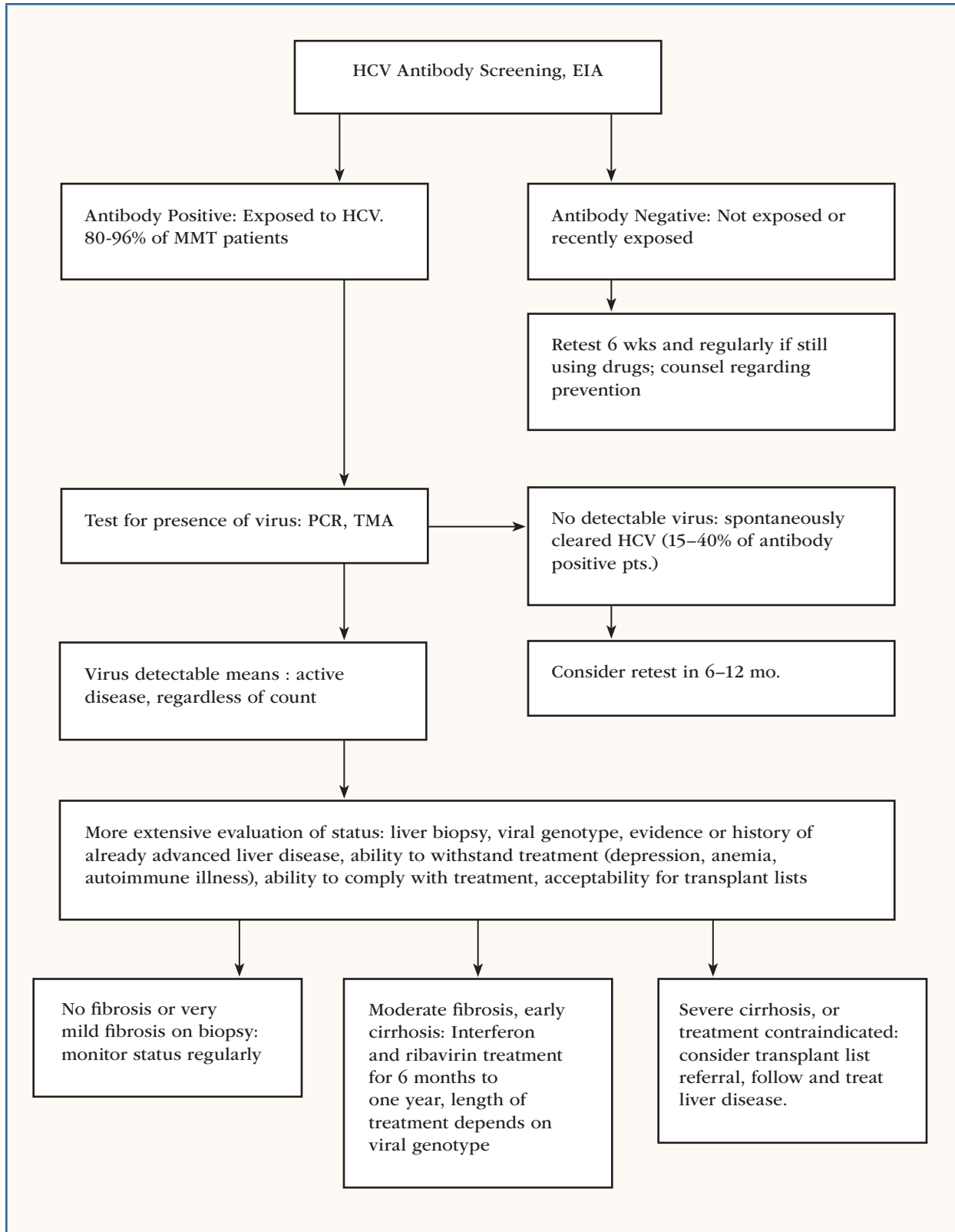
If a patient is known to be using or abusing alcohol, this problem should be addressed prior to providing treatment for HCV.

Transplant Advocacy

Some patients do not respond to treatment or have contraindications to treatment and may develop end stage liver disease. Although there are patients in OTPs who have had liver transplantation, some transplant lists do not accept methadone-maintained patients. The OTP clinician may need to advocate for patients who need transplantation and whose substance use disorders are in remission.

Cirrhosis

The patient with cirrhosis may be greatly debilitated and suffer effects on multiple systems. Symptoms may include anorexia, fatigue, muscle wasting, ascites and edema, and bleeding diathesis. In patients known to be active GI bleeders, opioid withdrawal with onset of nausea becomes potentially life threatening, so sudden dose drops should be avoided. Diuretics are frequently necessary. Males with cirrhosis may also experience impotence, gynecomastia, and testicular atrophy. High ammonia levels result in an organic brain syndrome, so the patient may have confusion and memory loss and may demonstrate erratic behavior. In end stage liver disease, the liver cannot adequately metabolize methadone, so the usual maintenance dose may require marked reduction to avoid sedation. Methadone blood levels and clinical observation assist in establishing the correct dose.

Table 15 ~ Hepatitis C Evaluation Flow sheet

Co-infection with HIV and Hepatitis C

Patients with a history of intravenous drug use are at increased risk for co-infection with HIV and HCV. The prevalence of HCV amongst patients with HIV/AIDS is more than three times higher when the HIV infection was acquired through intravenous drug use (Swan 2006).

HIV accelerates the progression of HCV, so patients who are co-infected with HIV and HCV experience more rapid liver disease progression. Co-infected patients with a CD4 cell count <200/ml are at greatest risk for end stage liver disease. In co-infected patients, spontaneous viral clearance and clearance with treatment are less likely. Compared with patients infected with HCV alone, co-infected patients are:

- more likely to develop liver fibrosis and symptoms,
- more than twice as likely to develop cirrhosis, which may develop much more rapidly (less than 10 years after infection),
- at greater risk for progression to liver cancer,
- six times more likely to experience hepatic decompensation, and survive for shorter periods after decompensation.

HCV is treatable, even in patients with HIV/AIDS. End-stage liver disease can be prevented in many patients, so it is critical that all patients with risk factors for sexually transmissible diseases and blood borne infections be offered testing for HIV and hepatitis B and C. Some patients entering methadone 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 they have decided that they would rather not know if they do. Very few these patients know the natural progression of these diseases, and most are not aware that early diagnosis and treatment can slow disease progression.

The treatment of co-infected patients is complex. Both infections must be treated. For each infection the choice of medication, the duration of treatment and the timing of treatment are critical. Physicians providing treatment for co-infected patients need specific and ongoing training.

In co-infected patients, pegylated interferon plus ribavirin is the only approved treatment for HCV. The duration of treatment is generally 48 weeks to 18 months depending on the HCV genotype. HIV treatment should be started first in patients with CD4 cell counts <200/ml. When HCV treatment is indicated, it should be started before HAART or after the patient is on a stable HAART regimen. Certain combinations of medications must be avoided (Swan 2006).

Pain: Acute and Chronic

Some patients in methadone maintenance treatment suffer from chronic pain. Some will experience acute pain as a result of either expected events, such as planned surgery or dental work, or unplanned events, such as emergency surgery or accidents.

The methadone that patients receive in their daily maintenance dose is not sufficient to control acute pain; separate pain management approaches are required. Use of opioids for management of acute pain for a patient in methadone maintenance treatment can be safe and effective. In cases of severe acute pain, short-acting opioids are often indicated. Because tolerance

is higher, the doses will be at the upper end of the therapeutic range and the lower end of the dosing frequency range. If the patient is unable to take methadone by mouth, it may be given intravenously (IV). **The IV dose of methadone is one-half of the oral dose.** “When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.” (PDR)

For chronic pain, treatment should be managed by the patient’s primary care physicians or a pain specialist in communication with the OTP physician and clinical staff. If opioids or other CNS depressants are prescribed by another treating physician, coordination is a high priority to avoid over-sedation or overdose. If the patient is unwilling to sign releases to the prescribing physician, it may be necessary to withdraw the patient from methadone maintenance.

In summary, the role of the OTP physician in regard to other medical conditions of the patients in methadone maintenance treatment:

- **Urgent medical conditions**
 - To screen for urgent medical conditions at intake and as needed thereafter and to arrange for prompt care when necessary.
 - To screen for infectious diseases at intake and at appropriate intervals thereafter.
- **Needle-related diseases**
 - To screen for hepatitis B and C and HIV, to provide medical education regarding these diseases to patients and staff; to ensure that patients receive vaccinations for hepatitis A and B if appropriate and ongoing care for chronic disease.
 - To ensure that patients with HIV are aware of the potential interactions between methadone and antiretrovirals; to ensure that prescribing physicians are aware of the patient's methadone treatment and coordinate care with other medical providers.
 - To screen for abscesses/cellulitis at admission and as needed thereafter, treating or arranging for care when necessary.
- **Tuberculosis**
 - To ensure that coughing patients are promptly identified and evaluated, while using measures to prevent spread of disease.
 - To ensure that patients with active TB are appropriately treated and separated from the general population until no longer contagious.
 - To ensure that patients with a positive PPD who do not have active disease are treated for latent tuberculosis infection according to CDC protocol.
- **Pulmonary disease**
 - To identify patients with pulmonary disease, to monitor for respiratory compromise, to coordinate care with the primary care physician and to adjust the methadone dose if necessary when patients experience exacerbations of their underlying condition.
- **Acute pain**
 - To coordinate with outside physicians treating acute pain in patients on methadone, to monitor patients for escalation when they present for dosing and to work with patients and alert prescribing physicians if there is evidence of abuse of prescribed medication.

Section on

LABORATORY DATA

Addiction specialists rely on urine drug tests to screen for drug use and to verify that methadone and its metabolite are present. Most urine drug testing provides only positive or negative results that do not differentiate between low dose and high dose use. Treatment of patients presenting for treatment of dependence on methadone are problematic particularly if their methadone is being obtained from non-medical sources.

Federal regulations require eight drug tests per calendar year but do not specify which drugs (other than methadone) must be included.

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. Since, in most cases, such a laboratory is off-site, the results are not available for use in immediate clinical intervention with the patient. Some OTPs utilize additional on-site testing which allows a prompt evaluation of acute clinical situations as they present. This “non-Title 9” testing is used for in-house decisions and for medical-exception take-home decisions, but not for the California specified ‘regular’ take-home criteria.

Saliva tests are available. The sensitivity of these tests varies; more sensitive tests are more expensive.

Many California 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. These panels often do not include tests for alcohol, marijuana, some benzodiazepines (notably clonazepam (Klonopin®) and lorazepam (Ativan®)) and other sedatives such as muscle relaxants. 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. 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 to identify patients who may not be able to stop drinking without medical assistance.

Table 16 ~ Urine Drug Testing Requirements: Federal vs. California

| | Frequency of Testing | Laboratory Used | Drugs Included in the Screen |
|---|-------------------------------|---|--|
| Federal Regulations 42 CFR Chapter 1, Part 8.12 f(6) | Eight times per calendar year | Not specified | Adequate testing or analysis for drugs of abuse |
| California Regulations CCR, Title 9, Division 4, Chapter 4, Subchapter 5, Article 3, section 10310-10320 | Once per calendar month | Lab must be licensed and certified by the state of CA | Must include methadone, methadone metabolite, opiates, cocaine, amphetamine and barbiturates |

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 in order to decrease the concentration of drug in their urine. To discourage tampering, programs are required to test on a random schedule; patients are not to be 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. Programs may require observed collection or specimen temperature testing. Programs may monitor urine creatinine levels to screen for dilution. If the urine creatinine level is below twenty, the specimen is considered to be a 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 twenty.

There are different drug testing technologies available. Most programs use thin layer chromatography (TLC) or EMIT (Enzyme Multiplied Immunoassay Test) as the screening instrument. The sensitivity of an immunoassay like EMIT is 200-300 ng. Because these screening instruments are not specific, a confirmatory test, usually GC/MS, is done when there is a positive result – that is, when drugs of abuse are present or methadone and/or metabolite is absent. Although costly, gas chromatography/mass spectrometry (GC/MS) is the standard confirmatory test because of its high specificity. Newer technologies, such as fluorescent 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 insure 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

When a urine drug screen is negative for methadone or metabolite, further investigation is necessary.

methadone diversion. Confirmatory testing with GC/MS will clarify whether methadone and metabolite are in fact present, but below the threshold for reporting on the screening test. Rapid metabolizers or patients on very low doses 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 methadone and metabolite after a more prolonged absence. **Patients who are positive for methadone but negative for metabolite need careful evaluation; this result is consistent with a tampered specimen: a urine from someone not on methadone to which methadone has been added to avoid detection.**

Laboratory results should be used therapeutically, as clinical data to support treatment objectives, not forensically to activate penalties or punishment. Testing should serve the clinical purpose of identifying ongoing or sporadic drug use and potential safety issues. 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 to identify strategies and resources to support future abstinence. 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 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 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 California and federal regulation. In these situations, it is necessary to submit an exception request to California 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 under the influence. However, saliva tests are not approved for regular use under Title 9. A California and CSAT exception would be required before the program could use these tests in place of urine testing for a particular patient.

In summary, the role of the OTP physician in regard to laboratory data:

- **At admission,** to order admission lab work and review results with patients.
- **Urine toxicology testing:** to ensure that patients are being screened for the relevant drugs and to interpret urine toxicology results, particularly when there are questions regarding the presence or absence of methadone or metabolite of methadone or whether the results are consistent with proper use of prescribed medications.
- **Methadone peak and trough levels:** to order, interpret and review results with patients.
- **Annual laboratory work:** to order laboratory work as clinically indicated and review results with patients.
- **Communicate with counseling staff** to ensure that patients' counselors are informed of significant blood and urine test results and their interpretation.

Table 17 ~ Detection Period for Various Drugs of Abuse

(Bi-Valley Medical Clinic, Inc., Sacramento, CA; 1998)

| Drug | Detection period |
|--|--|
| Amphetamine Methamphetamine | 2-4 days 2-4 days |
| Barbiturates: amobarbital butalbital pentobarbital secobarbital phenobarbital | 2-4 days up to 30 days |
| Benzodiazepines diazepam (Valium®) – 20-50 hours chlordiazepoxide (Librium®) – 5-30 hours clonazepam (Klonopin®) lorazepam (Ativan®) alprazolam/prazolam (Xanax®) | Chronic Use: up to 30 days Casual Use: Note: urine detection time is perhaps 3-5 half-lives. Half-lives: diazepam – 20-50 hours chlordiazepoxide – 5-30 hours alprazolam –19-60 hrs clonazepam –19-60 hrs lorazepam/Lorazepam – 9-16 |
| Cocaine | 12-72 hours |
| Cannabinoids (marijuana) casual use chronic use | 2-7 days up to 30 days |
| Ethanol | 12-24 hours |
| Opioids codeine hydromorphone (Dilaudid®) morphine (for heroin) | 2-4 days |
| Methaqualone (Quaalude®) | 2-4 days |
| Phencyclidine (PCP) casual use chronic use | 2-7 days up to 30 days |

Detection periods vary; rates of metabolism and excretion are different for each drug and each user. Detection periods should be viewed as estimates. Individual cases can always be found to contradict the approximations.

Section on

TAKE-HOME PRIVILEGES

Treatment staff, state regulators, and patients view take-home medications very differently.

Treatment staff, state regulatory staff, federal drug enforcement agencies and patients may view take-home medications very differently. 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 urines is effective in reducing drug use – in other words, as part of a therapeutic structure to support behavior change (Iguchi et al. 1988; Stitzer, Iguchi & Felch 1992). 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-homes 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 doses are unreasonable and interfere with their ability to work, travel and participate in other activities.

It is the OTP physician's responsibility to view take-home doses from a safety perspective, considering the patient's ability to safely transport, store and take the doses as prescribed. Home doses pose a risk of accidental overdose if the patient takes other sedating medications with methadone or if the patient inadvertently takes multiple doses of methadone on the same day. The later can occur if a patient is sleeping during the day then awakes and takes another dose thinking it is the next day.

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 doses, 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 doses from theft or accidental ingestion by a child or other non-opioid dependent person.

Because of concerns about diversion and overdose, federal and California regulations restrict who is eligible for take-home privileges. See Tables 17-19 for specific requirements. California regulations are very detailed and specific about the amount of time a person must have been in treatment and have tested negative to be eligible for take-home doses. The regulatory system tries to support and encourage abstinence by allowing patients with negative drug tests and adherence to clinic rules to move through a graduated take-home schedule from Step 1 (one take home per week) to Step 6 (six take-homes per week). Federal and California regulatory requirements concerning take-home medication differ. California regulations are generally more stringent than federal regulations. See Table 19 for 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 (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.

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

There are provisions in both California and federal regulations for granting exceptions to take-home regulations where there is compelling need and the physician attests to the responsibility of the patient. Physicians have the authority to grant exceptions to the restrictions governing take-home privileges, based on appropriate clinical judgment. For example, disabled patients who are in recovery but who do not meet the requirements for work or homemaking may merit exceptions. Medically ill patients may also be granted exceptions when warranted, provided they are able to handle take-home doses safely without risk of diversion. Program physicians are responsible for certifying the appropriateness for take-homes for each patient. Table 18 lists eight criteria to be considered by physicians prior to granting take-home doses.

Table 18 ~ 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 (opioid or non-narcotic) 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 decreasing frequency of clinic attendance outweighs the potential risk of diversion

**Table 19 ~ Time in Treatment Requirements for Take-Home Medication:
Federal vs. California**

Federal Regulations: 42 CFR Chapter 1, Part 8.12 I

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

| Time in Treatment | Federal Regulations | California Regulations |
|--|---|---|
| First 90 days of treatment | One dose/week allowed | No take-home doses allowed |
| Second 90 days of treatment | Two doses/week allowed | One dose/week allowed provided there is no evidence that the patient has used illicit drugs, abused alcohol or engaged in criminal activity within the last 30 days |
| Third 90 days of treatment | Three doses/week allowed | Two doses/week allowed provided there is no evidence that the patient has used illicit drugs, abused alcohol or engaged in criminal activity within the last 30 days |
| Remaining months of first year | Six-day supply allowed | Three doses/week allowed, but not more than a two-day supply at one time provided there is no evidence that the patient has used illicit drugs, abused alcohol or engaged in criminal activity within the last 30 days |
| After one year of continuous treatment | Fourteen-day supply allowed | Four doses/week allowed, but not more than a two-day supply at one time provided there is no evidence that the patient has used illicit drugs, abused alcohol or engaged in criminal activity within the last 30 days |
| After two year of continuous treatment | One-month supply allowed; patient must visit the clinic monthly | Five doses/week allowed, but not more than a three-day supply at one time provided there is no evidence that the patient has used illicit drugs, abused alcohol or engaged in criminal activity within the last 30 days |
| After three year of continuous treatment | One-month supply allowed; patient must visit the clinic monthly | Six-day supply allowed provided there is no evidence that the patient has used illicit drugs, abused alcohol or engaged in criminal activity within the last year |

Table 20 ~ Miscellaneous Regulations Concerning Take-Home Medication: Federal vs. California

Federal Regulations: 42 CFR Chapter 1, Part 8.12 I

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

| | Federal Regulation | California Regulation |
|--|---|---|
| Days Clinic is Closed for Business, Sundays and Federal or State Holidays | One dose allowed for all patients | No take-home doses allowed |
| Dosing Conflict | Not specified | Patient must be participating in gainful vocational, educational or responsible homemaking which conflicts with daily dosing in clinic. |
| Toxicology Test Results | Must meet requirement in the eight point criteria for absence of recent abuse of drugs (opioid or narcotic) including alcohol | Must be negative for illicit drugs and positive for methadone during the month that the take-home is granted AND must meet length of abstinence criteria as above |
| Short-term Detoxification Patients | No take-home doses allowed | No take-home doses allowed |
| Interim Maintenance Patients | No take-home doses allowed | No take-home doses allowed |
| Long-term Detoxification Patients | Same as for patients in MMT | Same as for patients in MMT |
| Take-Home Bottle Label Requirements | OTP's name, address and phone number | Federal + 24 hr emergency phone number, medication name/date issued, patient's name and prescribing physician/medical director's name, and the warning statement: "Poison – may be fatal to adult or child; keep out of reach of children." |
| Packaging for Take-Home Doses | Must be designed to reduce the risk of accidental ingestion, i.e., childproof containers | Same as Federal |
| Methadone Formulation | Must be an oral form that reduces potential for parenteral abuse | Liquid formulation required |

Take-home medications can support a patient's progress in recovery by facilitating the patient's ability to pursue vocational training, employment and drug-free activities with family and friends and by minimizing the patient's contact with unstable OTP patients at the clinic who are still using. In view of this, Federal regulations have permitted up to one month of take-home doses since 2001, and in 2002 California regulations established criteria for what are called 'extended take-homes' whereby patients who meet certain criteria may take up to a month's supply of methadone from the clinic.

Prior to granting extended take-homes to any patient, California regulations require the Medical Director or Program Physician to submit a proposed extended take home protocol to ADP for pre-approval. In addition to the program-wide protocol approval, each patient moving to extended take-home status requires a separate waiver to Title 9. The request for a waiver is submitted by faxing Form 8045 - "Physician Request for Temporary Exception to Regulations" (ADP Form 8045 appears in Appendix D) to the Sacramento office of ADP. A separate form ADP 8045 must be submitted and approved for each patient selected.

Table 21 ~ Protocol Elements that are Required by Programs in California for Take-Homes Beyond Six Days Per Week

1. Patients must have been at a Step 6 (i.e., once a week clinic attendance successfully) for 6 months.
2. The patient's last 6 months of toxicology testing must have been negative for illicit drugs and positive for methadone and metabolite of methadone.
3. The program must have in place a call back procedure, such as pill counts, to check on compliance with medications and possible diversion.
4. 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.
5. The program must have procedures for collecting at least eight samples for toxicology testing per year.
6. The program must have proper procedures for handling and labeling take-home bottles of medications.
7. The program must have procedures in place to restrict the take-homes of patients who relapse.

Exceptions to federal regulations are requested on SAMHSA's form SMA-168. The SMA-168 form may be submitted on-line, by fax or by mail. The SMA-168 form appears in Appendix D. SAMHSA's fax number and mailing address are on the form. To submit the form on-line, you must first register. This may be done online at otp-extranet@opioid.samhsa.gov or by calling the Exception Request Information Center at 1-866-OTP-CSAT (1-866-687-2728). The log-in page for the SAMHSA OTP Extranet web site is <http://otp.extranet.samhsa.gov>. On-line requests are processed the fastest; often SAMHSA's decision may be viewed on line within one hour of submission.

It is the physician who authorizes take-home doses and who requests exceptions when they are required.

For vacations or other out of town travel, California regulations require that the OTP attempt to arrange courtesy dosing by another OTP before granting take-home doses. The patient record must document the reason that courtesy dosing could not be arranged before take-home doses are granted for exceptional circumstances. In some situations, in particular for newly-admitted patients who have been in treatment less than three months, a federal and/or California exception waiver must be on file before take-home doses are granted. These regulations concerning take-home doses are subject to revision and should be reviewed carefully prior to granting take-home doses.

The physician should be familiar with regulatory criteria for take-homes, as it is the physician who specifically authorizes take-home doses and who specifically requests exceptions for extended take-homes. 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.

In summary, the role of the OTP physician is to **grant or revoke take-home doses:**

- To evaluate the ability of the patient to manage take home doses safely.
- To discontinue take home dosing if the patient appears unable to manage take home doses safely.
- To evaluate the potential for diversion prior to granting take home doses.
- To ensure that Federal and California regulatory requirements have been met or the appropriate waivers obtained.

Section on

DISCHARGE FROM TREATMENT AND TAPERING OFF METHADONE

The physician's role is to weigh the risks and benefits for the patient of remaining in treatment vs. discharge.

Patients leave methadone treatment for a variety of non-therapeutic reasons. Patients may leave abruptly due to incarceration, hospitalization or inability to find transportation to the clinic to dose. OTP physicians may initiate an involuntary methadone withdrawal for patients who routinely miss doses because they present to dose under the influence and so unsafe to dose or after the dispensary has closed. These patients cannot be stabilized on methadone. OTP physicians may be asked to taper patient off MMT due to non-payment of fees or for behavioral issues such as dealing, violence on clinic premises, or threatening clinic staff and/or patients. Discharge is not the result of planned withdrawal in any of these situations.

The physician's role is to weigh the risks and benefits for the patient of remaining in treatment vs. discharge, to determine the appropriateness of discharging the patient, to devise the best taper possible given the situation and to provide referrals as needed.

A small number of patients request to be tapered off methadone. **The patient must be advised that few patients are able to maintain abstinence after tapering off methadone and reminded that a successful outcome of the attempt at tapering is ongoing, sustained abstinence from illicit opioid use, whether the patient is able to discontinue methadone treatment or not.**

A successful taper is one that does not destabilize the patient. This may mean proceeding very slowly or stopping and restarting the taper as needed to control symptoms of withdrawal or craving. Patients undergoing voluntary tapers must be closely monitored for symptoms of withdrawal and signs of destabilization. Emergence of cravings or near slips are a definite indication to stop the taper and re-stabilize the patient. The completion of a methadone taper cannot be considered a "successful outcome" if the patient returns to illicit opioid use. It is the ultimate outcome, rather than the patient's comfort during the tapering process, is what determines success.

During the taper, the patient and clinic staff should accept as a possible outcome that the patient might need or want to remain on or return to methadone maintenance. Issues concerning taper reversal are an important part of counseling sessions, which should monitor progress or relapses. The taper reversal should be done without imparting a sense of failure, shame or guilt. Since the goal of methadone treatment is for the patient to remain free of illicit opioids, rather than to become methadone free, the patient should know that he/she is welcome to come back into treatment and that he/she will be given preferential treatment on waiting lists for readmission.

Methadone tapers are more comfortable when they are done slowly and are largely guided by the patient's ability to manage withdrawal symptoms. A comfortable taper will rarely take less than six to eight weeks and will more often take months to years. Tapers are more likely to be completed

Studies have shown that the eventual relapse rates approach 100% whether patients are tapered using proportional or linear taper schedules.

successfully when there is stability of physical health, mental health, and social environment.

When designing taper schedules, it is helpful to remember that patients are generally able to discern a difference when their methadone dose is adjusted by ten percent. For this reason, a taper will be more comfortable if the taper rate is based on percent of dose, rather than number of milligrams. For example, at 100 mg of methadone a day, a five mg drop is a 5% reduction; however at 15 mg a 5 mg drop is a 33% reduction of the dose, which is more likely to result in symptoms. When 3% versus 10% incremental decreases were compared, the 3% decrease was better tolerated. Studies have shown that the eventual relapse rates approach 100 percent whether patients are tapered using proportional or linear taper schedules. While tapering, the focus should be on maintaining a therapeutic relationship with the patient to facilitate a smooth transition back into treatment if needed.

Tapering schedules should incorporate frequent monitoring with rate adjustment or plateau whenever necessary. There may be specific dosage levels in the taper at which more intense physical withdrawal symptoms develop (“brick walls.”) These dosage levels vary significantly from patient to patient and may vary from one time to another. For example, a patient may develop discomfort at 70 mg during one taper and not until 20 mg at another time. As patients experience and pass these thresholds, they may need extra support from clinic staff, or they may need to halt the taper temporarily and hold or increase the dose to a more comfortable level. Once stable, the taper may be restarted more slowly.

Clonidine, an alpha-adrenergic blocker, may be useful at the end of a methadone taper to control discomfort. Although not an opioid, it is effective at specifically relieving opioid withdrawal symptoms, especially symptoms that are mild in nature, such as the insomnia seen in protracted withdrawal. There is no evidence that ancillary medications improve chances for sustained abstinence post-discharge, so use is generally limited to one to two weeks. If clonidine is used for longer than two weeks, the patient must be tapered off and monitored for rebound hypertension. If troublesome symptoms persist, re-induction on methadone and another attempt using a slower taper rate could be considered. Regular urine drug testing should be continued, perhaps more frequently to monitor for lapse to illicit opioids and/or other drugs of abuse, including alcohol. Breathalyzer testing to screen for alcohol use may be indicated as well. In the event of lapse or relapse, the patient should be advised to discontinue the taper, and re-stabilize on a therapeutic dose of methadone.

The psychological state of the patient should be monitored throughout treatment, meaning during the methadone taper and after the methadone has been discontinued and the patient is methadone free. Opioid withdrawal can destabilize mental illness, putting the patient at increased risk of decompensation. Patients need to be monitored closely for escalation or re-emergence of psychological symptoms, which should be addressed either by the OTP physician or by referral to another provider prior to discharge. Mental health providers following these patients need to be apprised of the recent methadone taper and the likelihood of residual symptoms of withdrawal. Psychotic or depressive symptoms may emerge. Relapse into depression carries a risk of relapse to drug use. Suicides have occurred as a result of the severe

loss of hope and self-esteem accompanying relapse after a long period of abstinence. This psychological crisis has been called the “abstinence violation effect.”

Another potential danger of a prolonged methadone taper is the loss of opioid tolerance. Patients must be counseled that relapse may result in inadvertent overdose.

Indications for Discharge

Discharging a patient from methadone treatment is clinically necessary in some situations. Appropriate indications for discharging a patient (tapering a patient off methadone) include the following:

- **The patient has requested** and completed medically supervised taper from methadone. The patient has made appropriate plans for post-treatment life, including other support, family, job, financial, housing, social, etc.
- In the judgment of the physician, **the patient has become too medically ill** to receive his or her methadone dose; e.g., a patient with an end stage illness, such as AIDS, cancer, or advanced liver disease. When illicit use is no longer a practical possibility, the patient’s care may be transferred to the hospice physician.
- **The patient has been diagnosed as having active tuberculosis and is unwilling to comply with recommended treatment.** (This is a public health issue within the clinic.) In this case, the appropriate health officer should be notified, and the patient may be impounded (seized and retained in legal custody).
- **The patient is diagnosed as psychotic or as having another psychiatric illness** that prevents successful participation in clinic and **is unwilling to follow through with psychiatric care.**
- **The patient is unable or unwilling to cooperate with treatment protocols** in spite of staff efforts to work with him or her.
- **The patient continually comes to the clinic too intoxicated** (with alcohol, benzodiazepine, stimulants, etc.) to allow safe administration of the methadone dose.
- **The patient misses his/her dose so frequently that he/she is unable to achieve a stable blood level.** Patients who miss 4-5 days of methadone need to be re-induced as if a new patient. Blood levels take about 5 days of consistent dosing to stabilize. Patients who miss so frequently that they do not stabilize are not getting the benefits of ‘maintenance’ and should be considered for taper and referral to another form of therapy. Continued intermittent methadone dosing becomes a part of a poly-drug abuse regimen/lifestyle and is not treatment.
- **The patient is taking other prescription opioids** or is found to be obtaining methadone from other sources and is unwilling to undergo dose evaluation or adjustment to achieve a sustained abstinence. In this situation, continued methadone maintenance is not meaningful and may not be safe.

- **The patient has become completely incapacitated** (e.g. coma) for such an extended duration such that withdrawal symptoms would not be an issue.
- **The patient has been violent or has threatened violence** to staff or other patients in the clinic. In this case, the patient may be summarily discharged with no taper. Efforts may be made to assist the patient to transfer to another clinic, for example by faxing OTP records promptly.
- **The patient is anticipating incarceration in prison** where methadone treatment will be discontinued without a taper. Although cessation of methadone treatment puts the patient at risk for symptoms of withdrawal and increases the risk of relapse, California does not currently make provision for methadone treatment in prison. Patients should be advised that (in accordance with California regulation) they may return to MMT without using opioids within one month of release, provided they have been incarcerated for at least one month.

No matter what the reason for the discharge, planning should include referral to appropriate aftercare. Aftercare from MMT may include psychosocial services, symptomatic treatment for withdrawal symptoms, transfer to treatment with buprenorphine or with the opioid antagonist naltrexone. Discharge planning should also include identification of sources of support for the patient, especially community recovery groups, that will help the patient maintain the commitment to recovery.

In summary, the role of the OTP physician in regard to discharge and tapering off methadone:

- **To weigh the risks and benefits** of continuing vs. discontinuing methadone treatment and to counsel patients regarding these risks/benefits.
- **To avoid withdrawal** from methadone whenever possible when a higher intensity of care would be more appropriate.
- **To monitor patients attempting withdrawal** for destabilization and restabilize as necessary.
- **To educate clinic staff, patients and the community** regarding the chronic nature of opioid dependence and the risk of premature, hasty, or ill-advised withdrawal from methadone maintenance.
- **To facilitate re-admission if needed** to ensure that patients who complete a voluntary taper are aware that they may return to treatment at any time within six months of discharge without relapse to opioids and to ensure that these patients are promptly re-admitted upon request to support ongoing abstinence.

Section on

TREATMENT OF PREGNANT WOMEN

Withdrawal puts the woman, the pregnancy and the baby at risk for adverse outcomes.

The most important point about the treatment of opioid-dependent pregnant women is that withdrawal puts the woman, the pregnancy and the baby at risk for adverse outcomes. In view of this risk, methadone maintenance is the treatment of choice for opioid addiction during pregnancy, and the methadone dose must completely suppress symptoms of opioid withdrawal. It should be noted that at some future time, buprenorphine, (specifically the mono product, Subutex®) might be an alternative maintenance treatment for opioid-dependent pregnant women. **At this time buprenorphine is not approved for use in pregnancy due to insufficient studies demonstrating its safety.** However, studies to date are promising. See Appendix B for more information regarding the use of buprenorphine in pregnancy.

Admission Criteria

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

A history and physical exam along with records documenting prior treatment episodes or documentation of opiate dependence while hospitalized or incarcerated are sufficient to comply with these regulations. Observation of objective signs of opiate withdrawal is the usual way of documenting physical dependence. However, withdrawal is best avoided during pregnancy because of the risk of precipitating premature labor, so women should be told that they should be neither intoxicated nor in withdrawal when they present for treatment. Patients are often able to time their last opioid use so that the earliest stages of withdrawal will begin within a few hours of presentation to the clinic. On site observation may be helpful if there is any question about a women's current physical dependence. Physical evidence of current and past use (e.g., tracks) documents IV use that is usually associated with physical dependence. An on-site opioid screening test may be used to confirm recent opioid use. The use of an antagonist challenge test to document opiate dependence is absolutely contraindicated in a pregnant woman.

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.

Medical Counsel Regarding Methadone Maintenance Treatment During Pregnancy

Many pregnant women seeking methadone maintenance treatment for opioid dependence feel bad about it. These feelings stem from a variety of beliefs and misconceptions, many promoted and endorsed by society or medical providers unfamiliar with addiction issues and treatment. Patients may believe that they cannot genuinely be in recovery while on methadone, that they should be able to achieve and maintain abstinence on their own, that friends, family and society will not accept them if they are on methadone, that methadone is bad for their health or bad for the baby, and that withdrawing from methadone is worse than withdrawing from heroin. Additionally, pregnant women often feel extremely guilty about using heroin while pregnant and wish to be medication-free to relieve this guilt.

Pregnant women often present for admission to methadone maintenance after being advised that detoxification is contraindicated during pregnancy. Despite this, many pregnant women feel guilty that they are pursuing a mode of treatment that will ensure their own comfort, assuming that it is at the baby's expense. Patients should be advised that the baby has been experiencing repeated episodes of withdrawal during the mother's periods of abuse of short-acting opioids, and that a proper dose of methadone for the mother during pregnancy will eliminate this fetal intrauterine withdrawal.

The physician should take time to explore the patient's beliefs and concerns about methadone and to address them. When a patient doesn't feel comfortable about being on methadone, she may be reluctant to volunteer information about symptoms of withdrawal, hoping to avoid dose increases. She may seek to withdraw from treatment prematurely or may miss doses on purpose, thinking it is beneficial to minimize her methadone exposure.

On the other hand, there are women who seek admission to the program in order to show Child Protective Services (CPS) they are in a drug treatment program, but do not truly desire to be on methadone maintenance. They may miss many doses and generally present compliance problems. The physician and staff should make every attempt to engage them. It may help to point out that CPS will be seeking information about participation in treatment including consistency of dosing, attendance of group/one-on-one counseling and cooperation with urine drug testing. **Patients must be reminded that program staff members are mandated CPS reporters. Failure to participate in treatment and failure to provide negative drug tests at the program after a stabilization period puts a woman at risk of loss of custody of her baby.**

Pregnant women who continue to use or are too chaotic to dose daily should be offered residential treatment while on MMT to enable them to achieve abstinence. Patients should be warned that they will be drug tested by the hospital at the time of delivery and informed that participation in treatment is viewed favorably as a sign that the woman is trying to get help and to stop using. Women who are not in treatment and test positive at delivery frequently lose custody of their children. The physician may also need to intervene directly with CPS staff, who may not understand methadone or who may have biases against this treatment. Methadone maintenance treatment is fully compatible with parenting, and the support of treatment staff can assist

A proper maternal methadone dose eliminates the repeated intrauterine fetal withdrawal that the baby was experiencing when the mother was abusing short-acting opioids.

the patient in her parenting role. The physician should assure the patient of assistance in dealing with CPS if necessary.

The admitting physician should explain the risks of continued use of heroin 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 consequences of opiate withdrawal during pregnancy should also be discussed: the baby experiences the stress of cyclical withdrawal states which compromises growth; the uterus (a muscle) may become hyperactive resulting in miscarriage or pre-term labor and delivery; hunger for heroin may make it extremely difficult for the woman to avoid heroin use; nausea may suppress the appetite resulting in malnourishment and maternal depletion; vomiting and diarrhea may lead to dehydration. The lifestyle associated with drug use increases the risk of trauma, STDs, lack of prenatal care and loss of custody of the baby. This information will need to be repeated at subsequent visits as many women absorb little at the time of admission.

The admitting physician should be familiar with the literature documenting methadone's safety and efficacy in pregnancy. He/she should be able to discuss with the patient the research that indicates that infants exposed to methadone in utero have normal physical and mental development as children (Kaltenbach & Finnegan 1987; Kaltenbach & Finnegan 1984; Kaltenbach, Graziani & Finnegan 1979; Kaltenbach & Finnegan 1989).

It is important that patients be advised of the risks of neonatal abstinence syndrome (NAS). In various studies, occurrence ranges from 50-80%. (Berghella et al. 2003) However, patients need to understand that the risk of NAS is unavoidable, that the intensity of NAS varies, and that NAS is readily treated in an experienced hospital nursery with the expectation of good outcomes.

Not all hospitals and pediatricians are equally experienced in the treatment of NAS. Pregnant women on MMT should be advised of the importance of selecting a hospital that will be expert in the evaluation and treatment of NAS. **It is helpful if the MMT physician is familiar with local hospitals and with the level of comfort of the medical staff in managing babies with NAS.** It is not uncommon for the MMT physician to receive phone calls from hospital or community physicians asking for guidance in the treatment of NAS. In such cases, referring the inquiring physician to an approachable pediatrician or neonatologist with expertise in this area may be the most prudent course.

There is a spectrum of NAS that ranges from mild symptoms, which will resolve with a supportive environment, to very severe symptoms, which can be serious, even fatal, if untreated. Symptoms of withdrawal may be present at birth or may emerge in the first two weeks of life. This is not something that should be evaluated over the phone or managed at home by the mother without MD evaluation and advice. Patients must understand that symptoms of withdrawal in the newborn must be evaluated in person by an experienced neonatologist or pediatrician. Prior to bringing the baby home from the hospital, the mother must know where she should bring the baby for medical evaluation should symptoms of withdrawal emerge. Risks of NAS may be reduced by cessation of smoking and by abstinence from illicit drugs. Stimulant

Symptoms of withdrawal in the newborn must be evaluated in person by an experienced neonatologist or pediatrician.

drug use, including cigarette smoking, may increase the risk for a more severe NAS.

California regulations require that all female patients of childbearing age be given information about a specific list of topics. By regulation, the patient record must include acknowledgement by the patient that she has received this information. Table 22 lists the specific topics that must be addressed.

Table 22 ~ Topics that Must be Discussed with Female Patients of Childbearing Age

CCR, Title 9 Division 4, Chapter 4, Subchapter 5, Article 3, section 10360

1. The reality that knowledge of the effects of medication used in replacement narcotic therapy on pregnant women and their unborn children is incomplete, making it impossible to guarantee that this medication may not produce significant or serious side effects.
2. The possibility that abrupt withdrawal from medication used in replacement narcotic therapy may adversely affect the unborn child.
3. The risk that use of other medications or illicit drugs in addition to medication used in replacement narcotic therapy may harm the patient and/or unborn child.
4. The recommendation that patients should consult with a physician before nursing
5. The chance that newborns exposed to medication used in narcotic replacement therapy may show irritability or other ill effects from the patient's use of these medications.

NOTE: Documentation of patient acknowledgement that the above topics have been discussed during orientation must be a part of the patient record.

Risks of Detoxification in Pregnancy

It is far better to treat NAS, if it occurs, in a fully grown, term baby than to allow a small incompletely developed baby to withdraw under somewhat blind conditions in utero.

Many patients are eager to get off methadone as soon as possible. Often they are motivated by guilt, external pressure from family members or friends, or misconceptions about methadone. Most patients will agree that their primary goal is to achieve complete and sustained abstinence from illicit opioids. However, many patients are unaware of the high risk of relapse after methadone detoxification. The physician should advise patients that the risk of relapse associated with withdrawal from methadone is 80% within the first year (Ball & Ross 1991). Further, pregnant patients need to be fully aware that fetal withdrawal will occur in-utero if they attempt to withdraw while pregnant. While gross measures of fetal distress may not accompany slow tapers off methadone, these measures are not sensitive to more subtle stress symptoms, such as hyperadrenergic states the baby may suffer during in-utero tapering. It is far better to treat neonatal abstinence syndrome (NAS), if it occurs, in a fully grown, term baby in an intensive care nursery setting with appropriate pharmacologic agents (methadone, paregoric, morphine and/or phenobarbital) than to allow a small incompletely developed baby to withdraw under somewhat blind conditions in utero by trying to taper the pregnant mother.

However, methadone treatment is voluntary. A patient's choice about how and when to withdraw from methadone must be honored. If a pregnant patient is adamant in her desire to withdraw from methadone, the physician should first obtain an informed consent for methadone detoxification during pregnancy and then help the patient to plan a very slow taper with obstetrical monitoring, preferably in the second trimester. The pregnant woman should be advised that the taper is reversible upon request and should be directed to seek obstetric evaluation promptly in the event of symptoms of premature labor. Tapering from methadone must be seen as secondary to the patient's maintaining abstinence and protecting the baby.

The Initial Assessment

The physician's most important task during the admission interview is to establish rapport with the patient. If this is not accomplished, the patient may not be forthcoming with information that is vital when planning treatment and may not be willing to follow through with future appointments or treatment recommendations. The physician should be non-judgmental and supportive of the decision to enter treatment.

The physician should review the patient's substance use history, asking specifically about the various illicit drugs as well as alcohol, over-the-counter medications, and nicotine. Mental health problems are an important area for inquiry as mental illness is especially prevalent in patients with opioid addiction. Opioid addicted women in particular have a very high incidence of both childhood and adult traumas, including molestations, rapes and physical violence. PTSD is common, and other Axis I mental health diagnoses must be assessed; untreated they are risk factors for continued drug use. Special focus on addiction-related diseases, such as HIV, hepatitis B and C and STDs is warranted.

If another physician is prescribing medication(s), the OTP physician must confirm that the medication(s) are indicated and are compatible with both

pregnancy and with methadone stabilization. For example lithium and valproate are contraindicated in pregnancy because of the risks of birth defects, and carbamazepine will severely complicate methadone stabilization. The OTP physician should make it clear to the patient that communication with the prescribing physician is necessary to ensure her baby's safety and comfort; **consent for such communication may be a condition of methadone treatment.**

Women who are HIV positive can reduce the incidence of HIV in 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.

An obstetrical history should note the patient's use of alcohol and other drugs during previous pregnancies, the outcome of each pregnancy, complications occurring during pregnancy and/or at delivery. The ages and custody status of previous children should be obtained. The physician should find out whether the current pregnancy was planned, what the patient's feelings are about it and whether the father is involved and supportive.

If the patient is ambivalent about the pregnancy, she should be referred for counseling to help her to consider all of her options and make a decision she feels comfortable with. Patients who express the intention of terminating the pregnancy should be provided with support and appropriate referrals. Until reliable documentation has been obtained that the pregnancy has been terminated, 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.

The physician must verify that the patient has a regular prenatal care provider, and written consent should be obtained to communicate with the provider.

The physician must verify that the patient has a regular prenatal care provider, and written consent should be obtained to communicate with the provider. Regular prenatal care has been shown to improve outcomes for methadone maintained pregnant patients, so barriers to keeping appointments, i.e., transportation, need to be addressed. Nutritional counseling specific to pregnancy, including the role of prenatal vitamins and iron, should be made available.

In addition to the usual complete physical examination, PAP and pelvic along with screening for sexually transmitted diseases should be performed or arranged via the physician providing obstetrical care.

Recommended admission lab studies include a complete blood count, chemistries, electrolytes, liver panel and screen for HIV, hepatitis B, hepatitis C, syphilis, medical urinalysis, toxicology screen and a serum or urine pregnancy test. Some of these tests may be omitted if they have already been done or are routinely done by the obstetrician following the patient.

If a woman is hepatitis C positive, there may be up to a 5 percent risk of transmission of the virus to the child. Pregnant women who screen positive for hepatitis C should be counseled about this risk and advised to make sure their 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. HIV counseling should be given to all patients and an HIV test offered. The physician should encourage all pregnant women to be tested for HIV in view of the data that treatment with AZT during pregnancy has been shown to reduce the risk of perinatal HIV transmission (European Collaborative Study 2005; McGowan & Shah 2000; Taylor et al. 1999; Wilkinson, Karim & Coovadia 1999). If the patient has identified risk factors within the preceding year, the HIV test should be repeated in each trimester and at delivery.

A PPD skin test should be placed unless the patient has a history of a prior positive result, in which case the physician should conduct a symptom review and consider a chest x-ray. If the patient is asymptomatic and low risk, the chest x-ray may be delayed until the second trimester. The patient should be given a tetanus shot if she has not received a booster in the last 10 years, or 5 years if she has an abscess or unclean wound.

Dose Determination

Methadone dosing is an area of continued controversy, with some obstetricians calling for low doses or even methadone tapers to avoid the risks of NAS (Dashe et al. 2002). However, the literature on the relationship of dose to withdrawal is inconclusive. **It is well established that therapeutic doses of methadone are associated with decreased illicit drug use, more prenatal care and longer retention in treatment.** In addition, it is clear that babies exposed to ongoing illicit drug use are at greater risk of adverse outcomes. It has not been established that babies exposed to higher doses of methadone in utero are at greater risk of adverse outcomes.

Two recent studies of 'high dose' treatment, up to 200mg/day, have shown no association between severity of neonatal withdrawal and methadone dose or maternal serum level (Berghella et al. 2003; McCarthy et al. 2005).

Berghella (Berghella et al. 2003) studied 100 mother/infant pairs on doses above and below 80 mgs daily, comparing the rates of illicit drug use before delivery, the NAS score, the need for treatment of NAS and the duration of treatment. They found that the NAS score, need for treatment of NAS, and duration of treatment was 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 (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. They found that high doses of methadone were not associated with higher rates of NAS symptoms or more days of infant hospitalization. However, high doses of methadone were associated with lower rates of maternal illicit drug use at

High doses of methadone were not associated with higher rates of NAS symptoms or more days of infant hospitalization, but rather with lower rates of maternal illicit drug use at delivery.

Treat pregnant women according to the same dosing guidelines as non-pregnant women; use a dose sufficient to eliminate withdrawal, drug use, and drug cravings.

delivery, despite the longer histories of opiate abuse amongst the women on high dose methadone.

Clinical experience has shown that after initial stabilization **many women require dose increases as pregnancy progresses** due to the re-emergence of signs and symptoms of withdrawal. There are several possible explanations. During pregnancy, there is an increasing volume of distribution. There is significant individual variability in the metabolism of methadone to its inactive metabolite. Furthermore, accelerated methadone metabolism and decreases in methadone bioavailability have been documented during pregnancy, which may precipitate withdrawal. **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.

The physician's objective should be to stabilize the pregnant woman on a therapeutic dose of methadone as quickly and as safely, as possible in order to decrease the risk of withdrawal or ongoing heroin use. In the ideal situation, a patient would receive an initial methadone dose and remain on the premises to be re-evaluated 4 hours later so that if withdrawal symptoms persist, additional methadone may be given. This cycle should be repeated every 3-4 hours until the patient no longer demonstrates any symptoms of withdrawal. Many programs are unable to provide this level of care. Daily re-assessments of dosing adequacy and safety are recommended during the first week of treatment.

A usual starting dose for a woman who reports using a "1/2 gram" of heroin or more per day is 30 to 40 mg. Under California regulation, no more than 30 mg may legally be administered at one time on the first dosing day. Additional methadone may be given on the first day, but it must be administered only after a physician-specified observation period. The physician must note the rationale for a dose above 40 mg on the first day. The patient should be advised that the first day's dose will not relieve all symptoms for a full 24 hours. Symptoms that begin as the methadone blood level falls (about 5 hours after dosing) may subside after the blood level of methadone has stabilized (about 5 days).

If symptoms of withdrawal do not completely resolve within 5 hours on the first day, the dose should be increased by 5-10 mg on the second day, and the dose must be evaluated on subsequent days until withdrawal is completely suppressed 3-5 hours after dosing, when the methadone blood level reaches its peak. At this point, further increases should be delayed for 3-5 days to allow steady state. If there is any question about the adequacy of the dose, the physician should evaluate the woman for signs of withdrawal prior to dosing. If any symptoms persist after 5 days, the dose must be raised. Dilated pupils (> 4 mm) are one specific and reliable indicator of opiate withdrawal. The dose should also be raised if the woman complains of cravings or ongoing use of heroin or other drugs. Peak and trough methadone blood levels may be helpful in determining a therapeutic dosing schedule. (See Section on Stabilizing on a Therapeutic Dose.)

Some programs monitor at least one serum level after a pregnant woman has been stabilized to more accurately assess fetal exposure. Fetal cord blood has about half the concentration of methadone as maternal blood. For women who

have difficulty stabilizing even on high doses, peak and trough serum levels may give information about the rapidity of methadone clearing. The peak should be below two times the trough. When the peak is twice or more than twice the trough, the woman may require a split dose to stabilize. Serum levels can be of considerable help in reassuring the expectant mother about the amount of methadone exposure. Mothers need to understand that it is not the oral methadone dose that determines fetal exposure; it is the mother's serum methadone level.

Common misconceptions that patients may have about methadone during pregnancy include projecting addictive traits onto the fetus. For example some patients will say, "My baby is eating up my methadone" when they require higher doses during pregnancy, or "My baby was born addicted to methadone," when their baby experiences NAS. Blood volume changes and dilution effect should be explained, and physical dependence differentiated from addiction. Another misconception is that the discomforts of late pregnancy, such as Braxton Hicks contractions, are emerging symptoms of opioid withdrawal. Interviewing the patient will help to differentiate the source of discomfort.

Split Dose

Dividing the daily dose into a morning and a late afternoon or evening dose (split dosing) can be of great help in stabilization. The physician must obtain pre-approval from CSAT in order to provide the patient with a daily take out for p.m. dosing if the patient has not been in treatment long enough to qualify for seven take-homes per week (270 days). The patient will continue to take the morning dose in the clinic under observation and will pick up a take home dose for the late afternoon or evening. There may be a particular benefit for splitting the dose during pregnancy. Split dosing provides a more stable blood methadone level for mother and fetus and may allow patients to stabilize on a lower methadone dose than they would with one daily dose. In one study (Wittmann & Segal 1991), 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, suggesting over sedation of the baby at peak blood levels and some withdrawal hyperactivity as methadone blood levels fall in the evening. Split dose patients had ultrasound exams with fetal movements similar to controls. For this reason, there are some physicians who routinely give all pregnant patients a split dose, sometimes prescribing a 3 times per day dosing schedule to achieve better stability. **For all patients, the physician must weigh the clinical benefits and the risks of take-home privileges, especially for unstable patients and for patients who have small children at home.**

As pregnancy progresses, some women will begin experiencing withdrawal in the late evening or early morning despite complete abstinence from illicit opiate use. In fact, on rare occasions, the urine drug screen could become negative for methadone or methadone metabolite, reflecting rapid clearance of methadone. The physician must review the situation to determine whether the most likely explanation is a low blood methadone level or diversion. The methadone dose should be re-evaluated after delivery; some women will become sedated as the metabolic changes of pregnancy reverse and the blood level rises.

Split dosing provides a more stable blood methadone level for mother and fetus.

Coordination with Prenatal Care Providers

Many prenatal care providers are unfamiliar with issues surrounding addiction, with methadone maintenance treatment during pregnancy and with proper doses of methadone during pregnancy. The physician should provide the prenatal care provider with basic information about methadone dose determination so that he/she will be supportive of the patient's treatment. In addition, the physician should discuss the use of analgesia during and after delivery, so that the prenatal care provider is aware that the maintenance dose of methadone provides no analgesia and poses no barrier to use of additional medications to provide analgesia as is appropriate for any woman. Partial agonists such as nalbuphine are contraindicated in women on methadone maintenance. (See below,) Whether the delivery is vaginal or by cesarean section the maintenance dose of methadone should be continued and other medications added as needed to control pain. If IV dosing is required, half the oral dose is equivalent.

There is an absolute contraindication to the use of mixed agonist/antagonist analgesics such as Nubain®.

It is vital that both the patient and the prenatal care provider are alerted about the absolute contraindication to the use of mixed agonist/antagonist analgesics, such as Nubain® (nalbuphine). Nubain is a very commonly used obstetrical analgesic because it causes less respiratory depression in the baby than morphine. However, it will immediately precipitate severe withdrawal in both the methadone dependent mother and the baby, which will require high doses of pure opiate agonists to reverse. Patients must be specifically educated about Nubain and told that they have a right to question every medication they are given. Because the use of Nubain in methadone patients creates an immediate obstetrical crisis, some providers have suggested that women say they are allergic to Nubain and have this posted on their chart.

The hospital of delivery should be noted in the chart. The physician should verify that the hospital is familiar with the management of methadone maintained women and methadone exposed newborns and provide consultation when needed or referral to a facility familiar with perinatal methadone issues.

Monthly Follow-up Appointments with the Physician

Under California regulation, the physician must meet with each pregnant woman at least once a month during pregnancy. The first follow-up visit with the physician should be scheduled within a few days of the pregnant woman's admission because of the high likelihood that she will have questions and that the methadone dose will need to be raised. The physician will need to arrange a mechanism for dose adjustments between scheduled appointments. Weekly visits should occur until the patient is stabilized on a therapeutic dose of methadone. It may be very helpful to have a specifically trained pregnancy counselor with whom the physician can have close consultation about the status of all pregnant and early post-partum women. This counselor can also monitor prenatal care appointments and report any problems with patient access and/or participation in prenatal care. General methadone maintenance counselors may not be versed in the special issues of pregnancy and should be trained not to give conflicting or inappropriate recommendations to pregnant patients about dosing.

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. It is important to review the basic information about methadone use during pregnancy and to allow the woman to ask any questions she may have. An interval drug use history should be taken and compared with the results of urine drug screens. This part of the interview must be done in such a way that the patient does not feel that she is being accused of being bad if she reports ongoing use. The physician should provide assurance that abstinence is achievable, remind the patient of prior successes, and point out progress she has already made.

The monthly follow-up visit is a good time to discuss the effects of substances of abuse on pregnancy and the risks of in utero exposure. While the discussion may emphasize substances the patient is known to have used, all of the substances of abuse should be touched on. It is not unusual to learn during this discussion that the woman is using substances not disclosed at admission. Tobacco should be included in the discussion. The risks of in-utero fetal exposure as well as second-hand smoke exposure of the infant, should be reviewed. Many patients are not aware that smoking during pregnancy increases the risks of SIDS, negative toddler behaviors, learning disabilities and ADHD, or that nicotine exposed babies may experience symptoms of withdrawal.

Smoking during pregnancy increases the risks of SIDS, negative toddler behaviors, learning disabilities and ADHD, and nicotine exposed babies may experience symptoms of withdrawal.

Other topics to be covered during monthly follow-up visits include:

- **The importance of dosing daily** and adjusting the dose as needed to avoid symptoms of sedation or withdrawal
- **The necessity of participation in the counseling portion** of the program to support progress in recovery
- **The importance of regular prenatal care**
- The need to discuss **use of any over-the-counter medications** with the prenatal care provider and to alert prescribing physicians that they are pregnant and on methadone maintenance

In the third trimester, important topics include:

- **Contraceptive options** with encouragement for the woman to decide on a method of contraception prior to delivery
- **Pain management** at delivery
- **Breastfeeding**
- **Postpartum changes** including symptoms of post-partum depression
- **The importance of staying connected to the program** after delivery to support ongoing abstinence
- Future treatment plans

Some of these topics will be discussed specifically in sections to follow.

Breastfeeding

The amount of methadone passed in breast milk is negligible (McCarthy & Posey 2000), so a woman's methadone dose should not be used as a contraindication to nursing. At least eight studies since 1974 have confirmed this. (Jansson, Velez & Harrow 2004). The American Academy of Pediatrics

A woman's methadone dose should not be used as a contraindication to nursing.

recently changed its longstanding recommendations against nursing on doses over 20mg/day, and has determined that methadone is compatible with nursing with no dose restrictions (Philipp, Merewood & O'Brien 2003). In addition to other well-documented benefits, nursing may provide some protection against SIDS, which is more prevalent in drug-exposed infants (Jansson, Velez & Harrow 2004) The improved bonding that accompanies nursing may also help the baby and reinforce the mother's recovery. However, any abuse of drugs is a contraindication to nursing.

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 nursing if she is in fact carrying the infection. 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 hepatitis C should be counseled to pump and discard if she experiences nipple trauma (until she has healed) based on concerns about the baby ingesting HCV infected blood. A woman who decides to breastfeed should ideally be smoke-free. (Cunningham 1997)

Patients on MMT who plan to breastfeed often request that the OTP physician talk with the prenatal care and pediatric care provider regarding methadone and nursing. It may be helpful to share with these providers a good review article on the topic. (Jansson, Velez & Harrow 2004). 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 can experience logistical problems with nursing. It may be difficult for the baby to achieve the necessary alert and aware stage; positioning may be awkward because of hypertonicity and nasal stuffiness may frustrate the baby's efforts to remain latched (Jansson, Velez & Harrow 2004).

Postpartum Changes

After delivery, many women find they are exhausted and achy, easily upset and emotional. Some experience frequent and severe episodes of diaphoresis. These symptoms remind many opioid-dependent women of opioid withdrawal. Preparing a woman for these changes before delivery can prevent her from becoming anxious and using the symptoms as a reason for relapsing. For many women, the baby's being inside of them provides strong motivation to avoid use; post-delivery, some women experience a return of cravings that may be aggravated by coping with a demanding infant. Discussing these issues prior to delivery is vital, so that each woman has a chance to think through how she will handle them in a healthy way.

Post-partum depression also puts a woman at risk of relapse. Women should be counseled regarding the symptoms and provided early assessment and treatment if depressive symptoms occur. Because of the many changes going on in a woman's body after delivery, it is best to avoid tapering the methadone dose during the first 6 weeks postpartum, unless the patient finds she is sleepy on her dose. Split dosing may need to continue for 6 weeks postpartum until normal methadone metabolism is resumed. Some women may be rapid metabolizers even when not pregnant and will require on-going split dosing to remain stable.

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. This visit provides a valuable opportunity to assess the patient's stability in recovery, as well as to evaluate the suitability of her methadone dose and to screen for post-partum depression.

Patients having problems should be seen promptly. The patient's counselor and dispensing staff may be asked to alert the MD if they have concerns. Post-delivery, some women report sleepiness on a dose that was therapeutic during the pregnancy. A reduction of the methadone dose by 5-10% (depending on the severity and duration of drowsiness) may be made immediately. If the patient is experiencing increased cravings or fears relapse, a dose increase may be necessary. The patient should be re-evaluated within 5-7 days to determine whether further dose adjustment is needed.

Post-delivery, some women report sleepiness on a dose that was therapeutic during the pregnancy.

Because of the post-partum hormonal changes and fatigue associated with the delivery process and caring for a new baby, a woman may experience a constellation of symptoms that reminds her of opioid withdrawal. These symptoms may include sweats, myalgias and arthralgias, mood swings and irritability. A careful history focusing on the nature of the symptoms, the time of onset of symptoms and whether they are relieved by the morning methadone dose will help to clarify the source. Reassurance should be provided that the symptoms associated with hormonal changes will resolve in about 6 weeks.

Contraceptive choices should be reviewed, and the physician should ensure that follow-up OB care occurs and that the baby has a pediatric care provider following discharge from the hospital. **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 and be prepared to treat the baby in this unusual event.

The physician should explore the patient's progress in recovery. Patients should be counseled concerning the benefits of remaining in treatment and strongly encouraged to participate consistently in group or individual counseling to support ongoing abstinence. Treatment is the best assurance that relapse will not compromise a mother's ability to provide appropriate care for her new baby.

Conceiving 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 opiate dependence, outcomes with methadone maintained pregnancies are good, and there are no known long-term negative consequences to children exposed to methadone. Contraceptive counseling should be provided to all women on methadone. Women can be assisted to try to taper off methadone prior to a planned pregnancy to see if such a plan can successfully avoid the complication of methadone dependence without jeopardizing the woman's

recovery. But the reality is that pregnancies will occur on methadone. In a recent study of 83 women who delivered babies in a Sacramento methadone program with a special pregnancy program, 26 (31%) were in treatment at the time of conception (McCarthy et al. 2005). These 26 women who conceived while on methadone had the best drug treatment and obstetrical outcomes, with lower levels of drug use, higher birth weights, and lower rates of treatable NAS (40%) than 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 whole pregnancy, there were better outcomes and less risk for NAS. This information should be part of the information conveyed to women to relieve some of the concerns about conceiving on methadone.

Discontinuing Methadone Treatment During Pregnancy

Methadone withdrawal during pregnancy should be avoided unless there is an irresolvable indication for it. Such indications are rare but include the situation when a woman is missing so many doses that it is impossible to achieve a stable blood level. Every effort should be made to ascertain and alleviate barriers to regular dosing prior to withdrawing the patient from methadone. In some cases, the woman is missing doses due to a chaotic home environment, transportation problems, or ongoing drug use. These patients may benefit from residential treatment, provided methadone dosing can continue while the patient is in the facility. A patient who is violent toward program staff or other patients or makes a threat of violence may need to be withdrawn from methadone if transfer to another program is not possible.

Pregnant women should not be withdrawn from methadone maintenance for issues such as sporadic attendance at program services (other than dosing), or failure to remain free of illicit drug use, provided her use is not putting her at high risk of overdose. Methadone maintenance is associated with a significant reduction in both 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 a woman in treatment are often successful. Programs that provide parent education, childcare and transportation facilitate participation, especially when a woman has young children.

If Methadone Treatment is Not Available

If a pregnant woman lives in an area where there are no opioid treatment programs, the available options may be limited to referral, detoxification, or treatment with sublingual forms of buprenorphine. The treatment of pregnant women with buprenorphine is discussed in Appendix C. Buprenorphine is a Category C medication and, as such, is not the treatment of choice, but may be preferable to illicit opioid use.

Methadone maintenance is the treatment of choice for opioid addiction during pregnancy, so every effort should be made to encourage and assist the patient to relocate to an area where methadone maintenance is available. In the event that the patient declines or that relocation is logistically impossible, non-

If a pregnant woman lives in an area where MMT is not available, every effort should be made to encourage and assist the patient to relocate.

opioid medications may be used to provide symptomatic relief for withdrawal in conjunction with close, obstetrical monitoring during the withdrawal. The patient's informed consent for the procedure must be obtained.

In the event that the patient requires hospitalization for another diagnosis, methadone may be used to prevent withdrawal while the primary medical condition is treated. Fetal distress responsive only to opioids may be considered a separate indication for administration of methadone to the mother. One can certainly argue that in cases of severe withdrawal, hospitalization and treatment with methadone is both medically appropriate, and at times necessary, to protect both fetus and mother. Fetal withdrawal is arguably the 'other diagnosis' required by regulations to prescribe methadone legally to treat addiction in a medical hospital. Methadone detoxification may be considered if the patient will be in the hospital long enough to accomplish detoxification.

It is strongly recommended that state and federal methadone authorities be contacted for guidance in cases of regulatory impediments to proper care. We are in an era where regulatory barriers to addiction treatment are being removed, and authorities are far more willing and able to make exceptions to allow proper medical care to occur.

In summary, the role of the OTP physician in the treatment of pregnant women:

- **Expedite admission**
 - Ensure that policies are in place to facilitate prompt admissions.
 - To intervene with individual admissions when needed.
- **Facilitate prompt prenatal care** assisting pregnant patients to obtain prenatal care promptly and coordinating care with the provider.
- **Adjust the methadone dose**
 - Throughout the pregnancy to completely suppress withdrawal between doses without sedation, dividing the dose when necessary.
 - After delivery, monitoring for sedation and adjusting the dose if necessary.
- **Provide medical counsel for pregnant patients**
 - To give information regarding the risks and benefits of methadone during pregnancy.
 - To ensure that pregnant patients are aware that symptoms of sedation or withdrawal between doses must be addressed promptly.
 - To advise pregnant patients regarding the risks of substance use (including alcohol and tobacco) during pregnancy.
 - to ensure that patients are aware of the absolute contra indication of the use of partial opioid agonists or antagonists for pain management .
 - To ensure that pregnant women know the symptoms of withdrawal in an infant and understand that emergence of withdrawal requires prompt medical attention by an experienced physician to avoid an adverse outcome.
 - To educate pregnant women about post-partum depression.
- **Educate clinic staff**
 - To ensure that the clinic staff understand the necessity of expediting admission of opioid dependent pregnant women.
 - To ensure that clinic staff are aware that symptoms of sedation or withdrawal between doses must be addressed promptly.
 - To ensure that clinic staff are informed about symptoms of post-partum depression, and enlist clinic staff to assist in monitoring patients for symptoms of depression after delivery and to treat/refer when needed.
- **Advocate for patients** regarding pain management and breastfeeding
- **Coordinate with obstetrical care providers**
 - To ensure provider is aware that the patient is on methadone treatment.
 - To alert to ongoing use/relapse.
 - To ensure that the provider is aware of the absolute contra-indication of the use of partial opioid agonists or antagonists for pain management .
 - To provide contact information to facilitate verification of dose upon hospitalization and discharge.

APPENDIX A – Opioid Detoxification

■ **NOTE** The term detoxification is being used here to be consistent with the language in federal and California regulations. Many programs are re-naming methadone detoxification programs to avoid the connotation of “toxicity” in relation to methadone. New names include “Medically Supervised Withdrawal” or “Medically Managed Withdrawal.”

Detoxification is not complete treatment for opioid dependence. The objectives of detoxification are short term and limited; they are to alleviate discomfort during opioid withdrawal and to allow the physician to identify concurrent medical disease and to refer for other forms of treatment. Clinical consensus and available research data suggest that the majority of patients do not complete detoxification or relapse shortly after its completion. Nonetheless, detoxification has been accepted as a necessary option as not all opioid dependent patients are eligible and appropriate for MMT, and not all opioid dependent patients are willing to consider it. In view of the danger of the spread of HIV and other infectious diseases associated with injection drug use, it is essential that all opioid dependent patients be offered some kind of treatment. Potential patients should be informed of the high rate of relapse and its accompanying danger and should receive information about additional or alternative treatment for opioid dependence, including Narcotics Anonymous and other 12 Step programs where these alternative treatments are available. Patients should not be denied detoxification if they refuse other treatment.

Federal and California regulations regarding detoxification differ. See Table 23. Since May of 2001, federal regulations allow for detoxification treatment lasting up to six months (42 CFR Chapter 1, part 8, subpart 8.2). California regulations limit the duration of detoxification treatment to 21 days (CCR Title 9, Division 4, Chapter 4, Subchapter 1, s.10000 (a) (2)). However in September 2001, the California Department of Alcohol and Drug Programs made allowance for long-term detoxification (up to 180 days) for individual patients with the submission of an exception request (ADP Form 8045). It is also possible to apply for a programmatic exception to allow the admission of patients to long-term detoxification without submitting a separate exception request for each patient. MediCal continues to cover only short-term detoxification (up to 30 days).

California regulations require at least seven days between detoxification treatment episodes. Federal regulations specify that no patient may be admitted to the same detoxification program more than twice in a one year period without a specific federal waiver for that patient. California regulations have no limit on the number of admissions for detoxification. Other than admission criteria, the requirements for patients in extended detoxification are the same as those for patients in methadone maintenance treatment except that federal regulations in addition to California regulations require monthly urine drug screening in this population.

Criteria for Admission to Detoxification Treatment

The purpose of opioid detoxification is to allow a person who is physically dependent on an opioid to stop using without experiencing acute symptoms of withdrawal. Hence verifying the presence of withdrawal is essential in the decision to offer this form of treatment. A positive initial urine toxicology screen is good evidence of recent opioid use, but is neither sufficient nor necessary in and of itself to determine whether detoxification is indicated. To verify opioid dependence, the physician must observe physical signs of opioid withdrawal.

It should be noted that symptoms and signs of opioid withdrawal are subject to the effects of environment (less intense in controlled settings). The earliest manifestations of opioid withdrawal are often subjective and dependent on the amount and timing of the last use prior to evaluation. Table 4 shows the anticipatory, early, and full-blown symptoms and signs of opioid withdrawal. The physician should expect to see at least the early signs of withdrawal. The Clinical Opioid Withdrawal Scale (COWS, see Table 6) is easily administered and can be used to quantify and document the presence and severity of opioid withdrawal.

Table 23 ~ REGULATIONS Concerning Detoxification Treatment: Federal Vs. California

Federal: 42 CFR Chapter 1, part 8, subpart 8.2

California: CCR Title 9, Division 4, Chapter 4, Subchapter 1, s.10000 (a) (2)

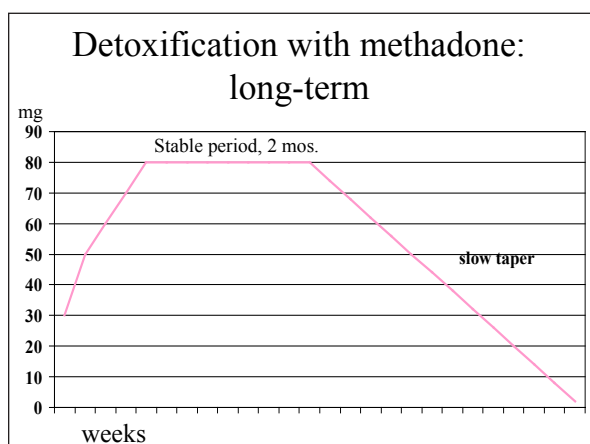
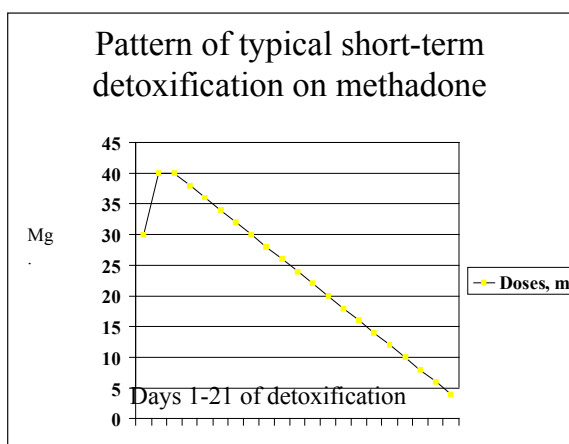
| | Federal Regulations | California Regulations |
|---|---|---|
| Physical Dependence at Admit | Required | Required |
| Duration of Treatment | Short-term: Up to 30 days Long-term: Up to 180 days | Short-term: 21 days Long-term: Waiver required. Long term is up to 180 days. |
| Time Between Detoxification Treatment Episodes | None required | Seven days required |
| Maximum Number of Admissions per year | Maximum of two admissions to the same detoxification program per year | No limit |
| Urine testing requirements | Short-term detox: one at intake Long-term detox: monthly | Short-term detox: one at intake Long-term detox: monthly |
| Take-home dose eligibility | Short-term detox: not eligible Long-term detox: same as MMT | Short-term detox: not eligible Long-term detox: same as MMT |

The physician should document that the patient agrees to detoxification by obtaining written consent for treatment. The physician should verify that patients under eighteen years of age have written consent from their parents or guardians prior to initial dosing.

Although detoxification rarely produces a sustained abstinence from opioids, detoxification can be a first step toward recovery from opioid addiction. Detoxification treatment may delay or prevent a patient from resuming heroin use with the associated risks and harms to the patient, family and society. It may reduce the patient's tolerance to opioids. It introduces the patient to the treatment setting in a non-threatening way and thus may facilitate the patient's entry into maintenance therapy. It gives the OTP physician an opportunity to establish rapport with the patient, to diagnose and treat infectious diseases and other medical complications, to counsel regarding preventive health care and good nutrition and to work with the patient to develop a long-term treatment strategy.

Several detoxification protocols exist (see Table 24). For short-term detoxification, withdrawal must be concluded within 21 days, so the initial dose should not be so high as to make the ensuing reductions steep enough to bring on withdrawal symptoms. Longer periods of detoxification may seem more logical, and indeed at times indicated, but they should not be construed as having better long-term outcomes. (Sees et al. 2000). Longer detoxification schedules allow some months of stabilization at a therapeutic dose and the patient may realize that maintenance treatment works best. Retention in treatment is still the mainstay of any effort to treat a chronic disorder, such as opioid dependence. By the same token, detoxification treatment (of any length) should not be viewed as futile, but rather as a opportunity to meet and engage a patient who might otherwise continue to incur further harm.

Table 24 ~ Two Protocols for Detoxification



Contraindications to Opioid Detoxification

Patients who have complicated medical conditions should be encouraged to seek maintenance treatment if they are able to cooperate and participate in treatment. If they cannot, the physician can consider detoxification treatment.

Methadone maintenance is the treatment of choice for pregnant opioid-dependent women. The physician should screen for pregnancy at admission and if positive refer for methadone maintenance treatment due to the risk of miscarriage or preterm labor and delivery associated with precipitous opioid withdrawal and the risks to pregnancy and baby associated with ongoing illicit opioid use. Pregnant women should also be assisted to obtain prenatal care. (See also the section on Treatment of Pregnant Women.)

In summary, the role of the OTP physician in opioid detoxification:

- **Assess for opioid dependence and document findings** to ensure that the patient's history, physical and laboratory findings are consistent with the diagnosis of opioid dependence and to ensure the historical, physical and laboratory findings are documented in the patient's record.
- **Determine medical fitness for opioid detoxification** to ensure that there is no medical contraindication to opioid detoxification, such as pregnancy (Refer to the section on Treatment of Pregnant Women) or another medical condition.
- **Counsel patients regarding detoxification treatment and alternatives** to ensure that the patient understands the advantages and disadvantages of detoxification compared to opioid maintenance or other treatment alternatives that are available.
- **Obtain informed consent for treatment** to ensure that the patient agrees to detoxification by obtaining written consent for treatment and to ensure that patients under eighteen years of age have written consent from their parents or guardians. Written consents must be obtained prior to the initial dose.
- **Obtain federal or California waivers** prior to admitting patients to detoxification treatment when needed to ensure that the patient meets the admission criteria specified by federal and California regulations or that appropriate waiver(s) are on file.

APPENDIX B – Sublingual Buprenorphine

Buprenorphine is a partial opioid agonist that was first used in an injectable formulation (Buprenex®) to treat pain and later in a sublingual (SL) tablet formulation to treat opioid dependence. The injectable formulation is not approved for the treatment of opioid dependence, and the SL formulation is not approved for the treatment of pain. The buprenorphine SL tablet is available as a monoprodut (Subutex®) or as a combination of buprenorphine and naloxone in a 4:1 ratio (Suboxone®). It is available in 2 mg and 8 mg SL tablets. Buprenorphine has been designated a Schedule III drug.

As a partial opioid agonist, buprenorphine binds to the opioid receptor and produces some opioid effects. It does not have as much opioid effect as a full agonist (methadone or morphine). In addition, it has a ceiling opioid effect, meaning that as the dose is increased, the opioid effect increases, but only to a certain point. Beyond that point, further dose increases do not increase the opioid effect. This ceiling effect decreases the risk of overdose with buprenorphine compared to that of a full agonist. However, if buprenorphine is taken with other sedatives, such as benzodiazepine, alcohol, barbiturates, etc, there is a very real risk of overdose. Overdose deaths have been reported in Europe and are most commonly associated with injectable buprenorphine taken with injectable benzodiazepine such as flunitrazepam. (Gueye et al. 2002; Kintz 2002)

Buprenorphine: Regulations Governing OTP Use for the Treatment of Opioid Dependence

The regulations governing how OTPs may use buprenorphine allow for two approaches.

1. **With the same restrictions that apply to methadone, Federal Regulations 42CFR Part 8** list buprenorphine as a medication that can be used in OTPs, and the Interim Final Rule of 2003 approved buprenorphine to be used under the same regulations that govern the use of methadone (e.g., no take home doses until criteria have been met; no limit on the number of patients who can be treated with buprenorphine in an OTP.) In California, a regulatory exemption allowing OTPs to use buprenorphine as authorized by Federal regulations became effective on January 1, 2005. (Buprenorphine is not covered under Drug MediCal benefits as of September, 2008.)
2. **With the authorization and restrictions under the Drug Addiction Treatment Act of 2000**, OTP physicians, as individuals, can apply for the waiver available under the Drug Addiction Treatment Act of 2000 (DATA 2000) and can treat up to 30 of their own patients with buprenorphine under the authorization and restrictions established by DATA 2000. Some sites with an OTP license also offer “other services.” Buprenorphine treatment according to DATA 2000 restrictions may be offered as one of these additional, non-OTP services, taking advantage of the skill and experience of clinicians who know about opioid addiction and who work in the OTP at the same site.

Admission Criteria / Patient Selection for Treatment with Buprenorphine

Patients dependent on heroin or prescription opioids such as oxycodone, hydrocodone, hydromorphone, etc, are appropriate candidates for treatment with buprenorphine. Buprenorphine is effective in reducing heroin and prescription opioid use.

Patients who have a history of opioid dependence and are at risk for relapse to abuse/dependence may also be good candidates for buprenorphine treatment. This includes patients released from controlled environments who may relapse without treatment.

Contraindications

- Patients abusing alcohol or sedative hypnotics. Use/abuse of alcohol or sedative hypnotics in combination with buprenorphine increases the risk of respiratory depression and may compromise the safety of buprenorphine treatment. Continuing abuse or dependence on CNS depressants (alcohol, sedative-hypnotics) should be considered a relative contraindication to buprenorphine treatment. Patients may need a medically managed withdrawal to safely discontinue alcohol or other sedatives. There are reports of deaths associated with the combination of buprenorphine and benzodiazepine. These reports have been limited to patients with IV use of buprenorphine and benzodiazepine. No reports of deaths have come from the US studies. However, caution is warranted. (Brooner et al. 1997)
- Patients who are pregnant. Methadone is the treatment of choice for pregnant, opioid dependent women. (See Section on Treatment of Pregnant Women.)
- Patients with very high tolerance may require a full agonist (i.e., methadone) to stabilize. There is no direct measure of tolerance, and cross tolerance between different opioids is not complete, so a therapeutic trial with buprenorphine may be reasonable even in heavy users.

Buprenorphine and Pregnancy: Data and Recommendations

Methadone maintenance continues to be the treatment of choice for opioid dependent pregnant patients. Buprenorphine is labeled as pregnancy category C because of limited data regarding its use in humans during pregnancy. To date, there is insufficient evidence to establish the safety of buprenorphine during pregnancy. Preliminary studies indicate that buprenorphine may be as safe as methadone. Neonatal abstinence syndrome (NAS) may occur earlier and be of slightly shorter duration with buprenorphine (Jones et al. 2005). Buprenorphine studies in pregnancy have been limited by small numbers, low medication doses (methadone and buprenorphine) and/or by participants' concurrent use of non-opioid drugs. The few case studies and ongoing small research studies do not show any adverse effects, and it is possible, that in future, buprenorphine will be useful in pregnancy. (Johnson, Jones & Fischer 2003) (Lacroix et al. 2004).

The ideal setting for opioid dependent pregnant women is an OTP that specializes in the treatment of this population. Prompt prenatal care is

essential with coordination between the prenatal care provider and the physician treating opioid dependence. Pregnant patient should be referred for prenatal care as soon as pregnancy is diagnosed and assisted to obtain an appointment in a timely fashion.

Pregnant opioid dependent patients, not yet in treatment and seeking buprenorphine, should be immediately referred to a specialized treatment program for opioid dependent pregnant women if it is available. Advise the prenatal care provider of the patient's opioid dependence and the delay in or lack of appropriate treatment.

Under most circumstances, patients who become pregnant while maintained on buprenorphine should be referred to a methadone clinic, since buprenorphine is not approved for use in pregnant women. If methadone treatment is not available for some reason, or if the patient declines to be transferred to methadone, she should be counseled about the risks and benefits of continued buprenorphine treatment and should be changed to the buprenorphine monoproduct to minimize risk of naloxone exposure. While naloxone is not a known teratogen, its safety has not been established, so exposure of the fetus should be minimized to avoid potential risk. The patient's record should include documentation that she has been counseled regarding the risks and benefits of methadone vs. buprenorphine treatment during pregnancy.

Induction Dosing with Buprenorphine for the Treatment of Opioid Dependence

The goal of induction is to safely suppress inter-dose opioid withdrawal as rapidly as possible with adequate doses of buprenorphine. The same induction procedures for sublingual buprenorphine tablets are applicable for initiating maintenance or detoxification.

Because buprenorphine is a partial agonist with a ceiling opioid effect, a buprenorphine induction regimen can be more aggressive than induction with a full agonist such as methadone. The risk of serious adverse effects such as overdose or treatment dropout is greater if patients are under-treated with buprenorphine and continue to manage symptoms of withdrawal by using outside opioids, alcohol or other sedative-hypnotics. Overdose risk is particularly high if the patient uses benzodiazepine. Deaths have been reported in Europe and are most commonly associated with injectable buprenorphine taken with injectable benzodiazepine such as flunitrazepam. (Gueye et al. 2002) (Kintz 2002).

In the US, the practice of observing the first induction dose of buprenorphine evolved from the clinical trials. There is no specific requirement in law or clinical practice that the first dose be administered in the office. Advantages of observing the first dose include increased assurance that the first dose is delayed until the patient is observed to be in sufficient opioid withdrawal. Observed dosing provides an opportunity to teach the patient how to take the sublingual tablet. Most patients can master sublingual ingestion, but may need coaching at first with instructions such as, "don't talk, don't swallow" during the ten to twenty minutes it generally takes for the tablet to dissolve under the tongue. Disadvantages include the necessity of patients getting themselves to

the office while in opioid withdrawal and needing to arrange transportation home in the event it is inadvisable for them to drive after the first dose.

Induction can usually be completed in 2-3 days. In some cases, it may take an additional day or two. Most patients will be able to be stabilized on 2-16 mg of buprenorphine/naloxone daily. Some patients will require 24 mg; the maximum dose is 32 mg.

In the event that the dose stops working suddenly with no apparent explanation, the patient's dosing technique should be observed. The most common reason is failure to take the dose sublingually; the patient may be swishing and swallowing the tablet or may be talking or eating while dosing.

The initial clinical trials used the buprenorphine mono-product (Subutex®) during induction and then switched to the buprenorphine/naloxone combination product (Suboxone®) when the patient was stable enough to begin dosing outside of the office. Since that time, experience has shown that the buprenorphine/naloxone combination product (Suboxone®) may be used when inducing patients as the naloxone is not significantly bioavailable. Several studies have used exclusively buprenorphine/naloxone (Suboxone®) with documented safety and efficacy. (Fudala et al. 2003) (Stoller et al. 2001)

Table 25 ~ Buprenorphine Induction: Steps for Inducing Patients Dependent on Short-acting Opioids Such as Heroin, Oxycodone

1. Provide Information sheet about induction. Instruct the patient to present to the clinic in moderate withdrawal.
2. On **Day 1**, delay the first dose until moderate opioid withdrawal symptoms have developed. Consider use of opioid withdrawal scales for patient assessment. Remind patients that opioid withdrawal symptoms are usually alleviated in 20-40 minutes following the first dose of buprenorphine.
3. Teach the patient how to take a sublingual tablet.
4. Administer the first dose and observe for patient response. For patients who are physically dependent on short-acting opiates, the first dose is usually 4 mg of buprenorphine. but ranges from 2-8 mg.
5. If symptoms of withdrawal are suppressed after the first dose, additional doses of buprenorphine may be dispensed or prescribed (2mg or 4mg tablets are usually used on the first day) to be taken later in the day, at bedtime or the following morning. **Remind the patient that use of opioids during buprenorphine induction may make opioid withdrawal symptoms more protracted. Some patients may be too unstable to manage a take-home dose safely. Some clinics require the patient to come into the clinic for observed ingestion for the first three days, with no take-homes.**
6. If signs of withdrawal persist after the first dose, an additional dose, usually 4 mg, but ranging from 2-8 mg, is given and patient response observed. Additional doses of buprenorphine may be dispensed or prescribed to be taken later in the day, at bedtime or the following morning.
7. **Based on doses used in the clinical trials, the CSAT guidelines** (available in TIP 40, "Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction") **recommend that the total dose on day 1 be no higher than 8mg.** Experienced clinicians have found that doses of 16 mg may be safely used on the first day.
8. On **Day 2**, assess patient's response to the first day's dosing. If opioid withdrawal symptoms were fully suppressed, and the patient experienced no sedation, and no symptoms of withdrawal between doses then hold at the total dose given on day 1. If the patient experienced sedation, decrease the dose. If the patient experienced symptoms of withdrawal, increase the dose by 4-8 mg. The patient may be dosed in clinic and observed at peak (~2 hrs) or sent home with additional dispensed or prescribed doses to be taken later in the day. At higher doses, 8mg tablets are more convenient and cost effective. The patient may be given a prescription for or supply of enough medication until the next clinic visit.
9. **Based on initial studies, the CSAT guidelines recommend that the total dose on day 2 not exceed 16 mg.** Experienced clinicians have found that 24 mg may be safely given.
10. On **Day 3**, assess patient's response to second day's dosing. If opioid withdrawal symptoms were fully suppressed and patient is feeling no withdrawal between doses, then keep dose at day two level; otherwise increase further.
11. After Day 3, if patient is still experiencing opioid withdrawal symptoms or is using outside opioids, re-evaluate. Is the patient actually letting the tablet dissolve? Is there a measurable effect after the dose? If the patient is correctly taking sublingually 24 mg and is still in documented opioid withdrawal, consider increasing the dose to the maximum recommended of 32 mg and re-evaluating.

Transfer to Buprenorphine from Methadone

Patients who are doing well on methadone should be encouraged to stay in treatment with methadone. The process of transitioning to buprenorphine is destabilizing because patients will have to experience symptoms of opioid withdrawal, putting them at increased risk of relapse until they can be re-stabilized on a therapeutic dose of buprenorphine.

For patients who choose to transfer from methadone to buprenorphine, a taper of the methadone dose is generally recommended, as methadone's long-action and high tissue stores can lead to precipitated (relative) withdrawal upon buprenorphine ingestion. Buprenorphine has a stronger attachment to the opioid receptor than methadone and will displace the methadone.

“The key to a smooth transition is not the length of time since the last methadone dose, but rather how much objective withdrawal the patient is experiencing when he or she comes for the first buprenorphine dose.”

(Physician Clinical Support System (PCSS) Guidance) www.pcssmentor.org.

Pupil size is a very sensitive and objective sign of opioid status. While baseline pupil size varies somewhat from one patient to the next, a given patient's pupil size will increase as withdrawal progresses.

The care of patients being treated in a methadone maintenance program should be coordinated with the program until the last day of methadone dosing at the program. There should also be a discussion with the methadone program about the possibility of the patient needing to transfer back to methadone in the event that they are unable to stabilize on buprenorphine.

The transfer is usually accomplished in one of two ways. One method involves tapering the patient's methadone dose to 30 mg and holding the dose there for one week to allow a new lower steady state to be established. At the end of the week, methadone is discontinued, and the patient is evaluated daily until moderate symptoms of opioid withdrawal have developed (usually 24-48 hours). Patients may experience significant opioid withdrawal symptoms while the methadone dose is being decreased to 30 mg/day and during induction. As a practical matter, it will be very difficult for some methadone maintained patients to get down to 30 mg/day for the switchover to sublingual buprenorphine.

The second method is to taper the methadone dose as much as can be comfortable tolerated and then discontinue methadone completely and observe the patient daily until moderate opioid withdrawal symptoms have developed. This approach shortens the duration of opioid withdrawal symptoms.

There are some medical situations that may make it necessary for methadone to be abruptly and permanently discontinued (notably, some cardiac arrhythmias). However, the patient may not be medically able to tolerate emerging symptoms of withdrawal until his or her medical condition has been stabilized. In the long-term, the patient may need to be on maintenance agonist treatment to avoid relapsing.

In this situation, a third method of transition from methadone to buprenorphine may be indicated. When the patient's methadone is discontinued, a shorter-acting opioid (such as morphine) may be started to prevent withdrawal. Once a comfortable dose of the short-acting opioid has been established, the patient should continue on this dose for about a week

to allow the methadone to be cleared. After this, and when the patient is medically able, the short-acting opioid may be discontinued and the patient observed until moderate signs and symptoms of opioid withdrawal have emerged and buprenorphine can be started.

As a rule, this method involving short-acting opioids is not appropriate for routine use in outpatient settings. Federal and California regulations do not allow the use of opioid medications other than methadone or buprenorphine for the treatment of opioid addiction. However the use of short-acting opioids may be unavoidable in a hospitalized, seriously ill patient to prevent life-threatening destabilization when methadone must be abruptly discontinued and buprenorphine cannot be safely initiated. In this situation, the short-acting opioid is not being used to treat the addiction per se, rather it is part of a larger treatment strategy to stabilize a patient's medical condition. When in doubt a consultation with the California and/or federal methadone authority may be helpful.

With any approach, patients transferring from methadone to buprenorphine may have significant opioid withdrawal symptoms. **Patients must understand that delaying the first dose until moderate symptoms of withdrawal are present ensures that the medication will suppress rather than precipitate withdrawal.** Presenting patients with the available options will allow them to select the method least disruptive to their schedule and to arrange obligations accordingly.

Whether the patient has been at 30mg for a week or discontinued methadone abruptly, induction to buprenorphine must be delayed until moderate symptoms of opioid withdrawal are observed. A standardized opioid withdrawal scale may be used to evaluate the severity of withdrawal. The patient should be instructed to come into the clinic daily for evaluation. Because the rate of metabolism of methadone is highly variable between patients, opiate withdrawal may develop within the first 24 hours after a methadone dose for some patients, but may not occur for several days for others. When moderate opioid withdrawal is clinically observable, the induction process may begin, using the same steps as those used for inducing patients dependent on short-acting opioids.

Maintenance Dosing on Buprenorphine/Naloxone

The goal of maintenance is to prevent the emergence of inter-dose opioid withdrawal symptoms, to suppress the patient's craving for opioids, and to greatly attenuate the effect of self-administered opioids in patients who continue to episodically use illicit opioids.

The appropriate maintenance dose is variable but for most patients will be in the range of 12-24 mg /day. During maintenance, most patients are able to take buprenorphine once/day, but some patients feel more comfortable on a twice/day schedule.

Less frequent than daily dosing regimens have been used but are applicable primarily in a clinic setting with observed dosing. Several studies have shown that alternate day, or three times a week doses are effective, if the in between days' doses are added to the observed day's dose. (Amass, Kamien & Mikulich

2001) For self-administered medications, adherence to a daily dosing regimen is likely to be higher and will usually produce fewer withdrawal symptoms between doses.

After induction, dosing adjustments can generally be made in 2 mg/day increments. Because buprenorphine has a long plasma half-life and an even longer duration of action at the mu opiate receptor, 5 days should be allowed between dose adjustments to assess the effect of the new dose following adjustment.

As Suboxone® has less potential for intravenous abuse, most patients should be maintained on Suboxone® during maintenance to minimize diversion/misuse of medication.

Managing Acute and Chronic Pain for a Patient Taking Buprenorphine

The principles of pain management for a patient who is taking buprenorphine are very similar to those for a patient on methadone maintenance.

Buprenorphine maintenance therapy provides little, if any analgesia for acute pain. Buprenorphine maintenance therapy, like other opioid maintenance therapy, produces neural changes – tolerance and hyperalgesia, meaning opioid-induced increased sensitivity to pain. As a result, when opioid analgesics are used, they will need to be administered at higher doses and more frequent intervals. In addition, the high attachment of a partial agonist (buprenorphine) to the opioid receptor poses at least theoretical potential problems in a patient who is in pain and needs more opioids.

Acute Pain

Consider in advance how unanticipated acute pain (e.g., emergency surgery) will be managed for patients maintained on buprenorphine. General principles: use non-pharmacological pain-relieving interventions aggressively. Use multimodal analgesia (i.e., NSAIDs and acetaminophen) and adjuvant analgesics (like tricyclic antidepressants) to enhance effects of opioid medication. Use scheduled or continuous dosing, not prn, to avoid allowing re-emergence of pain. Consider regional analgesia. When opioid analgesia is required, it can be used in a variety of ways.

- Continue buprenorphine and add short-action opioid analgesics (for pain of short duration).
- Divide the regular buprenorphine dose and administer every 4-6 hours. Consider adding a short acting opioid or increasing the buprenorphine dose.
- Discontinue buprenorphine and use other opioids to avoid opioid withdrawal. Add pain management to this (SR and IR morphine.) When pain management is no longer needed, discontinue pain medication and methadone and re-induce with buprenorphine.
- Discontinue buprenorphine and start methadone, usually 30-40 mg of methadone/day, increasing by 5-10 mg/day to control withdrawal. Add other opioids for pain relief. When pain management is no longer needed, discontinue pain medication and methadone and re-induce with buprenorphine (Alford, Compton & Samet 2006)

Chronic pain

Patients maintained on buprenorphine may also suffer from chronic pain. While the sublingual forms of buprenorphine are approved by the FDA for treatment of opioid dependence, they are not approved for the treatment of chronic pain. Their use for the sole indication of pain would be an “off label” use.

Buprenorphine’s strong attachment to the opioid receptor may interfere with use of additional opioids. If additional opioid medications are to be used in the treatment of chronic pain, consider switching the patient from buprenorphine to methadone for maintenance medication. Dividing the daily dose of buprenorphine or methadone, so that it is taken 3 or even 4 times/day may also be helpful. This will provide more stable blood levels; pain is aggravated by withdrawal. In addition, some patients do notice improvement in pain for the first 4-6 hours after dosing.

Ambulatory Discontinuation of Buprenorphine

In general, the principles for medically supervised withdrawal from methadone apply to medically supervised withdrawal from buprenorphine.

Medical indication to Discontinue

If a patient cannot be stabilized on buprenorphine, the patient should be referred for treatment with methadone.

Voluntary Withdrawal from Buprenorphine

When the patient wants to discontinue pharmacotherapy, a discontinuation trial can be planned. Although there is little evidence-based guidance on medically supervised withdrawal from buprenorphine, in general, a slower taper schedule (longer than one month) is to be preferred over a shorter one (less than 1 month). Tapering over a period of one month or longer may provide a more comfortable experience for the patient. The goal is to discontinue maintenance treatment while minimizing the risk that the patient will relapse to opioid abuse. Psychosocial treatments should continue throughout the period of the taper and preferably after buprenorphine has been discontinued. The long-term relapse rates after buprenorphine withdrawal are unknown.

Suggested Procedures for Medically Supervised

Withdrawal from Buprenorphine

- Decrease buprenorphine in 2 mg increments (not more frequent than weekly) and assess the effect on the patient’s opioid use/craving, inter-dose opioid withdrawal, and overall well-being.
- If a dose decrease results in inter-dose opiate withdrawal, increase the frequency of dosing to bid or tid
- If a dose decrease induces increased opioid cravings/use or a decrement in patient’s overall well being, increase the daily dose by 2 mg and try to decrease again after several weeks.
- In the event that repeated taper attempts are unsuccessful, re-stabilization on a therapeutic dose is indicated.

Generally discontinuation of treatment for opioid dependence is associated with a high risk of relapse. Patients should be cautioned of this prior to taper attempts and encouraged to return to treatment in the event of return to illicit opioid use or fear of imminent relapse.

Use of Buprenorphine for Opioid Detoxification

Studies published in recent years show that Suboxone® for short-term detoxification is well tolerated and feasible in a variety of settings, including outpatient (Amass et al. 2004) In addition, studies conclude that for detoxification, buprenorphine is more effective than clonidine, methadone and dihydrocodeine, meaning that patients have less symptoms and side effects during the detoxification with buprenorphine, and are more likely to complete the detoxification and to enroll in outpatient treatment. (Caldiero et al. 2006; Gowing, Ali & White 2006; Kovaš et al. 2007; Ponizovsky et al. 2006; Reed et al. 2007; Wallen, Lorman & Gosciniak 2006).

However, it has not been established that long-term abstinence is an anticipated outcome. One study (Wright et al. 2007) that compared opioid detoxification with buprenorphine vs. dihydrocodeine showed that the majority of patients in both groups did not complete the detoxification and that very few patients were abstinent at completion, at 3 months and at 6 months. Another study (Kornor, Waal & Sandvik 2007) compared the rate of opioid abstinence, substance use and psychosocial performance amongst completers vs. non-completers of a 9-month buprenorphine program and amongst participants who were in agonist therapy vs. those who were not. The authors concluded “Retaining patients in agonist replacement therapy over time is more likely than completion of a time-limited program to influence long-term outcomes. Time limited buprenorphine replacement therapy appears to be inappropriate for persons with opioid dependence.”

APPENDIX C – Office-Based Opioid Agonist Treatment (OBOT)

Office-based treatment with methadone usually takes the form of “medical maintenance” – a model in which the OTP refers a suitable methadone maintenance patient to an office-based setting where a qualified physician continues to provide the methadone and perhaps other aspects of care as well. In this model, there is a close affiliation between the office practice and the OTP that refers patients. OBOT physicians must be affiliated with a sponsoring OTP, and there should be a well-functioning collaborative relationship between the OBOT physician and the OTP clinical staff.

The Benefits for the Patient

There are at least two benefits to the patient. First, general medical and/or psychiatric care can be integrated with treatment of opioid dependence. Second, the potential for “graduation” to a less structured, more convenient setting can be a motivating element to a patient.

Feasibility/Efficacy

Mintzer et al studied the safety and efficacy of treating opioid addicted patients in two non-research, primary care settings, a neighborhood health center and a hospital-based primary care clinic and concluded that opioid addicted patients can be treated safely and effectively in these settings (Mintzer et al. 2007).

Alford et al studied the efficacy of office-based buprenorphine treatment for homeless opioid addicted patients. Comparing homeless to housed patients, they found similar outcomes in terms of treatment failure, illicit opioid use and participation in substance abuse treatment (counseling and self-help groups.) The homeless group had more severe addiction histories, more comorbidities and more social instability. The homeless patients needed more clinical support from a nurse care manager during the first month of treatment. At the end of one year, 36% of the homeless were no longer homeless (Alford, Compton & Samet 2006) (Alford et al. 2007)

Frequency of Clinic Visits

To date, the optimal intensity of counseling and frequency of clinic visits for medication pick-up have not been established. In 2006 Fiellin et al compared the clinical efficacy of brief weekly counseling plus either once weekly or thrice weekly medication dispensing with extended weekly counseling plus thrice weekly medication dispensing.(Fiellin et al. 2006) They found no significant outcome differences in terms of treatment retention, compliance with dosing illicit opioid use and maximum number of consecutive weeks of abstinence.

How to Establish an OBOT Program

Exemptions must be requested from CSAT by OTPs. The first step is to establish a relationship with a qualified physician. The American Society of

Addiction Medicine recommends that the physicians selected to provide OBOT with methadone should have completed certain (relevant) training. (2004 ASAM Public Policy Statement “Opioid Agonist Treatment in Office-based Practice” available from ASAM website www.asam.org.) The second step is to develop a protocol. The third step is to apply to CSAT for the necessary exemption. The application takes the form of a letter; no application form is used. Address the letter to Office of Pharmacological Therapies, CSAT, 1 Choke Cherry, Rm 2-1075, Rockville, MD 20850

California statutes adopted by the legislature in 2000 (SB1807) authorize OBOT programs in California, but not until the California Department of Alcohol and Drug Programs develops regulations for them. As of September 2008, the Department has not prepared such regulations. (California Health & Safety Division 10, Chapter 9.8, section 11877.2)

APPENDIX D – Sample Forms

Initial Medical History and Physical Examination / Treatment Disposition

■ **NOTE** This form is designed to be comprehensive, It may not be necessary or desirable to include all of these questions in every clinic setting.

Name: _____ **Sex:** _____ **Occupation:** _____
Date of Birth: _____ **Age:** _____ **Marital Status:** _____

Allergies to Medication(s)?

Describe reaction: _____

Substance Abuse History

Opiates: Type(s): _____
 Age at First Use: _____ Route(s) of Administration: _____
 Current Use–Duration: _____ Usual Daily Amount: _____
 Date of Last Use: _____ Time: _____ Amount: _____
 Previous Use and Treatment History: _____

Other Drugs: (Ask about methamphetamine, cocaine, marijuana, PCP, LSD, mushrooms, ecstasy, benzodiazepines, other prescription drugs, over-the-counter sleeping pills and inhalants)

| | | | |
|--------------------------|-------|-------|-------|
| Type(s): | _____ | _____ | _____ |
| Route of Administration: | _____ | _____ | _____ |
| Age at First Use: | _____ | _____ | _____ |
| Date of Last Use: | _____ | _____ | _____ |
| Frequency: | _____ | _____ | _____ |
| Type(s): | _____ | _____ | _____ |
| Route of Administration: | _____ | _____ | _____ |
| Age at First Use: | _____ | _____ | _____ |
| Date of Last Use: | _____ | _____ | _____ |
| Frequency: | _____ | _____ | _____ |

MD Signature: _____ Date: _____
 Patient Name: _____ ID# _____

Cigarettes: Ever smoked? _____ Age when started _____ # per day now _____

Have you ever tried to cut down or quit smoking? _____ How?/When?/For How long? _____

Are you interested in quitting or cutting down now? _____

If yes, how? _____

Alcohol: (ask about wine coolers, beer, wine and liquor) _____

Age/experience when **first tasted** alcohol? _____

Last drink (when/what/how much?) _____

Ever been intoxicated? _____ How many drinks does it take? _____

Last intoxicated? (when/what/how much?) _____

Current Pattern: (what/how many/how often?) _____

Do you feel okay if you don't drink for a day or more? _____

Past Pattern, if different than now (when/what/how many/how often?) _____

Ever felt concerned about your alcohol use? (If yes, when/why?) _____

Hx DUI? (when?) _____ Loss of job/relationship? _____

Medical problems related to alcohol? (include accidents/ER visits) _____

Ever drink daily? _____ When? _____

Ever experienced alcohol withdrawals? _____ When? _____

Symptoms: _____ shaking _____ nausea _____ vomiting _____ hallucinations _____ seizures

Ever hospitalized or given medication for alcohol withdrawals? _____

MD Signature: _____ Date: _____

Patient Name: _____ ID# _____

Current Medical Providers of Care

Primary Care? _____

Ob/Gyn? _____

Psychiatrist? _____

Other? (Specialty?) _____

Recent Medical Care? (if yes, provider and reason): _____

Medications/Purpose (Ask about prescription, OTC and herbal): _____

Dentist: _____

Last dental care (when/reason): _____

Infectious Disease

Date of Last **Tetanus Booster?** _____ Flu shot? _____

Date of Last **TB skin test?** _____ Result? _____

Have you ever had a **positive TB test** (PPD skin test)? _____

If yes, CXR(date/location/result): _____

Symptoms of active TB? _____ fever _____ weight loss _____ chronic cough _____ night sweats

Any Treatment? _____ If yes, _____ **to treat** active TB OR _____ **to prevent** getting active TB

If treated, When? Did you complete treatment? _____

Date of **last exposure:** _____

_____ Blood (Transfusion/Accident) _____ Someone else's Needle/Paraphernalia

_____ Unprotected Sexual Contact _____ Someone else's shaver/toothbrush

Hepatitis (date/type(s): _____

Vaccinated for Hepatitis A/B? _____ Series complete? _____

Hepatitis C status? _____

Date/result of last **HIV test?** _____

Testing Recommendations: Hepatitis B Hepatitis C HIV

MD Signature: _____ Date: _____

Patient Name: _____ ID# _____

Past Medical History

- Kidney problems Breast lumps/tumors Hypertension
- Thyroid problems Epilepsy/Seizures Cancer
- Liver Disease Heart Disease Lung Disease
- Diabetes Endocarditis Stomach ulcers

Other PMH/Comments: _____

Operations/Surgeries? (Date? Type?) _____

Hospitalizations? (Endocarditis? Overdose? Trauma? Other?) _____

Family History (Heart disease? HTN? Diabetes? Cancer? Addiction to Alcohol/Other Drugs?)

Who/What? _____ Age at Dx _____

Who/What? _____ Age at Dx _____

Who/What? _____ Age at Dx _____

Mental Health

Are you currently having **any problems** with

- Sleep Appetite Ability to concentrate
- Mood Irritability Crying spells

Are you **under the care of a doctor** for depression, anxiety or other mental health diagnoses? _____

Are you **taking medication(s)** for depression, anxiety or similar issues? _____

Have you taken medications in the past? (what/when/helpful?) _____

Ever hospitalized for a MH concern? _____

Ever wanted to harm yourself? _____ Someone Else? _____ Suicidal Now? _____

Explain any yes: _____

Are you feeling safe in your current living situation? _____

Is anyone threatening or intimidating you? _____

MD Signature: _____ Date: _____

Patient Name: _____ ID# _____

Ob/Gyn History

Gravida _____ **Para** _____ **SAB** _____ **TAB** _____ **LC** _____

First Day of **LMP**? _____ Was it a Normal Period? _____

Date of **last PAP**? _____ Result? _____

History of Abnormal PAP? (treatment?) _____

History of Breast Lump? _____ When? _____ Dx/Tx: _____

Ever had a mammogram? _____ When? _____ Result? _____

Ever had a Sexually Transmitted Disease? (Chlamydia? Syphilis? Gonorrhea? Herpes? Genital Warts? PID?) If yes, when? Were you treated? _____

Contraception? (current/plans): _____

If Pregnant

Prenatal Care: First appt? _____ Most Recent? _____ Next? _____

Plan if No Care to Date _____

Hospital of Delivery? _____

Considering TAB? _____ Where? _____ Appt scheduled? _____

Cramping? _____ **Spotting?** _____ **Fetal Movement?** _____

Ob Concerns/Complications (PIH, Diabetes, Placenta Previa, Premature labor, IUGR, Planned C/S)? _____

Medication & Drugs used during the pregnancy (especially before pregnancy was diagnosed)

Ask about medications (prescription, OTC, herbal), cigarettes, alcohol and other drugs

What? _____ When _____

What? _____ When _____

What? _____ When _____

What? _____ When _____

Problems with previous pregnancies? (Miscarriage, Toxemia, Diabetes, Placenta Previa, IUGR, Premature Labor/Delivery, C/S)? _____

MD Signature: _____ Date: _____

Patient Name: _____ ID# _____

Review of Systems/Concerns

Mental _____ Neuro _____
 HEENT _____ Dental _____
 Respiratory _____ Cardiac _____
 GI _____ GU _____
 Musculoskeletal _____ Skin _____
 General: _____

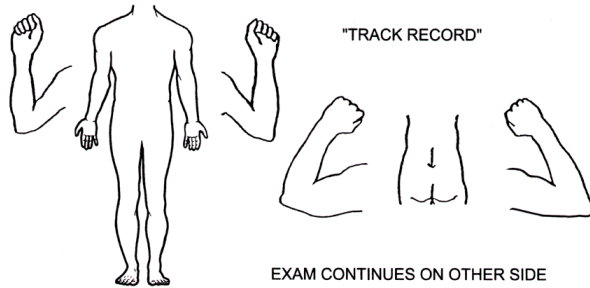
Physical Examination

Date of the Physical Exam _____

Temp: _____ Pulse: _____ BP: _____ Resp: _____ Height: _____ Weight _____

General _____

Skin (incl tracks: location/recent/old) _____



HEENT _____ Pupil Size _____ Reactive? _____
 Dental _____ Neck/Nodes _____
 Heart _____ Lungs _____
 Breast _____ Back _____
 Abdomen _____ Extremities _____
 Genitalia/Rectum _____ Neuro _____
 Other Physical Findings: _____

MD Signature: _____ Date: _____

Patient Name: _____ ID# _____

Opioid Withdrawal: Symptoms & Signs

| | | |
|-------------------|--------------------|-------------------|
| _____ anxiety | _____ irritability | _____ insomnia |
| _____ nausea | _____ cramps | _____ myalgia |
| _____ arthralgia | | |
| _____ yawning | _____ rhinorrhea | _____ lacrimation |
| _____ diaphoresis | _____ piloerection | _____ chills |
| _____ tremor | _____ vomiting | _____ diarrhea |

 Naloxone Administration Waived:

- Naloxone is not indicated due to the presence of opiate withdrawal symptoms/signs at this time
- Transferring Methadone Treatment From: _____
Last methadone dose: _____ mg Date: _____
- Naloxone contraindicated due to pregnancy (documentation of pregnancy on file)

 Naloxone Administration Required:

- Naloxone Consent on File in record
- Protocol completed
 - Withdrawal observed
 - Withdrawal not observed

Admission Labwork

- Blood drawn
- Blood waived Unable to draw Recent labs OK
- Urine Tox Screens complete
 - On Site Rapid Opiate Screen: Positive Negative
 - VMC/Toxicology Opiates Methadone Other Drugs
 - Multi-Reg check requested

MD Signature: _____ Date: _____

Patient Name: _____ ID# _____

Treatment Disposition***Admit to Methadone Maintenance Treatment (MMT)***

- Based upon the medical history, physical examination, and laboratory findings, it is determined that this patient is currently physiologically dependent upon opiates, has been addicted to/continuously dependent on opiates for all or most of the year prior to this date, and is fit for methadone treatment.
- Patient is admitted to methadone maintenance due to pregnancy.
 - SAMHSA exception required; Form SMA-168 on file.
 - California exception required; California exception on file.
- Patient is currently opioid dependent, does not meet regulatory requirements for MMT, and is at risk of life or health-endangering problems if MMT is withheld.
 - SAMHSA exception required; Form SMA-168 on file.
 - California exception required; California exception on file.

Initial Dose: _____ Observation: _____

Comments: _____

Physician signature: _____ Admission Date: _____

Admit to Medically Supervised Withdrawal (MSW)

- Admit to short-term detoxification (maximum of 30 days)
- Admit to long-term detoxification (maximum of 180 days)
- Based upon the medical history, physical examination and laboratory findings, it is determined that this patient is currently physiologically dependent on opiates and is fit for methadone treatment.

Initial Dose: _____ Observation: _____

Comments: _____

Physician signature: _____ Admission Date: _____

MD Signature: _____ Date: _____

Patient Name: _____ ID# _____

Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-AR)

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT OF ALCOHOL SCALE, REVISED (CIWA-AR)

Patient: _____ Date: _____ Time: _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute: _____ Blood pressure: _____

NAUSEA AND VOMITING — Ask “Do you feel sick to your stomach? Have you vomited?” Observation.
 0 no nausea and no vomiting
 1 mild nausea with no vomiting
 2
 3
 4 intermittent nausea with dry heaves
 5
 6
 7 constant nausea, frequent dry heaves and vomiting

TREMOR — Arms extended and fingers spread apart. Observation.
 0 no tremor
 1 not visible, but can be felt fingertip to fingertip
 2
 3
 4 moderate, with patient’s arms extended
 5
 6
 7 severe, even with arms not extended

PAROXYSMAL SWEATS — Observation.
 0 no sweat visible
 1 barely perceptible sweating, palms moist
 2
 3
 4 beads of sweat obvious on forehead
 5
 6
 7 drenching sweats

ANXIETY — Ask “Do you feel nervous?” Observation.
 0 no anxiety, at ease
 1 mild anxious
 2
 3
 4 moderately anxious, or guarded, so anxiety is inferred
 5
 6
 7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

AGITATION — Observation.
 0 normal activity
 1 somewhat more than normal activity
 2
 3
 4 moderately fidgety and restless
 5
 6
 7 paces back and forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCES — Ask “Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?” Observation.
 0 none
 1 very mild itching, pins and needles, burning or numbness
 2 mild itching, pins and needles, burning or numbness
 3 moderate itching, pins and needles, burning or numbness
 4 moderately severe hallucinations
 5 severe hallucinations
 6 extremely severe hallucinations
 7 continuous hallucinations

AUDITORY DISTURBANCES — Ask “Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?” Observation.
 0 not present
 1 very mild harshness or ability to frighten
 2 mild harshness or ability to frighten
 3 moderate harshness or ability to frighten
 4 moderately severe hallucinations
 5 severe hallucinations
 6 extremely severe hallucinations
 7 continuous hallucinations

VISUAL DISTURBANCES — Ask “Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?” Observation.
 0 not present
 1 very mild sensitivity
 2 mild sensitivity
 3 moderate sensitivity
 4 moderately severe hallucinations
 5 severe hallucinations
 6 extremely severe hallucinations
 7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD — Ask “Does your head feel different? Does it feel like there is a band around your head?” Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
 0 no present
 1 very mild
 2 mild
 3 moderate
 4 moderately severe
 5 severe
 6 very severe
 7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM — Ask “What day is this? Where are you? Who am I?”
 0 oriented and can do serial additions
 1 cannot do serial additions or is uncertain about date
 2 disoriented for date by no more than 2 calendar days
 3 disoriented for date by more than 2 calendar days
 4 disoriented for place/or person

The CIWA-AR is not copyrighted and may be reproduced freely. Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-AR). *British Journal of Addiction* 84:1353-1357, 1989.

Patients scoring less than 10 do not usually need additional medication for withdrawal.

Total CIWA-AR Score _____

Rater’s Initials _____

Maximum Possible Score 67

ADP Form 8045 Physician Request for a Temporary Exception to Regulations

Narcotic Treatment Program Licensing Branch

Physician Request for a Temporary Exception to Regulations



Pursuant to Health and Safety Code, Section 11876(a)(7), the Director of the Department of Alcohol and Drug Programs (ADP), may grant an exception to the State Narcotic Treatment Program Regulations when it is determined the action would improve treatment services or achieve greater protection to the health and safety of patients, local community, or the general public.

FAX PHYSICIAN'S SIGNED REQUEST TO: (916) 323-5086

| | |
|---|---|
| <p>Narcotic Treatment Program Information:</p> <p>NTP License Number: _____</p> <p>Licensee Name: _____</p> <p>Program Address: _____</p> <p>Telephone Number: _____</p> <p>Fax Number: _____</p> <p>Contact Person: _____</p> | <p>NTP Patient Information:</p> <p>Medical Record Number: _____</p> <p>Continuous Treatment Admission Date: _____</p> <p>Primary Medication (circle one): Methadone LAAM</p> <p>Dosage Level: _____ mgs.</p> <p>If patient currently has medication take-home privileges, provide step level (circle one): 1 2 3 4 5 6</p> |
|---|---|

Type of request. If marked with ►►, may require U.S. Center for Substance Abuse Treatment approval.

More than 21-Day Detoxification Episode – 10355(a)(1)(C). NOTE: Not to exceed 180 days – 42 CFR 8.2.

Maintenance Admission Exception to 2-Year History of Addiction – CCR 10270(d)(1).

More than 1-Week Take-Home Supply for Travel or Crisis-Related Hardship – CCR 10385(a)(2).
 ►► If time in continuous treatment episode less than 270 days, attach copy of CSAT approval – 42 CFR 8.12(i)(3).

More than 2-Week Take-Home Supply for Medical-Related Hardship – CCR 10385(a)(1).
 ►► If time in continuous treatment episode less than one year, attach copy of CSAT approval – 42 CFR 8.12(i)(3).

Exception to Random, Periodic Urinalysis – CCR 10310(e) & 10360(c)(2).**
 ►► If frequency less than eight tests per year, attach copy of CSAT approval – 42 CFR 8.12(f)(6).

Other: _____ Cite NTP regulation: **CCR** _____

Program Physician Rationale for Requesting Exception (What is the hardship or health-endangering situation if not approved):

| | |
|--|---|
| <p>For admission exception request, discharge dates of two prior treatment failures: (1) _____ and (2) _____ (MM-DD-YY) (MM-DD-YY)</p> | <p>For take-home supply exception request, dates patient will use take-home supply: From: _____ : _____ (MM-DD-YY) (MM-DD-YY)</p> |
|--|---|

For travel out of area, program's attempt to arrange for courtesy dosing in: _____ (TRAVEL DESTINATION)
 was not successful because: _____

Program Physician Acceptance of Conditions: *I certify that the above information is true and accept the following conditions: 1) Approval does not exempt the program from complying with all other applicable state, federal, and foreign country laws and regulations. 2) A detox episode more than 30 days will require compliance with requirements for federal long-term detoxification and state maintenance treatment. 3) Prior to granting take-home exceptions, programs will inform patients that the use and possession of methadone may violate other laws (e.g., commercial motor vehicle and opiate importation restrictions). 4) A urinalysis exception will expire if there is a change in the patient's condition that makes this exception no longer necessary or in one year from the approval date, whichever comes first.** 5) Documentation concerning this exception will be filed in the patient's record.*

_____ (SIGNATURE OF PROGRAM PHYSICIAN) _____ (PRINTED NAME) _____ (DATE)

ADP Use Only: *I grant this exception pursuant to a delegation of authority granted by the Director of ADP and, if applicable, concur with the approval of the U.S. Center for Substance Abuse Treatment, as required in 42 CFR 8.12.*

Approval Signature: _____ **Approval Date:** _____

SAMSHA Form SMA 168 Exception Request

| | | | |
|--|---|--|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION CENTER FOR SUBSTANCE ABUSE TREATMENT | | Form Approved: OMB Number 0930-0206 Expiration Date: 01/31/2010 See OMB Statement on Reverse | Reset |
| Exception Request and Record of Justification Under 42 CFR § 8.11(h) | | DATE OF SUBMISSION: _____ | |
| Note: This form was created to assist in the interagency review of patient exceptions in opioid treatment programs (OTPs) under 42 CFR § 8.11(h). | | | |
| Detailed INSTRUCTIONS are on the cover page of this form. PLEASE complete ALL applicable items on this form. Your cooperation will result in a speedy reply. Thank you. | | | |
| BACKGROUND INFORMATION | Program OTP No: <input type="text"/> - <input type="text"/> - <input type="text"/> | Patient ID No: <input type="text"/> | |
| | Program Name: _____ | | |
| | Telephone: _____ | Fax: _____ | E-mail: _____ |
| | Name & Title of Requestor: _____ | | |
| | Patient's Admission Date: _____ | Patient's current dosage level: _____ mg | _____ Methadone _____ LAAM _____ Buprenorphine |
| | Patient's program attendance schedule per week (Place an "X" next to all days that the patient attends): _____ S _____ M _____ T _____ W _____ T _____ F _____ S | | |
| | *If current attendance is less than once per week, please enter the schedule: _____ | | |
| | Patient status: _____ Employed _____ Homemaker _____ Student _____ Disabled Other: _____ | | |
| | Nature of Request: Temporary take-home medication _____ Temporary change in protocol _____ Detoxification exception _____ Other: _____ | | |
| | REQUEST FOR CHANGE | Decrease regular attendance to (Place an "X" next to appropriate days): _____ S _____ M _____ T _____ W _____ T _____ F _____ S Beginning date: _____ | |
| *If new attendance is less than once per week, please enter the schedule: _____ | | | |
| Dates of Exception: From _____ to _____ | | # of doses needed: _____ | |
| Justification: _____ Family Emergency _____ Incarceration _____ Funeral _____ Vacation _____ Transportation Hardship _____ Step/Level Change _____ Employment _____ Medical _____ Long-Term Care Facility _____ Other Residential Treatment _____ Homebound _____ Split Dose _____ Other: _____ | | | |
| REQUIREMENTS | Regulation Requirements: | | |
| | 1. For take-home medication: Has the patient been informed of the dangers of children ingesting methadone or LAAM? _____ Yes _____ No _____ N/A | | |
| | 2. For take-home medication: Has the program physician determined that the patient meets the 8-point evaluation criteria to determine whether the patient is responsible enough to handle methadone as outlined in 42 CFR § 8.12(i)(2)(i)-(viii)? _____ Yes _____ No _____ N/A | | |
| 3. For multiple detoxification admissions: Did the physician justify more than 2 detoxification episodes per year and assess the patient for other forms of treatment (include dates of detoxification episodes) as required by 42 CFR § 8.12(e)(4)? _____ Yes _____ No _____ N/A | | | |
| Submitted by: _____ | | | _____ |
| Printed Name of Physician | | Signature of Physician | Date |
| APPROVAL | State response to request: _____ Approved _____ Denied | | |
| | State Methadone Authority | | Date |
| | Explanation: _____ | | |
| Federal response to request: _____ Approved _____ Denied | | | _____ |
| Public Health Advisor, Center for Substance Abuse Treatment | | Date | |
| Explanation: _____ | | | |
| Please fax to CSAT/DPT at (240) 276-1630 or e-mail: otp@samhsa.hhs.gov | | | |
| This exception is contingent upon approval by your State Methadone Authority (as applicable) and may not be implemented until you receive such approval. | | | |

FORM SMA-168 (revised January 2007) (FRONT)

Authorization for the Release of Confidential Patient Information

**Santa Clara Valley Health and Hospital System
 Department of Alcohol and Drug Services
 Page One of Two**

AUTHORIZATION FOR THE RELEASE OF CONFIDENTIAL CLIENT INFORMATION

CLIENT NAME: _____ DATE OF BIRTH: _____

SOCIAL SECURITY NUMBER: _____ ID NUMBER: _____

NOTICE TO RECIPIENT: Federal Regulations prohibit further disclosure of information without specific written consent from the person to whom the information pertains. A general authorization for release of medical or other information is NOT sufficient for this purpose.

I, _____, hereby authorize _____
 (Please print-Client/Participant Name) (Person/Agency Name)
 at _____ to disclose records/information obtained in the course of
 (Telephone Number) services rendered to me to: _____
 (Person/Agency Name)

The disclosure of records/information authorized herein is required for the following purpose(s):
 and shall be limited to the following specific types of information (select one or more):

| Clt Initials | Clt Initials | | |
|--------------------------|-------------------------------------|--------------------------|--|
| <input type="checkbox"/> | Demographic | <input type="checkbox"/> | Physical examination results |
| <input type="checkbox"/> | Financial | <input type="checkbox"/> | Psychiatric examination results |
| <input type="checkbox"/> | Assessment/intake summary | <input type="checkbox"/> | Medications (current and past) |
| <input type="checkbox"/> | Dates/attendance/types of services | <input type="checkbox"/> | Correspondence |
| <input type="checkbox"/> | Alcohol and other drug test results | <input type="checkbox"/> | Discharge summary |
| <input type="checkbox"/> | Treatment progress | <input type="checkbox"/> | |
| <input type="checkbox"/> | Continuum of care referral summary | <input type="checkbox"/> | Any information in my treatment record |
| <input type="checkbox"/> | Other (specify): | <input type="checkbox"/> | |

*I understand that this information may be provided in person or by phone, fax, mail, and/or email.
 By signing below, I am consenting to the communications as indicated above. I understand that my Alcohol and Drug treatment records are protected under the federal regulations governing Confidentiality of Alcohol and Drug Abuse Patient Records, 42 CFR Part 2, and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), 45 CRR, Parts 160 and 164, and cannot be disclosed without my written consent unless otherwise provided for in the regulations. The exceptions are set forth in the Notice of Privacy Practices.*

SEE NEXT PAGE---

Santa Clara Valley Health and Hospital System
Department of Alcohol and Drug Services
Page Two of Two

CLIENT NAME: _____ DATE OF BIRTH: _____

SOCIAL SECURITY NUMBER: _____ ID NUMBER: _____

I also understand that I may revoke this authorization in writing at any time except to the extent that action has been taken on it by providing a copy of the written notice withdrawing my consent to the Department of Alcohol and Drug Services Privacy Officer at the address set forth in the Notice of Privacy Practices. I have received a copy of this consent. In any event this consent expires automatically as follows: _____

(Date/event/condition upon which this consent expires).

DADS may not condition treatment, payment, enrollment or eligibility for benefits on whether the client signs this authorization except if it is for research related treatment, or, if it is used for determining enrollment in the health plan or eligibility for benefits if relating to individual or for its underwriting or risk rating determinations, and it does not provide for the use or disclosure of psychotherapy notes; or when treatment is provided for the sole purpose of providing information to third party.

Client _____ received _____ declined copy of completed consent.

(Client Signature)

(Date)

(Legal representative on behalf of client)

(Date)

Legal authority to sign on behalf of client:

Physician Request for a Patient's Controlled Substance Profile

Effective January 1, 2003, California physicians are entitled to make a written request for and receive the history of controlled substances dispensed to an individual under his or her care. The information comes from California's prescription monitoring program, the Controlled Substance Utilization Review and Evaluation System (CURES).

The form prepared for making that request is called the "Patient Activity Report" (PAR) (formerly the "Physician Request For Patient Controlled Substance Profile.") It can be downloaded from website of the California Attorney General: <http://ag.ca.gov/bne/pdfs/BNE1176.pdf>

The profile prepared by the Department of Justice will provide the physician with **a list of all Schedule II controlled substances prescriptions to the patient that have been filled within the last three months**, the name of the physician issuing the prescription, and the pharmacy where the prescription was filled.

A PAR printout "contains prescribing history contained in the CURES data system for that patient by medical prescribers in California. Verification by the California Department of Justice staff is required to substantiate the validity of the requesting medical prescriber or pharmacist before information on a PAR is released." (quote from the website of the CA Office of the Attorney General, CURES section, viewed 8-13-04).

A copy of the form is on page 143.

California Department of Justice
 P.O. Box 160447, Sacramento, CA 95816
 Telephone: (916) 319-9062
 Fax: (916) 319-9448

Clear Form



Patient Activity Report (PAR)

Please complete the following information by typing or printing in the required fields.

| PHYSICIAN INFORMATION | | | |
|---|-------|--------------|-----------|
| Physician DEA No.: | | License No.: | |
| Physician Name (As it Appears on your DEA Certificate) | | | |
| Physician Address | | | |
| | City: | State: | Zip Code: |
| Telephone No.: | | Fax No.: | |

| PATIENT INFORMATION | | | |
|----------------------|-------|------------|---------------|
| Last Name | | First Name | |
| AKA (Also Known As) | | | |
| Patient Address | | | |
| | City: | State: | Zip Code: |
| Telephone No.: | | | |
| Social Security No.: | | | Date of Birth |

| ADDITIONAL COMMENTS OR INFORMATION |
|------------------------------------|
| |

AUTHORIZATION

By signing below, I certify that I am a licensed health care practitioner eligible to obtain controlled substance history dispensed to the patient in my care identified above, based on data contained in the Controlled Substance Utilization Review and Evaluation System (CURES). I understand that any request for, or release of a controlled substance history shall be made in accordance with Department of Justice guidelines, that the history shall be considered medical information subject to the provisions of the Confidentiality of Medical Information Act (Civil Code §§ 56 et seq.)

Please FAX your request to (916) 319-9448
 Or mail to: California Department of Justice, P.O. Box 160447, Sacramento, CA 95816

Physician Signature _____ Date _____

| | | | |
|---|---------------|----------------|----------|
| For Department of Justice Use Only | Date Received | Date Completed | Initials |
| | Comments | | |

Print Form

Sample Letter to Physicians and Dentists about Methadone Maintenance Treatment

To Whom It May Concern:

The bearer of this letter is a patient in an opioid treatment program (OTP).

While methadone is the medication most commonly used in treatment, buprenorphine is also approved for this purpose. Methadone-maintained patients often need treatment for medical, psychiatric, surgical, and dental conditions. Health care professionals are not always familiar with addictive disease and the various forms of treatment, including methadone. Many patients are reluctant to provide information to health professionals about their addiction and treatment with methadone because of previous bad experiences. The purpose of this letter is to describe the most common problems encountered and to offer any assistance we might be able to provide.

Addiction is widely accepted to be a disease or a group of diseases. Addictive disease can be characterized as a chronic, progressive, probably incurable, and often fatal disorder. The principal diagnostic features are obsession, compulsion, and continued use despite adverse consequences. Our program provides counseling, education, medication, structure and accountability services to help the patient make the life-style changes needed to address the many dimensions of this disorder.

Methadone has been used in the treatment of opioid dependence for about 50 years. Its long-term administration has been found to be both effective and safe. Methadone-maintained patients develop nearly complete tolerance to the analgesic, sedative, and euphorogenic effects of methadone at an established maintenance dose. In most patients, methadone has a half-life in excess of 24 hours. It has a relatively flat blood plasma level curve that will prevent the onset of the abstinence syndrome for more than 24 hours without causing any sedation, euphoria, or impairment of function.

The management of pain in a methadone-maintained patient is a common problem. Because the patient is fully tolerant to the maintenance dose of methadone, no analgesia is realized from the regular daily dose of methadone. Relief of pain depends on maintaining the established tolerance threshold with methadone and then providing additional analgesia. Non-narcotic analgesics should be used when pain is not severe. In the event of more severe pain, the use of opioid-agonist drugs is appropriate. The dose of an opioid-agonist drug may need to be increased because of the cross-tolerance to methadone. Also, the duration of analgesia may be less than usual. Opioid-agonist/antagonist drugs such as pentazocine (Talwin®), butorphanol tartrate (Stadol®), and nalbuphine hydrochloride (Nubain®) should never be used in a methadone-tolerant person. Drugs of this type will precipitate severe opioid abstinence syndrome. Tramadol (Ultram®) may also produce symptoms of withdrawal.

The administration of opioid-agonist medications should be closely supervised in terms of quantities and duration. Similar precautions are indicated in the prescribing of sedative-hypnotic and central nervous system-stimulating drugs. The abuse potential of all benzodiazepines is high, particularly in opioid dependent patients.

At times, admitting physicians are tempted to treat the physical opioid dependence itself. This is usually attempted by starting a graded reduction of the methadone dose. The graded reduction may result in a reduction or elimination of the physiologic dependence but has no effect on the disease of addiction itself. After the methadone is discontinued, significant signs and symptoms of withdrawal may persist for 6-8 weeks. Withdrawal from the methadone maintenance treatment is not advised because the relapse rate associated with withdrawal from methadone approaches 100%. A relapse to street or illicit drugs increases the risk of overdose, hepatitis, AIDS, and a host of other biomedical, psychosocial, and legal complications.

If you have any questions or concerns about our mutual patient in relation to methadone or drug dependence, please call us. We would be delighted to hear from you.

Sample Letter to Physicians Prescribing Medications with Abuse Potential

Dear Dr. _____

Your patient, _____, is currently under our care for management of opioid dependence and is receiving a daily dose of methadone.

The patient reports that he/she is also taking _____ prescribed by you. According to treatment guidelines for methadone maintenance, we need to verify the medical indication for all medications with potential for abuse (i.e., supplemental opioids, benzodiazepines, other sedatives) for patients in an outpatient Opioid Treatment Program due to the risk of toxicity when combined with methadone.

Attached is a signed consent authorizing communication between you and the methadone clinic staff regarding his or her medication history and current progress in treatment.

Please complete the following and fax back to our office.

| | |
|---|-------------|
| Patient Name: _____ | DOB: _____ |
| Medication(s) prescribed: _____ | |
| Diagnosis/reason prescribed: _____ | |
| _____ | |
| Alternative medication(s) prescribed: _____ | |
| Is the patient making progress/improving? _____ | |
| Date of last Rx: _____ # of Pills: _____ # of Refills: _____ F/U date: _____ | |
| Prescription Contract? <input type="checkbox"/> Yes <input type="checkbox"/> No | |
| Please describe any concerns you have about patient's use of the medication(s)? _____ | |
| _____ | |
| Any other information you would like us to know about this patient's treatment? _____ | |
| _____ | |
| Physician Signature: _____ | Date: _____ |
| Physician's Specialty: _____ | |

Because this patient suffers from chemical dependency, we respectfully ask that you consider alternative non-habit forming medication(s) to minimize risk. Referral to a psychiatrist may be helpful. We will alert you to any concerns we have and will contact you regularly to request updates. We appreciate your willingness to coordinate care. Your prompt response to this letter will assist us in our treatment of this patient.

If you have any questions concerning this patient's methadone treatment, please don't hesitate to contact us at the number above.

Respectfully,

Medical Director

Primary Counselor

Sample Concurrent Medication Driving Agreement

■ **NOTE** Some physicians/clinics use agreements like this as a way of documenting that patients have been counseled about the risks of driving while under the influence of drugs or sedating prescribed medications. Other providers/clinics have concerns about use of this kind of form. These are some of the concerns:

- Whether the clinic can meet the objective of getting such a form into the chart in a timely fashion for every patient with a positive urine toxicology report or prescription on file.
- Practical difficulty of determining which prescriptions to include, with the understanding that many over the counter medications are sedating.
- Whether the clinic assumes additional responsibility for patients with such agreements. In general, providers/clinics continually educate all patients at admission and at intervals regarding the risks of driving when sedated.

I, _____, am currently enrolled in Medication Assisted Treatment at _____, receiving a daily dose of methadone for the treatment of opioid dependence.

Currently, I am also taking the following prescriptions and/or non-prescribed drugs, alcohol, marijuana: _____

I acknowledge that I have been advised by the Medical staff at my treatment program that I should not drive or operate heavy machinery while I am taking the above medications or using the above drugs. In addition, I agree that I will alert the Medical staff if I am feeling drowsy, sleepy or unable to drive for any reason, so that I may be assisted to find a safe ride home.

I further acknowledge that if I choose to engage in the above activities while under the influence of prescribed medications or other drugs, I am doing so in direct opposition to the directives of the clinic medical staff, and I will be solely responsible for any outcome arising from my decision.

If any of the above information about prescriptions/drugs I am taking changes, I will notify the staff immediately.

Patient signature: _____ Date: _____

Medical Staff signature: _____ Date: _____

Patient Request for Clinic to Hold and Dispense Medications

From Santa Clara Valley Health and Hospital System Department of Alcohol and Drug Services

PATIENT REQUEST FOR CLINIC
TO HOLD AND DISPENSE MEDICATIONS

I am requesting that the dispensary of CVC, AHC, SCC (circle which clinic) hold my prescribed medication(s) at the clinic location where I am enrolled as a patient. This will help me take my medication(s) in a more consistent and controlled manner than if I had them in my own possession.

Further, when I am at the clinic for my methadone dosing, I am authorizing the clinic to dispense my medication(s) to me as indicated by my prescribing physician.

I can at any time rescind this authorization in writing and have my medication(s) returned to me. Thank you.

Patient Name

I.D. Number

Patient Signature

Date

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