CHAPTER 2 MEDICATION-ASSISTED TREATMENT

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2.1 METHADONE

2.1.1. Introduction to Methadone Treatment

Clarification of Terms

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

Methadone: Description, Properties & Black Box Warning

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

The bioavailability of oral methadone is high, usually 70-80%, but varies from 36% to 100%. The onset of action is 30-60 minutes, the peak effect of any one dose is usually achieved in 2.5-4 hours, and the half-life is long, about 25 hours in most patients. Methadone undergoes extensive first-pass metabolism in the liver. It binds to albumin and other proteins in the lung, kidney, liver and spleen. Tissue stores in these areas build up over time, and there is a gradual equilibration between tissue stores and methadone in circulation. This buildup of tissue levels produces daily increases in the medication's impact on the patient until steady state is reached, which takes about 5 days.

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

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

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

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

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

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

2.1.2. Criteria for Admission to Methadone Treatment

Methadone Treatment Options: Detoxification and Maintenance

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

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

Criteria for admission to Methadone Treatment – Detoxification

Any patient who meets DSM 5 criteria for OUD and has been using opioids long enough to develop physical dependence, meaning that they cannot stop using opioids without symptoms of withdrawal, is eligible for admission to Methadone Detoxification Treatment. Because this treatment is so unsuccessful, its use is generally limited to patients who do not meet criteria for admission to methadone maintenance or who decline methadone maintenance. Strong consideration should be given to offering these patients buprenorphine treatment as they are eligible for buprenorphine maintenance, and detoxification would be more comfortable, if not more successful.

Criteria for admission to Methadone Treatment - Maintenance

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

Regulatory Exceptions to Federal and California Admission Criteria

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

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

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

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

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

Admission Criteria for Minors

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

Program-Wide Exceptions

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

Individual Patient Exception

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

MMT for High Relapse Risk Patients

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

Submitting an Exception Request

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

Table 2.1.1

Methadone Maintenance Admission Criteria Federal vs. California

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

Table 2.1.2

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

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

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

Patient Suitability for MMT

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

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

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

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

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

2.1.3. Methadone – Determining and Adjusting the Dose

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

Induction

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

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

The Initial Dose

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

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

Note: *There is no direct way to measure tolerance. While the presence of withdrawal confirms the diagnosis of physical dependence, the severity of withdrawal is not correlated with the level of tolerance, meaning that severe withdrawal does not necessitate a higher starting dose.*

Tolerance is assessed indirectly by considering the following factors:

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

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

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

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

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

Safety Concerns and Patient Expectations

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

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

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

Screening for and Responding to Overmedication During Induction

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

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

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

Mild sedation (feeling sleepy but able to stay awake) that occurs at the time of the peak and does not last more than an hour or two may be addressed by decreasing the methadone dose by 20-30%. For example, a 20 mg dose would be lowered to 15 mg, a 30 mg dose would be lowered to 20 mg. Sedation that is severe (patient unable to stay awake after dosing) or long lasting (persisting until bedtime) is best managed by holding the dose for a day and reassessing the following morning. Before establishing a new dose, it is necessary to evaluate carefully to determine whether there are any other factors that would explain the sedation, such as use of another drug or medication.

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

Establishing Tissue Stores Safely

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

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

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

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

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

Table 2.1.3

Methadone Dose Assessment Form

Date:_____

Patient Name:_____ ID#_____

Vitals: BP_____ P_____ R_____ O2 sat_____ BAL_____ COWS _____**

Current Methadone Dose: _____ Date of last dose change: _____

1. Did you experience any sedation after taking your methadone dose yesterday? _____
2. **Four hours after** taking your methadone dose were you feeling completely well? _____
   If not, what symptoms were you having?

___Chills	___Nausea	___Yawning
___Sweats	___Stomach cramping	___Sneezing
___Runny nose	___Vomiting	___Body aches
___Watery eyes	___Diarrhea	___Anxiety/irritability

3. Did you use or take anything yesterday? _____

   If so, what and when?_____

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

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

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

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

Stabilizing on a Therapeutic Dose

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

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

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

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

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

Summary: Definition of a Therapeutic Dose of Methadone

A therapeutic dose of methadone is one that:

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

Methadone Blood Levels

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

Obtaining and Interpreting Blood Levels

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

Methadone levels should not replace good clinical judgment, but they can provide a point of reference. Thomas Payte notes that adequate trough levels in the highly tolerant opioid dependent patient are in the 400 to 600 ng/mL range. However, there are patients who stabilize with trough levels of 100 to 200 ng/mL. Payte [17] notes that absolute numbers in evaluating trough levels are less useful than a comparison of peak and trough levels. The ratio of the peak to trough level indicates a patient's rate of methadone metabolism. A patient with a normal metabolic rate will have a peak to trough ratio that is less than two. A peak to trough ratio that is more than two suggests a rapid rate of methadone metabolism.

Dividing the Dose

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

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

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

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

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

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

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

Re-evaluating the dose in the event of clinical change

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

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

Common reasons for destabilization

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

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

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

Drug Interactions with Methadone

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

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

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

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

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

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

Other drugs (such as macrolide antibiotics, Luvox® fluvoxamine, etc.,) may decrease metabolism and require a decrease in the methadone dose. Ciprofloxacin can significantly increase the methadone blood level, resulting in severe sedation and/or respiratory failure. The combination of methadone and a trycyclic antidepressant may increase trycyclic toxicity. Medications used to treat HIV infections may affect methadone. The U.S. Department of Health and Human Services provides an excellent reference for HIV medication interactions at the interactive database AIDSinfo. Underlying medical conditions such as cirrhosis, pregnancy, chronic pain and psychiatric disorders must be considered when assessing dose adjustments and safety. Consultation with a pharmacist is recommended for new medications taken alongside methadone. The National Library of Medicine's MedlinePlus provides a list of medications that may interact with methadone [18].

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

Comorbid Medical or Psychiatric Conditions

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

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

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

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

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

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

Management of Pain with MMT Patients

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

Summary:

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

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

Table 2.1.4

Studies testing effects of methadone on the QT interval

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

2.1.4. Adverse Reactions

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

Black Box Warnings

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

Potential Cardiotoxicity

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

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

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

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

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

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

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

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

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

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

Sedation

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

Most Frequently Observed Adverse Reactions

The most frequently observed adverse reactions in methadone maintenance patients are sweating, constipation, sedation (see above) and decreased libido. Many patients gain weight when they achieve abstinence from heroin use and attribute it to methadone. Often patients' eating habits change dramatically when they stop using heroin, so it is unclear how much of a role methadone plays in the weight gain.

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

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

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

Endocrine Issues

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

Male Patients:

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

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

Table 2.1.5

Adverse Reactions as listed in the 2006 Methadone Label

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

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, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsades 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.

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

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

Female Patients:

The gonadal function problems experienced by women maintained on methadone or other opioids include luteal and follicular phase disruptions. (Santin 1975) These abnormalities are likely due to opioid-induced impairment of hypothalamic gonadotrophin releasing horomone (GnRH) production and impaired ovarian and adrenal steroidogenesis. Clinically, women experience decreased libido and menstrual irregularities, amenorrhea and oligomenorrhea. Due to irregular menses, some women mistakenly believe they cannot become pregnant; others suspect they are pregnant when they are not. (Daniell 2007)

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

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

2.1.5. Managing Methadone Maintenance Treatment

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

Treatment Planning

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

Counseling Services

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

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

Dose Determination

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

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

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

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

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

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

2.1.5. Take-Home Privileges

Perspectives

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

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

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

Regulatory Requirements

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

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

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

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

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

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

Determining if Take-home is Appropriate

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

Table 2.1.6

Federal Criteria for Considering Eligibility for Take-Home Privileges

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

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

Table 2.1.7

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

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

*Federal Regulations: 42 CFR Chapter 1, Part 8.12 I
**California Regulations: CCR, Title 9 Division 4, Chapter 4, Subchapter 5, Article 4

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

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

Table 2.1.8

Other Federal vs. California Regulations of Take-Home Medication

	Federal Regulation*	California Regulation**
Days clinic is closed for business: Sundays & Federal or State Holidays	One dose allowed for all patients	One dose allowed for patients that are determined responsible in handling medication
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 other) including alcohol	Meet Federal criteria for urine toxicology. In the month take-home is granted, must be negative for illicit drugs and positive for methadone and its metabolite [35]
Short-term detoxifcation patients	No take-home medication allowed	No take-home medication allowed
Interim maintenance patients	No take-home medication allowed	No take-home medication allowed
Long-term detoxification patients	Same as for patients in MMT	Same as for patients in MMT
Requirements for take-home bottle label	OTP's name, address and phone number	Federal requirements ■ 24-hour emergency telephone number ■ Medication name ■ Name of prescribing medical director/ MD ■ Patient's name ■ Date issued WARNING: poison, may be fatal to adult or child, keep out of reach of children
Packaging for take-home doses	Designed to reduce the risk of accidental ingestion (e.g., childproof containers)	Same as Federal
Methadone formulation	Oral form that reduces potential for parenteral abuse	Liquid formulation required
Emergency Disaster	Unknown	California may grant exceptions to take-home medication in the case of an emergency or natural disaster, such as fire, flood, or earthquake

*Federal Regulations: 42 CFR Chapter 1, Part 8.12 I
**California Regulations: CCR, Title 9 Division 4, Chapter 4, Subchapter 5, Article 4

Table 2.1.9

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

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

Take Home Doses and Terminal Illness

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

Extended Take-Homes

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

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

Courtesy Dosing

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

Discontinuation of MMT

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

Regulations in Flux

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

When OUD Patients are Hospitalized

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

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

2.2 BUPRENORPHINE

2.2.1. Introduction to Buprenorphine Treatment – Medication and Mindset

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

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

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

Chemistry of Buprenorphine Preparations Used to Treat OUD

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

Pharmacokinetics and Metabolism

Buprenorphine is not well absorbed when orally ingested (10% of injected), and much of what is absorbed is destroyed in the liver. Alternatively, it is well absorbed through the lining of the oral cavity, and when given sublingually, it reaches 60-70% of the plasma concentration achieved by the parenteral route. After absorption, buprenorphine is widely distributed throughout the body with peak plasma concentration reached at approximately 60-90 minutes and with a half-life of 2-3 hours. Plasma levels of buprenorphine increase with sublingual doses of the mono-product and of the buprenorphine/naloxone combination product, and plasma levels of naloxone increase with sublingual doses of the combination. A wide inter-subject variability exists with regard to sublingual absorption of both buprenorphine and naloxone. Both maximum concentration of drug in seruxm (Cmax) and the area under the concentration-time curve (AUC) of buprenorphine appear to increase in a linear fashion with an increase in dose (in the 4-16 mg range), although the increase is not directly dose-proportional [39]. The bioavailability of sublingual buprenorphine after a single administration is about 40 percent; with repeated dosing

Table 2.2.1

Buprenorphine Transmucosal Products for OUD Treatment

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

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

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

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

Pharmacodynamics

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

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

History: Buprenorphine's Development

Dr. Donald Jasinski, recognizing that buprenorphine has properties like those of methadone that patients like, and properties like those of naltrexone that patients hate but clinicians like, believed it would be just the thing to treat opioid use disorder. Patients would take something like methadone and in time have something in them that acts like naltrexone. He conducted a series of studies in the 1970s and published the results in the Archives of General Psychiatry in 1978. A series of NIDA-sponsored trials compared buprenorphine to methadone, buprenorphine to placebo, and buprenorphine in various doses [40-42], and established buprenorphine as safe and effective (see Clinical Implications below), leading to its approval by the FDA, along with the passage in 2000 of the Drug Addiction Treatment Act (DATA). It became clinically available to clinicians in 2002 with some special requirements of physician training and provision of certain ancillary clinical services. Today, buprenorphine is an established pharmacotherapy in MAT. Development of extended-release formulations further extends buprenorphine's clinical usefulness [43].

Clinical Implications

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

FDA Approval and Requirement to Prescribe Buprenorphine

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

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

Requirements for Physicians to Prescribe Buprenorphine

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

Buprenorphine Induction

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

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

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

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

Tips for Monitoring Patients during Inductions

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

Home Induction

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

> *We have learned over time that a reasonably safe time to initiate buprenorphine is when the patient goes from "mild withdrawal" into "moderate withdrawal", which is why the original suggestion was a COWS score of 12—end of mild withdrawal and beginning of moderate withdrawal. A COWS score of 8 seemed to separate those who did well from those did not do as well. We also found that after the initial 4 mg. dose, we almost always had to give another 4 mg., and began to give 8 mg. as the first dose.*
>
> *For home induction, also vary the COWS scores according to the patient. For example, in an obsessive patient who sticks to the rules, a COWS score of 8 is fine, but in a patient who is likely to fudge, the patient should wait until they get past 10-12 (give them the actual signs to look for) and then wait another 10 minutes. (They usually do not, but they have a better chance to go past 8.)*

Use of Ancillary Medications during Induction and Early in Buprenorphine Treatment

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

Dosing Across the Course of Treatment

The initial daily stabilization dose of buprenorphine ranges from 4-24 mg. It is important to recognize the distinction between pharmacological stabilization and clinical stabilization. Pharmacologically stabilization means a steady blood level, which takes approximately 5 half-lives, or 5-7 days for buprenorphine. Thus, seven days of a steady daily dose that prevents between-dose symptoms of withdrawal, without symptoms of over-medication such as sedation, will likely be the adequate daily dose to continue treatment. However, this is not clinical stabilization, which encompasses a broader range of treatment goals: staying off drugs and getting a life.

Dose Adjustment

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

Discontinuing Buprenorphine Treatment (or any form of MAT)

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

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

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

Counseling, Support Groups, and Recovery

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

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

Extended-release Buprenorphine Preparations

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

Buprenorphine Sub-dermal Implant

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

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

Extended-release Injectable Buprenorphine

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

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

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

Additional Information

Physicians authorized to prescribe buprenorphine should have acquired from their required training certain basic information about the clinical pharmacology and clinical applications of buprenorphine in treating OUDs. These guidelines are not, therefore, exhaustive; some topics are regulated and specified by Federal and State authorities, such as the REMS, the drug labeling, which list indications and contraindications, side effects, adverse reactions, and cautions [46]. Other topics are too large or changing too quickly to be suitable for inclusion in this type of guide, such as buprenorphine drug interactions; still others are covered under other chapters of this guidelines; see also the Chapters on Pain and Pregnancy. More detail and regulatory information can be found here:

- CSAM
- SAMHSA
- NIDA
- ASAM

2.3 NALTREXONE

2.3.1. Introduction to Naltrexone Treatment

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

2.3.2. Naltrexone Pharmacology

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

2.3.3. Naltrexone Pharmacokinetics

Absorption of Naltrexone

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

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

Distribution of Naltrexone

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

Metabolism of Naltrexone

The metabolism of naltrexone is not catalyzed by CYP 450 enzymes but by aldo-keto reductase enzymes AKR1C1, AKR1C2, and AKR1C4, previously designated as dihydrodiol dehydrogenase enzymes (DD1, 2, and 4) [55]. Naltrexone undergoes reduction via these enzymes to the active metabolite 6-β-naltrexol. Both parent and metabolite can also undergo glucuronidation [56]. 2-Hydroxy-3-O-methyl-6-β-naltrexol is a minor metabolite found in trace amounts. The main route of elimination for both parent drug and metabolites is renal, with much lower amounts in the feces [57]. After oral dosing 6-β-naltrexol levels peak at one hour, and the half-life is about 13 hours [51]. After the long acting injection, 6-β-naltrexol levels peak at 3 days, and after repeated dosing the half-life is about 5 days [51]. Ratios of plasma levels of metabolite and parent drug are quite different between oral dosing and injection because of decreased first pass metabolism with the injection. For oral dosing the ratio of 6-β-naltrexol to naltrexone is 10:1, but for injection it is 1:1 [51]. The extended release injection of 380 mg displays an area under the curve of naltrexone exposure over 28 days 4 times the area under the curve for the oral form given at 50 mg per day for 28 days [51].

Naltrexone Pharmacodynamics

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

2.3.4. Clinical Use of Naltrexone

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

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

Naloxone Challenge and Initiation of Naltrexone

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

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

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

2.3.5. Naltrexone Drug Interactions

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

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

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

2.3.6. Naltrexone Side Effects

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

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

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

2.3.7. Efficacy of Naltrexone for Opioid Use Disorder

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

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

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

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

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

2.3.8. Naltrexone – An Editor's Epilogue

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

One of its great virtues, it was said, is that people who take it feel as if they have taken nothing; however it is evidently for this reason that patients do not keep taking it and then relapse. Still, four years after its synthesis in 1967, Congress designated it a high priority and gave specific funding for Nixon's Special Action Office for Drug Abuse Prevention (SAODAP) to develop its use in treating opioid dependence; as its director put it, SAODAP really had no choice in the matter.

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

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