

# Safe Methadone Induction and Stabilization

## Report of an Expert Panel

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The views, opinions, and contents of this document are those of the ASAM Methadone Action Group and other referenced sources and do not necessarily reflect the views, opinions, or policies of SAMHSA or any other part of the US Department of Health and Human Services. The authors report no conflicts of interest.

This report is intended to enhance patient care, but it does not supplant clinical judgment. Therefore, the advice given here may not apply to all patients or clinical scenarios. No advice is an adequate substitute for the knowledge and skills of a physician who is engaged in developing a treatment regimen tailored to the needs of an individual patient. Members of the Methadone Action Group recognize that not all treatment providers will be able to conform to each of the strategies recommended here. Instead, physicians and other staff are encouraged to consider these conclusions and strategies to the extent they and their patients are able to do so. Nothing in this document is intended to create a legal standard of care for any physician or to interfere with his or her clinical judgment or practice of medicine.

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**Objectives:** Methadone is a well-studied, safe, and effective medication when dispensed and consumed properly. However, a number of studies have identified elevated rates of overdose and death in patients being treated with methadone for either addiction or chronic pain. Among patients being treated with methadone in federally certified opioid treatment programs, deaths most often occur during the induction and stabilization phases of treatment. To address this issue, the federal Substance Abuse and Mental Health Services Administration invited the American Society of Addiction Medicine to convene an expert panel to develop a consensus statement on methadone induction and stabilization, with recommendations to reduce the risk of patient overdose or death related to methadone maintenance treatment of addiction.

**Methods:** A comprehensive literature search of English-language publications (1979-2011) was conducted via MEDLINE and EMBASE. Methadone Action Group members evaluated the resulting information and collaborated in formulating the consensus statement presented here, which subsequently was reviewed by more than 100 experts in the field.

**Results:** Published data indicate that deaths during methadone induction occur because the initial dose is too high, the dose is increased too rapidly, or the prescribed methadone interacts with another drug. Therefore, the Methadone Action Group has developed recommendations to help methadone providers avoid or minimize these risks.

**Conclusions:** Careful management of methadone induction and stabilization, coupled with patient education and increased clinical vigilance, can save lives in this vulnerable patient population.

**Key Words:** methadone, methadone dosing, methadone induction, methadone mortality, methadone overdose, opioid agonist treatment

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Methadone is among the most thoroughly studied medications in modern medicine. A synthetic opioid, methadone was approved by the Food and Drug Administration (FDA) in 1947 as an analgesic. By 1950, it was being used to treat the symptoms of withdrawal from heroin and other opioids. In 1964, researchers discovered that continuous, daily maintenance doses of oral methadone allowed

individuals with opioid addiction to function well in daily life without the symptoms of withdrawal or craving (Gearing and Schweitzer, 1974; Zweben and Payte, 1990; Payte, 1991; Dole, 1988). Subsequent experience shows that methadone maintenance treatment is effective in reducing morbidity and mortality associated with continued use of heroin and other illicit opiates and prescription opioids (Marsch, 1998; Bell and Zador, 2000; Mattick et al., 2003; Gibson et al., 2008; Modesto-Lowe et al., 2010).

Despite its proven efficacy, methadone's relatively short duration of analgesic effect, coupled with its long elimination half-life and potential for interactions with multiple drugs, increases the risk of toxicity and adverse events (FDA, 2007). As a result, methadone-related visits to emergency departments occur at a rate that is approximately 23 times greater than for other prescribed opioids (Substance Abuse and Mental Health Services Administration [SAMHSA], 2010). Moreover, a number of studies have found increased mortality associated with therapeutic use of methadone (SAMHSA, 2003, 2010; Paulozzi and Annet, 2007; Government Accountability Office, 2009; Warner et al., 2009). These reports emanate from almost every geographic region of the United States and reflect the experience of multiple patient populations (Davoli, 2007; Shields et al., 2007; Shah, 2005; Paulozzi, 2009; Piercefield et al., 2010). Overall, although methadone represents less than 5% of all opioid prescriptions dispensed in the United States each year, it is identified in more than a third of opioid-related deaths (National Drug Intelligence Center, 2007; Webster et al., 2011).

Experts have concluded that methadone dispensed in federally certified opioid treatment programs (OTPs) is not a major contributor to this high rate of fatalities (SAMHSA, 2004a,b, 2007a,b, 2010; Government Accountability Office, 2009); nevertheless, it is a factor in some overdose deaths. To promote the safe use of methadone in addiction treatment, the Substance Abuse and Mental Health Services Administration of the US Department of Health and Human Services invited the American Society of Addiction Medicine (ASAM) to convene an expert panel (the Methadone Action Group) to develop recommendations for safe induction and stabilization of methadone patients in OTPs.

In doing so, SAMHSA's and ASAM's goals for the project were to achieve consensus as to:

- How to calculate the initial (induction) dose of methadone.
- How to adjust the dose to meet each patient's evolving needs.
- How to identify factors that affect the dosing regimen.
- How to avoid overdose and other adverse events associated with methadone induction and stabilization.

Although the Methadone Action Group's work involved a critical appraisal of the literature on methadone, this consensus statement also reflects the clinical expertise and experience of Action Group members. It is intended solely for clinicians who are attempting to develop and implement induction and stabilization protocols for methadone maintenance treatment in federally certified OTPs.

This consensus statement is part of a comprehensive educational initiative by SAMHSA, which also involves reviews of drug interactions with methadone (McCance-Katz

et al., 2010), advice on screening patients for risk of adverse cardiac events associated with methadone (Martin, 2011), and proposed uniform definitions and standards for classifying methadone-related overdoses and deaths (Goldberger et al., 2013).

## METHODS

The ASAM Methadone Action Group includes representatives of organizations that share a commitment to ensuring the safety and effectiveness of opioid addiction treatment. Action Group members are experienced educators, researchers, and practitioners of addiction medicine, methadone maintenance treatment, pharmacology, and medical education.

In support of the Action Group's efforts, a comprehensive literature search was performed via MEDLINE and EMBASE for articles published from 1970 through 2011 that address various aspects of methadone induction and stabilization. English-language articles were reviewed, as were official opioid treatment guidelines published in the United States, Canada, and the United Kingdom, and relevant reports produced by SAMHSA and other government agencies (Batki, 2005; College of Physicians and Surgeons of Ontario, 2005; Medicines and Healthcare Products Regulatory Agency, 2006; SAMHSA, 2007a, 2009; Kauffman, 2008; Stephenson, 2008; Government Accountability Office, 2009).

Members of the Action Group were asked to evaluate the published literature for relevance to this topic. In their review, they took into account the fact that treatment outcomes often depend as much on self-management or nonpharmacologic therapies as on the characteristics of a particular medication (SAMHSA, 2007a). This is an important caveat in evaluating reports of clinical trials, as is the fact that studies tend to use fixed doses of medication rather than adjusting the dose to meet patients' changing medication needs (whereas such individualization of treatment is strongly endorsed by the Action Group).

Members of the Action Group also were aware that there may be a difference in outcomes between studies in which patients were randomized to various medication or control groups, as compared with studies in which patients were able to select their medication (patients tend to have better outcomes if they are treated with a medication they have chosen) (Liang et al., 2008; Christensen et al., 2010; Udell and Redelmeier, 2011).

Finally, Action Group members considered the challenges of disseminating and promoting practice change within OTPs, as well as current regulations, guidance documents from other countries, and the effects of the FDA's new program of Risk Evaluation and Mitigation Strategies.

Because methadone has been associated with a reduction in overall mortality and morbidity in treated versus untreated populations (Mattick et al., 2003; SAMHSA, 2004a,b, 2007a,b, 2010; Gibson et al., 2008), the Action Group operated on the premise that methadone must remain widely available in the United States for the treatment of opioid addiction.

On the basis of their review of the evidence and their clinical experience, Action Group members prepared a preliminary document, which was subjected to an extensive field review, eliciting more than 100 responses from researchers and

specialists in the treatment of opioid addiction. Input from the field review was incorporated into the Action Group's consensus statement, which is presented here.

## RESULTS

Reports in the peer-reviewed literature underscore the fact that methadone has a number of unique pharmacologic properties. These include slow onset and long duration of action, relatively small need for dose escalation because of tolerance, and very modest cost—all of which make it an appropriate agent for opioid addiction therapy (Kreek, 1993; Joseph and Woods, 1994; Payte et al., 1994; SAMHSA, 2004a,b, 2007a,b).

### Formulations, Mechanisms of Action, and Metabolism

Oral methadone is available as a solid tablet, a rapidly dissolving wafer (diskettes are not soluble and are referred to as dispersible tablets), and a premixed liquid, all of which are essentially bioequivalent (Mallinckrodt Inc, 1995, 2000; Roxane Laboratories, 1995, 1998, 2006). Each of the formulations is 80% to 95% bioavailable and readily absorbed (Inturrisi and Verebely, 1972; Eap et al., 2000).

Methadone is stored extensively in the liver and secondarily in other body tissues. Its elimination half-life averages 24 to 36 hours at steady state, but may range from 4 to 91 hours. Because of this long half-life, achieving steady-state serum methadone levels (SMLs)—in which drug elimination is in balance with the amount of drug remaining in the body—requires 4 to 5 days on average, although it can take much longer in some individuals. When methadone is initiated, a rule of thumb is that half of each day's dose remains in the body and is added to the next day's new dose, producing rising SMLs (which can reach dangerous levels if doses are excessive) until steady state is achieved. The SML typically reaches a peak at 3 to 4 hours after each dose (with a range of 1-5 hours). However, individual physiologic responses to an oral dose of methadone can differ for several reasons, including the rate of gastric emptying, the presence of sufficient glycoproteins to bind with methadone, and genetic variability between individuals in the rate of methadone metabolism by liver and intestinal enzymes (Eap et al., 2000, 2002; Brown et al., 2004).

Methadone blood levels found in patients who die of methadone overdose sometimes are the same as methadone blood levels that are therapeutic for other individuals (Gagajewski and Apple, 2003). For example, review articles have cited fatal methadone plasma concentrations ranging from 60 to 450 mg/mL (Mikolaenko et al., 2002; Wolff, 2002). Therefore, it is essential that clinicians monitor patients for signs and symptoms of toxicity, which may involve assessing laboratory values in addition to following trough and peak SMLs.

Largely as a function of liver enzyme activity, methadone is metabolized to form a number of inactive metabolites (Kreek, 1993; Foster et al., 1999). Drugs that *induce* activity of these enzymes can accelerate methadone metabolism, abbreviate the duration of methadone effects, lower the SML, and precipitate an abstinence (withdrawal) syndrome. Conversely, drugs that *inhibit* these enzymes can slow methadone metabolism, raise the SML, and extend the duration of drug effects (Eap et al., 1999). When interactions

with other substances occur, changes in SMLs can result in under- or overmedication. Genetic and environmental factors also act on the enzymes, leading to considerable variation in methadone potency from one patient to another (Robinson and Williams, 1971; Nakamura et al., 1982; McCance-Katz et al., 2010). Equally important to this kinetic variability is the wide interindividual and intraindividual variation in opioid tolerance, which is highly dependent on dosing history and also may reflect external stimuli and environmental factors (Eap et al., 1988, 2002). For these reasons, even if a patient is known to be tolerant to other opiates, he or she cannot be assumed to be tolerant to methadone (Parran, 2010).

### Safety Profile

Through many years of clinical trials and experience, methadone has been shown to have a favorable safety profile when used as indicated (Zweben and Payte, 1990; Payte and Zweben, 2003; Stine et al., 2003). In fact, mortality from all causes is many-fold lower in methadone-treated patients than in untreated persons with opioid addiction (Gronbladh et al., 1990; Gibson et al., 2008). Nevertheless, the rate of overdoses and fatalities associated with methadone prompts continuing concern (Srivastava and Kahan, 2006; Shields et al., 2007; Warner et al., 2009; Albion et al., 2010; Paulozzi et al., 2011; Webster et al., 2011).

In general, 3 patterns of methadone use are associated with overdose deaths (Harding-Pink, 1993; White and Irvine, 1999; Karch and Stephens, 2000; Bell et al., 2009; McCance-Katz et al., 2010; Modesto-Lowe et al., 2010).

1. *Single overdose*: In some cases, overdose occurs with the initial dose. This typically occurs with accidental ingestion in an intolerant individual (such as a child) or in a previously tolerant user whose use has been interrupted long enough to cause a loss of tolerance. As with most other opioids, the primary toxic effect of excessive methadone is respiratory depression and hypoxia, sometimes accompanied by pulmonary edema and/or aspiration pneumonia.
2. *Accumulated toxicity*: More often, doses accumulate over several days and toxicity develops gradually. (Today's dose is not lethal, tomorrow's dose is not lethal, but the entire third day's dose combined with half of the second day's and one quarter of the first day's dose accumulate to a lethal level.) Overly aggressive induction protocols often are the cause.
3. *Combining the prescribed methadone with another drug*: Methadone can be lethal when used in combination with other central nervous system (CNS) depressants, including other opioids, sedative or hypnotic drugs, or alcohol. In such cases, none of the agents alone is lethal, but when used in combination, a greater level of toxicity results. Benzodiazepines are the drugs most frequently reported in deaths attributed to combined use of methadone and another agent. Medications prescribed for psychiatric problems (such as fluoxetine, amitriptyline, quetiapine, and alprazolam) also can increase methadone accumulation and risk of toxicity.

Among patients in OTPs, the largest proportion of methadone-associated deaths have occurred during the first 2 weeks (induction phase) of treatment, often because treatment

personnel overestimated the patient's tolerance to opioids or the patient used opioids or other CNS depressants in addition to the methadone dose given as part of addiction treatment (Srivastava and Kahan, 2006; Shields et al., 2007; CSAT, 2008; Modesto-Lowe et al., 2010; Webster et al., 2011).

When a patient death occurs after the first 2 weeks of methadone treatment, other drugs usually are detected at post-mortem examination (Appel et al., 2000; Shah et al., 2008; Albion et al., 2010). One study found evidence of polydrug use in 92% of methadone-related deaths (Zador and Sunjic, 2000). In another study, concurrent benzodiazepine use caused a 5-fold increase in risk of fatal overdose (Caplehorn and Drummer, 2002).

In response to these concerns, the FDA issued a physician safety alert in 2006 regarding fatalities and cardiac arrhythmias associated with methadone (FDA, 2007). This was followed by a "black box warning" in the manufacturer's product labeling (Roxane Laboratories, 2006).

### RECOMMENDATIONS: METHADONE INDUCTION (WEEKS 1 AND 2)

Induction begins with the first dose of methadone and extends through the first 2 weeks of methadone treatment. It is during this period that patients are at the greatest risk of overdose and death, so safety precautions should be assigned very high priority.

#### Educate the Patient and Family and Obtain Informed Consent

Patient and family education should begin at intake into methadone treatment. The process of methadone induction should be explained and the patient cautioned that it may take several weeks to achieve a stable dose. Patients also should be warned that peak blood levels of methadone can increase daily until steady state is achieved, even if the dose stays the same.

During induction, patients should be instructed to judge their doses by how they feel during the peak period (the point of maximum concentration of medication in the blood) rather than during the trough period (the low point of medication concentration in blood just before the next dose—generally about 24 hours after ingestion). Otherwise, patients who experience symptoms of withdrawal during the first few days of methadone treatment could become convinced that they need a dose increase, when, in fact, they need more time for tissue stores to reach steady state. In contrast, patients who experience withdrawal symptoms after the first week of treatment—when tissue stores have reached steady-state levels—may in fact need a higher dose.

The patient and family members also should be educated about signs of impending overdose and methadone toxicity and urged to seek emergency care as needed. (Asking patients about symptoms daily during the first 5 days of induction is an important safeguard.) Patients also should be cautioned that it is dangerous to try to relieve withdrawal symptoms with benzodiazepines, other opioid medications, or with illicitly obtained methadone, other drugs, or alcohol.

Patients should be warned to limit driving or use of machinery in the period immediately after a dose increase, particularly in the first few hours after ingestion. They also

should be advised that it is important to take their methadone dose in the morning, because the risk of overdose increases at night.

Resources that may be useful in educating patients and their families about methadone induction and the risk of overdose are cited in the Appendix.

Informed consent for methadone treatment should be obtained after the patient has been educated about the treatment process. It should include the following elements (Bell et al., 2003):

1. Information about the potential risks of treatment, including the risk of overdose if methadone is discontinued and opioid use resumed at former levels.
2. Relative contraindications and cautions to use of methadone.
3. Availability of support services and expectations regarding compliance with recommendations for their use.

The patient's acceptance of these recommendations and understanding of the treatment process should be documented in a written informed consent, which should be part of the patient's medical record.

#### Estimate Tolerance

Tolerance is difficult to establish by history, and there is no direct way to measure its presence or extent. The amount of opioid use reported by the patient typically yields only a rough estimate of tolerance. Such histories should not be used as a guide in calculating the induction dose, nor should initial doses be determined on the basis of previous treatment episodes or patient estimates of dollars spent per day on the acquisition of illicit opioids.

In addition to interviewing patients about their substance use history, it is helpful to access any pharmacy records, medical records from referring physicians, or data from state prescription drug monitoring programs to identify unreported medications that may affect tolerance (Parran, 2010; Paulozzi et al., 2011).

Although the presence of withdrawal confirms the diagnosis of physical dependence, the severity of withdrawal does not reliably indicate the level of tolerance. In other words, severe withdrawal at intake does not necessarily indicate the need for a higher starting dose. If in doubt, it is safer to initiate methadone at a lower dose and observe the response. The dose always can be increased, but toxicity cannot always be reversed.

Lower levels of tolerance may be seen in patients who report nondaily opioid use, daily use of low-potency opioids (such as codeine), or daily use of oral opioid drugs at moderate doses. Loss of tolerance should be considered in any patient who has abstained from opioids for more than 5 days.

Patients who are tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern in patients who are tolerant to other mu-agonist opioids and who are being transitioned to treatment with methadone, thus complicating the determination of dose during the conversion period. Deaths have been reported during conversion to methadone from chronic high-dose treatment with other opioid agonists.

## Calculate the Initial Dose

The supervising physician is responsible for determining, on a case-by-case basis, the initial dose of medication and all subsequent dose adjustments. In the OTP setting, the initial methadone dose should be administered, under supervision, at a point at which the patient shows no signs of sedation or intoxication. (It is desirable, but not required, to observe the initial signs of opioid withdrawal.)

In general, the safety principle of “start low, go slow” applies to the induction dose. Determination of the initial dose should reflect the following:

- Knowledge of the approved product labeling
- Knowledge of federal regulations for initial dosing
- Knowledge of methadone’s pharmacokinetic and pharmacodynamic properties
- Knowledge of the individual patient’s characteristics
- Knowledge of any other medications the patient is using
- Knowledge of the patient’s level of tolerance, if any

The initial dose of methadone typically is in the range of 10–30 mg per day. If the initial dose is not sufficient to relieve withdrawal symptoms, the patient should be asked to wait for reassessment in 2 to 4 hours, when peak levels have been reached. At that time, an additional 5 to 10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of methadone on the first day of treatment should not exceed 40 mg.

In the following high-risk situations, an initial dose of 10–20 mg, with careful dose titration, is recommended:

1. The patient is older than age 60. Changes in metabolism that accompany aging warrant lower initial methadone doses.
2. The patient recently used benzodiazepines or other sedatives for therapeutic purposes or abuse. An exception might be the patient who has been on a small dose of benzodiazepines for at least several months.
3. The patient has used other sedating drugs such as antipsychotics and sedating antidepressants, particularly if the sedating drug was initiated or increased within the preceding two months or the dose is moderate to high.
4. The patient is engaged in problem drinking or is alcohol-dependent. Problem alcohol use can be identified through an alcohol history, use of screening questionnaires such as the AUDIT or CAGE, and laboratory measures such as the GGT and MCV. (Patients taking methadone always should be advised to abstain from alcohol. Those who are at risk for withdrawal on sudden cessation of alcohol use should undergo detoxification from alcohol before methadone is initiated.)
5. The patient has a respiratory disorder, cor pulmonale, morbid obesity, sleep apnea syndrome, myxedema, or kyphoscoliosis, or central nervous system (CNS) depression. In such patients, even customary therapeutic doses of methadone can suppress respiratory drive while simultaneously increasing airway resistance to the point of apnea. In such patients, methadone should be used at the lowest effective dose and only under careful medical supervision.

6. The patient has known cardiac risk factors, such as prolonged QT interval, known cardiac arrhythmias, a recent myocardial infarction, or a family history of early cardiac death (Martin, 2011).
7. The patient is taking a prescribed medication that inhibits methadone metabolism or otherwise increases methadone’s effects, such as delavirdine, fluconazole, voriconazole, ciprofloxacin, clarithromycin, fluoxetine, fluvoxamine, amitriptyline, quetiapine, sertraline, lidocaine or progesterone (McCance-Katz et al., 2010; Brown et al., 2004).
8. The patient is taking a prescribed medication that promotes methadone metabolism or inhibits methadone’s effects. Patients should avoid abrupt cessation of such medications, which include nevirapine and ritonavir (HIV medications), phenytoin, phenobarbital, carbamazepine, St. John’s Wort, and cocaine (McCance-Katz et al., 2010; Brown et al., 2004).

The first day’s dose should be titrated upward every five or more days in increments of 5 mg or less, and accompanied by careful assessment throughout the first two weeks of treatment.

In most cases, if a patient reports no recent opioid use and is judged not to be physically dependent, or has a negative initial urine drug screen, methadone should not be initiated unless there is evidence that the patient recently achieved abstinence in a supervised setting (incarceration, inpatient program, etc.) and/or is experiencing opioid craving and is at risk for relapse. To be an appropriate candidate for methadone, such a patient must have a significant history of opioid dependence, strong urges to use, and/or a good response to methadone maintenance treatment in the past.

The Action Group does not recommend the use of equianalgesic dose tables to determine the methadone dose. Such conversion tables compare the effect of one dose of methadone with one dose of morphine or other opioid, but typically do not take into account the effect of methadone accumulation before steady state is reached. As a result, the “equivalent” dose given for methadone in some tables is too large when methadone is used in a daily dose for addiction treatment (Patanwala, 2007).

## Monitor the Patient’s Response

Documented daily assessment of the response at the expected peak of each day’s dose is the only reliable guide in determining subsequent doses. It is essential to evaluate the patient at the time of peak effect to determine whether the patient continues to experience withdrawal symptoms at the time of maximum blood levels of methadone and to ensure that the patient is not experiencing intoxication (Caplehorn and Bell, 1991; Martin, 2010). Retention in treatment and reduction in use of illicit drugs generally improve as the dose increases, but it may be several weeks before an optimal dose can be achieved safely (Preston et al., 2000; Bao et al., 2009).

The following responses are indicators of optimal dosing (Joseph and Woods, 1994; Batki, 2005):

1. Prevention of opioid withdrawal for 24 hours or longer, including both early subjective symptoms and objective signs typical of abstinence

2. Elimination of drug hunger or craving
3. Blockade of euphoric effects of self-administered opioids (this is not a true blockade like that achieved with an antagonist such as naltrexone, but reflects cross-tolerance to other opioids so that the desired sensations are attenuated or eliminated when illicit or prescription opioids are self-administered). The increasing purity of heroin and the wide availability of highly potent prescription opioids have made it increasingly difficult to achieve complete blockade in patients through cross-tolerance; consequently, some patients require doses larger than 120 mg/d to achieve this effect.
4. Tolerance to the sedative effects of methadone, so that the patient can function normally without impairment of perception or physical or emotional response

Side effects that are frequently reported during the first few weeks of methadone therapy include somnolence, insomnia, weight gain, sexual dysfunction, and constipation. Many of these resolve once the patient develops tolerance to methadone (Brown et al., 2004).

Insomnia is common in patients being treated for addiction, and it can be difficult to determine whether the methadone dose should be adjusted. As a first step, stimulant use and/or excessive caffeine intake should be ruled out. Many opioid-dependent patients have sleep disorders that require behavioral therapies or nonopioid treatment. However, insomnia also may indicate that methadone blood levels are dropping to subtherapeutic levels during the night, leading to withdrawal-mediated insomnia. If a patient has been unable to rest during the night because of withdrawal, he or she may fall asleep during the day when blood levels are adequate and thus may seem to be oversedated by his or her dose, when the dose actually is too low to maintain steady blood levels throughout the night. In such cases, careful discussions with the patient and close monitoring can help determine the clinical decision (Stephenson, 2008). (OTP patients are presumed to be in recovery, but there always is a possibility that a patient is engaged in illicit use of alcohol or other drugs. Or the patient may be obtaining a prescribed medication that is enhancing the sedative effects of methadone through additive or synergistic CNS effects, or by increasing the effective plasma level of methadone [Hamilton et al., 2000; Herrlin et al., 2000; Tarumi et al., 2002; McCance-Katz et al., 2010].)

In some OTPs, counselors are specifically trained to interview patients about symptoms of withdrawal, craving, and the adequacy of the dose, and to report that information to medical staff when patients continue to exhibit symptoms. This integration of care—where counselor, dispensing nurse, and physician all are alert to the need for therapeutic doses—supports the patient's adherence to treatment and may improve treatment outcomes (Stephenson, 2008).

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. Instead, the underlying condition must be treated with appropriate psychotropic medications and/or counseling. Coexisting mood disorders are common in patients seeking treatment for substance use disorders (see

SAMHSA, 2004b, TIP 42). Antidepressant medications rather than benzodiazepines are the first-line pharmacologic treatments for anxiety disorders in OTP patients, but care should be taken to select an antidepressant that does not interact with methadone.

Minor colds and flu may feel like withdrawal. In such situations, patients need reassurance and suggestions for symptomatic relief.

### Address Vomited Doses

Repeated dose replacements pose the risk of unexpected overdose, so vomited methadone doses should not be replaced, in full or in part, unless a staff member has directly observed emesis. The color and volume of the emesis should be noted and, if the vomitus consists only of a small amount of mucous material, the dose need not be replaced. (Note that it is impossible to completely empty the gut, even with violent emesis.) Whenever possible, underlying causes of the vomiting should be addressed.

Guidelines for replacing vomited doses include the following (College of Physicians and Surgeons of Ontario, 2004):

1. If emesis occurs less than 15 minutes after consumption, consider replacing 50% to 75% of the full dose. If the dose is more than 120 mg, consider replacing only 50% of the full dose.
2. If emesis occurs at 15 to 30 minutes after consumption, consider replacing 25% to 50% of the full dose.
3. If emesis occurs at more than 30 minutes after consumption, do not replace the dose.

### Avoid Overdose

As noted earlier, the greatest risk of overdose occurs during the induction phase of treatment. Deaths have been associated with starting doses as small as 30 to 50 mg (Drummer and Opekin, 1992). Relative to other medications, the ratio between the maximum recommended initial dose of methadone and a potentially fatal single dose is exceedingly narrow (Repchinsky, 2003). Overdose typically is marked by obtundation, apnea, respiratory failure, and hypoxia—ultimately leading to coma, seizures, hypotension, and death. Symptoms of overmedication also may include unusual feelings of excess energy, with or without euphoria.

Overdose can have an insidious onset. Patients in whom the first dose suppresses withdrawal completely for a full 24 hours may experience symptoms of toxicity as tissue stores accumulate. The patient may seem relatively alert during the day but succumb to an overdose during a nap or at night (Batki, 2005).

Program staff should alert a physician if the patient seems sedated or intoxicated. In such cases, it is important to note the time of the last dose, because the sedation can be expected to worsen for many hours after that dose (Modesto-Lowe et al., 2010). Similarly, when an overdose is diagnosed and treated, it is important to monitor the patient for at least 48 hours because the period of toxicity can extend to many hours or even days (Anderson and Kearney, 2000).

Opioid treatment programs should establish protocols for emergency response to and management of patient overdoses, including onsite availability of naloxone and any necessary support and education for families (Winstock et al., 2000; SAMHSA, 2013).

### RECOMMENDATIONS: EARLY STABILIZATION PHASE (WEEKS 3 AND 4)

The objective of the stabilization period is to achieve a maintenance dose that allows the patient to conduct activities of daily living without intoxication, excessive sedation, withdrawal, or distressing drug craving.

During the early stabilization phase, patients should be given the same dose for 3 to 4 consecutive days, with no missed doses, before the dose is increased. As stores of medication accumulate in body tissues, the effects begin to last longer (Batki, 2005). For this reason, it usually is more helpful to ask the patient whether a dose completely controlled symptoms of withdrawal for 2 to 4 hours after dosing, rather than whether the dose “held” for the full 24 hours.

If a patient misses consecutive doses during the stabilization phase, it becomes difficult to evaluate the effect of a particular dose. Missed doses may indicate continued illicit drug use or alcoholism, or may be related to issues such as lack of transportation or homelessness. Such absences prevent proper tissue stores of methadone, and a protracted absence should prompt concern that tolerance to opioids may have been lost, making the “regular” dose a dangerous one. As a safety precaution, clinicians should reconsider the methadone dose if a patient misses 3 or more consecutive doses, and lower the dose or restart the induction process after 4 to 5 days of absence from treatment.

Once tolerance to the reduced dose is demonstrated, the dose can be increased by no more than 10 mg/d. Slower dose escalation is suggested for patients with an unstable clinical picture or concurrent benzodiazepine use. The patient should be assessed every 2 to 3 days during this rapid titration.

### Adjust the Dose

In general, 4 to 5 half-lives (~5 days) are required to reach steady state at a given methadone dose. Once steady state is achieved, methadone administered once daily should maintain the patient in an asymptomatic state for 24 hours, without episodes of overmedication or withdrawal.

Dose adjustments require great care. After an initial steady state is achieved, adjusting the dose in increments of 5 to 10 mgs every 3 to 5 days (according to symptoms of withdrawal or sedation) usually is adequate.

For safety reasons, automatic dose adjustments (such as those seen in “standing orders,” automatic electronic “build-up schedules,” verbal telephone orders without direct medical assessment, or assessment by nonmedical personnel) should be avoided.

### RECOMMENDATIONS: LATE STABILIZATION PHASE (WEEKS 5+)

After being stabilized on a therapeutic dose of methadone, some patients continue on the same dose for years.

More commonly, however, the dose needs to be adjusted from time to time.

Changes in a patient’s health, medications, schedule, events that trigger craving, and stress may result in the emergence of symptoms of withdrawal or overmedication or may make a patient more sensitive to methadone’s side effects. In such situations, changing the dose may solve the problem.

Other conditions and medication interactions can change the metabolism of methadone and mimic symptoms of withdrawal or trigger craving (Stephenson, 2008). Screening for coexisting problems or use of motivational interviewing may be helpful in such clinical situations.

Nonspecific stress can lead to withdrawal symptoms, possibly because of deficits in the stress response system. In the event of a reemergence of withdrawal related to increased life stressors, an increase in the daily methadone dose may be indicated. Conversely, when patients achieve stability in their lives and no longer confront daily “triggers,” they may no longer need a blocking dose and could do well at a lower dose than the one initially indicated (Stephenson, 2008).

Patients have a tendency to reflexively attribute new symptoms or discomforts to the methadone dose. When the clinical picture changes, the physician needs to reassess the patient. Input from nursing and counseling staff and/or a meeting with the patient may be helpful.

If a patient requires a higher dose to stabilize, the physician or another staff member should reevaluate the entire clinical picture: Is the patient continuing to use illicit opioids? Is the patient experiencing side effects such as the severe form of cardiac arrhythmia known as Torsades de Pointes? Is the patient taking another medication that interacts with the methadone? Does the patient have a medical or psychiatric condition that is masquerading as withdrawal? Is the patient a rapid metabolizer who may be comfortable only at peak? Reevaluation may involve a medical visit, consultation with a specialist, or laboratory testing.

Relapse always should be ruled out as a reason for loss of stability. Continued or resumed use of short-acting opioids during methadone treatment may increase tolerance and render the current dose inadequate. In such a situation, in addition to an increase in the methadone dose, efforts to encourage abstinence from nonprescribed substances or intensification of addiction treatment are indicated.

The use of drugs such as alcohol and benzodiazepines may require methadone dose reductions to counter oversedation, and this can significantly interfere with adequate control of opioid craving. If the patient is using a sedative known to produce a medically significant withdrawal syndrome, the physician must determine whether medically supervised withdrawal from the sedative is necessary and where and how such withdrawal should be accomplished. Withholding or reducing the methadone dose may help prevent oversedation.

If use of a short-acting opioid continues to produce euphoria, an increased methadone dose sufficient to block the effect may be offered. A dose increase also may help suppress drug craving. Coordination with other prescribing physicians to limit the number of short-acting opioids being prescribed also is important (Kauffman, 2008; Paulozzi et al., 2011).

## SUMMARY

Methadone maintenance treatment has been the subject of hundreds of clinical studies and outcomes assessments. Overall, such studies have found that treatment with methadone is safe and effective for most patients. Experience suggests that most methadone deaths in OTPs occur during the induction period because the initial dose is too high, the dose is increased too rapidly, or the methadone interacts with another drug.

The ASAM Methadone Action Group affirms that methadone can be dispensed safely and effectively so long as the potential risks are recognized and appropriate action is taken to prevent problems, where that is possible, and to address them rapidly and effectively if they arise. Careful prescribing, patient education, and intervention at the first sign of toxicity can reduce the risk of overdose.

The Action Group acknowledges that these clinical recommendations present certain implementation challenges. However, members of the group are convinced that the use of careful protocols for methadone induction and stabilization, coupled with increased clinical vigilance, will save lives in this vulnerable patient population.

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## APPENDIX

### **Sources of Information About Methadone Induction and Stabilization**

<http://www.dpt.samhsa.gov>: Contains extensive resources about methadone for providers and patients.

<http://www.kap.samhsa.gov/products/manuals/tips/numerical.htm>: The following Knowledge Application Program publications are representative of multiple resource

documents that can be ordered or downloaded at no cost:

- Substance Abuse and Mental Health Services Administration. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 08-4214. Rockville, Maryland, 2005; reprinted 2006, 2008, and 2010.
- Substance Abuse and Mental Health Services Administration. Treatment for Persons with Co-Occurring Disorders. Treatment Improvement Protocol (TIP) Series 42. HHS Publication No. (SMA) 08-3992. Rockville, Maryland, 2004; reprinted 2005, 2006, 2008, and 2009.
- Substance Abuse and Mental Health Services Administration. SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 13-4742. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013 (download from: <http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/All-New-Products/SMA13-4742>).

<http://QTdrugs.org>: Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes Ventricular Arrhythmia. Tucson, AZ: University of Arizona Center for Education and Research on Therapeutics (CERT). Periodically updated.

<http://drug-interactions.com>: Flockhart D. Cytochrome P450 Drug Interaction Tables: Indiana University School of Medicine. Periodically updated.