ADDICTION TREATMENT

Forum

Methadone Dosing & Safety

in the Treatment of Opioid Addiction

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ABSTRACT

Methadone maintenance treatment (MMT) has a long history of effectiveness and safety as a therapy for opioid addiction. However, since it is a highly potent drug, methadone's improper prescription and/or its misuse can be harmful or even fatal.

The most adequate methadone dose provides an effective response in the patient, with a margin for safety, for an appropriate duration of time. However, there is wide variation in patient response, due in part to the complexities of how methadone works and individual patient differences. Methadone dosing should be determined on an individual basis, *without* artificial dose limits, while exercising caution to avoid adverse effects.

The key to initiating methadone dosing is to start low and go slow. However, research evidence confirms that maintenance doses ultimately greater than commonly considered in some MMT programs may be necessary for many patients. Clinical signs and patient-reported symptoms of either overmedication or withdrawal, along with drug craving and/or continuing illicit-opioid use, are vital indicators for achieving dose adequacy.

Finally, patient education is an essential component of safety in MMT. This should be combined with efforts to foster open, trusting relationships between patients and clinic staff, which will produce the most successful treatment outcomes.

Evidence-Based Perspectives

Methadone, a synthetic-opioid medication, is among the oldest and most thoroughly studied drugs in modern medicine. Since the advent of methadone maintenance therapy (MMT) in the mid-1960s for treating opioid addiction, it has helped millions of persons worldwide in recovery to achieve more normal and productive lives.

When properly prescribed and used, methadone is an effective and safe medication. Yet, many MMT professionals have been guided in their methadone-prescribing practices more by philosophical, moral, or psychological rationales than by sound pharmacological and clinical principles (Loimer and Schmid 1992).

This paper examines evidence-based principles and expert opinions regarding "best practice" approaches. Such information can help shape clinical intuition allowing practitioners to reliably prescribe more adequate and safe doses of methadone for better patient care and achieving favorable treatment outcomes.

Balancing Risks & Benefits

There are three immediate objectives of methadone maintenance (Maremmani et al. 2002, 2003; Payte 2002):

1) suppress signs and symptoms of opioid withdrawal,
2) extinguish opioid-drug craving, and
3) block the reinforcing effects of illicit opioids ("blockade").

Each of these objectives is accomplished in phases, rather than at once, relying on the administration of *adequate* methadone doses to achieve and sustain optimum blood levels of the drug (Health Canada 2001). Although too much methadone can be harmful, insufficient methadone is largely ineffective (Verster and Buning 2000).

Methadone has been demonstrated throughout many years of clinical study as having a favorable safety profile. No serious adverse reactions or other organ damage have been associated with continued MMT (Kreek 1973a) extending more than 20 years in some patients (Novick et al. 1993).

All-cause mortality in methadone-treated patients is typically many-fold lower than in untreated opioid addicts (Gearing and Schweitzer 1974; NIH 1997), and studies have consistently shown that the risk of communicable infection is significantly reduced by participation in MMT, even in patients falling short of total abstinence from illicit drugs (Leshner 1999). Studies over the years have demonstrated that the relative risk of death is at least 3 to 4 times *less* for patients continuing in MMT compared with those who discontinue treatment (Bell and Zador 2000; Humeniuk et al. 2000).

Still, methadone is a potent drug and there have been reported cases of fatal poisoning associated with it. The primary toxic effect of excessive methadone in the non-tolerant individual is respiratory depression with pulmonary edema and/or aspiration pneumonia (Harding-Pink 1993b; Humeniuk et al. 2000; White and Irvine 1999). Relatively large proportions of methadone-associated deaths, beginning with the earliest reports, occurred during start-up of methadone maintenance, usually linked to a failure to determine the presence and extent of existing opioid tolerance in new patients and/or patients' continued substance abuse.

During later stages of MMT, other drugs in addition to methadone have been detected in most but not all cases of drug-induced death. Deaths among MMT patients often have been associated with physical disorders related to pretreatment lifestyles (e.g., infectious diseases), and deaths in those leaving MMT often were connected to drug-related violence, accidents, or overdose, which had been diminished during participation in treatment (Appel et al. 2000; Petry et al 1998).

How Methadone Works - Pharmacology

In the treatment of opioid addiction, methadone works primarily via μ-opioid receptors in the brain, where it attaches and, in sufficient quantity, blocks effects of other opioid agents, such as heroin. Oral methadone is 80 to 95% bioavailable, compared with only 30% for oral morphine, and readily enters the circulation after ingestion (Eap et al. 2002).

Methadone is broken down (metabolized) to form a number of metabolites that are essentially inactive and nontoxic (Moody et al. 1997). The elimination half-life of methadone averages 24 to 36 hours at steady state, but may range from 4 to 91 hours, and its rate of clearance from the body can vary by a factor of almost 100 (Inturrisi and Verebely 1972; Loimer and Schmid, 1992; Payte and Zweben 1998).

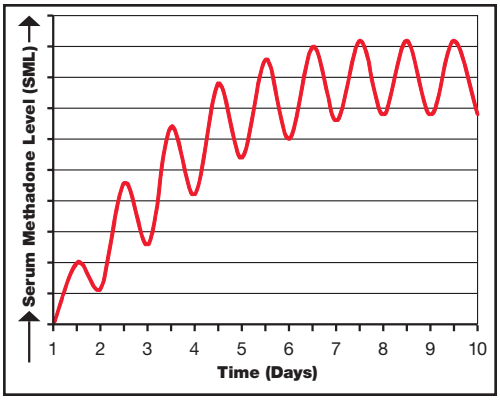
Methadone is stored extensively in the liver and secondarily in other body tissues (Humeniuk et al. 2000). The amount in the blood stream – the serum methadone level or *SML* – is kept relatively constant by the slow release of methadone from tissues, which helps account for its long half-life (Borg and Kreek, 2003).

Typically, 4 to 5 half-lives of a drug are required to attain steady-state SMLs, wherein elimination of the drug is in balance with the amount of drug remaining in the body (Benet et al. 1996). In the case of methadone, steady-state usually requires 4 to 5 days; although, it can take much longer in some individuals (Eap et al. 2002; Payte and Khuri 1993). Once steady state concentration is reached, peak (high) and trough (low) SMLs remain about the same from one dosing interval to the next (***Figure 1***), unless something offsets the balance; such as, physical illness or an interacting substance.

During the start-up methadone-induction period, prior to steady-state, an essential consideration is that half of each day's dose remains in the body and is added to the next day's, producing rising SMLs *even without any increase in dose* (Payte 2002). Therefore, dose increases until full steady-state is reached must be considered cautiously. After each increase in methadone, it will take 4 to 5 days, or more, to achieve steady-state at the new total dose (Payte et al. 2003).

Figure 1: Steady-state methadone concentration reached in about 5 days.

Adapted from Payte 2002.



The SML typically reaches a peak in 2 to 4 hours on average (range 1-5 hours) after dosing, but its elimination half-life and the patient's physiologic response may be influenced by numerous factors (***Table 1***). Considerable flexibility in dosing is required to stabilize patients in whom methadone's actions may be so variably affected (Borg and Kreek 2003; Eap et al. 2002; Leavitt et al. 2000; Payte et al. 2003).

Table 1: Factors Affecting Response to Methadone

- Alcohol, tobacco use
- Illicit drug use
- Prescribed and OTC medications or vitamins
- Herbal/alternative products
- Diet, nutritional state
- Psychological stress
- Psychiatric illness
- Physical disorders, disease, infection
- Liver, GI, renal function
- Pregnancy, menopause
- Genetic variations in metabolism

Source: Leavitt 2003

Oral methadone used in MMT comes as solid tablets, dispersible tablets, or premixed liquid. Research has demonstrated that the three formulations are equally potent in effect (Kreek 1973b, Gourevitch et al. 1999), although *subjective* reactions of patients to each formulation can vary.

Methadone metabolism is largely a function of liver enzyme activity involving cytochrome P450 isoforms (CYP450 enzymes). Drugs that *induce* activity of these enzymes can accelerate methadone metabolism, abbreviate the duration of its effect, lower the SML, and precipitate abstinence (withdrawal) syndrome. Conversely, CYP450 *inhibitors* may slow methadone metabolism, raise the SML, and extend the duration of its effects (Kreek et al. 1976; Leavitt et al. 2000; Payte and Zweben 1998). Several CYP450 isoforms — CYP3A4, CYP2D6, and to a smaller extent CYP1A2— are significantly involved in methadone metabolism (Eap et al. 2002; Foster et al. 1999).

Genetic and environmental factors can act on those enzymes, leading to a high degree of individual variation in methadone's apparent potency. In patients taking exactly the same dose of methadone, corrected for body weight, concentrations of active methadone can vary extensively even in the absence of interacting substances (Eap et al. 2002).

When interactions with other substances occur, changes in SMLs could result in problematic methadone under- or overmedication. Various sources may be consulted regarding drugs/substances that are metabolized via CYP450 enzymes and could alter methadone blood levels (DeMaria 2003; Eap et al. 2002; Gourevitch 2001; Leavitt 1997) or have metabolic potential for interacting with methadone (Flockhart 2003 at http://drug-interactions.com).

SMLs vs Signs/Symptoms

Some researchers have recommended using serum methadone levels (SMLs) as a diagnostic tool for guiding dosing decisions (Loimer and Schmid 1992), and have noted a correlation between "poor performance" in MMT and lower methadone plasma levels (Tennant et al. 1984). Measuring SMLs — in nanograms (1-billionth gram) per milliLiter, ng/mL — might be a helpful diagnostic aid in difficult cases; however, the methadone dose does not always correlate with the SML.

Although a strong correlation between methadone dose and SML was originally reported by Wolff et al. (1991), extensive differences across individual patients must be considered (Leavitt et al. 2000; Okruhlica et al. 2002). Recent data have demonstrated virtually no correlation between trough or peak SMLs at doses above 100 mg/d (Dorsey 2003, see ***Figure 2***). Thus, it appears that methadone dose may have poor overall predictive value for estimating trough *or* peak SML values.

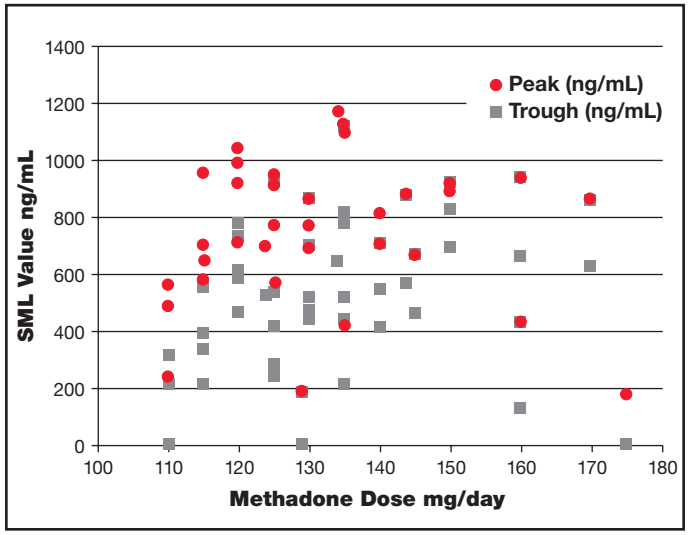


Figure 2: Lack of correlation between methadone dose and either trough *or* peak SML values in methadone-maintained patients (Dorsey 2003).

Payte and colleagues (2003) have emphasized that the ratio between peak and trough SML measures can be most clinically useful. The peak SML occurring at roughly 2 to 4 hours post-dosing should be no more than twice the trough level. This would provide an optimal peak-to-trough ratio of 2 or less.

Regardless of particular serum level readings or ratios the patient may not be properly dosed (Leavitt et al. 2000; Maxwell and Shinderman 1999). Clinical signs and patient-reported symptoms can be the most effective indicators of dose adequacy (***Table 2***).

Table 2: Signs/Symptoms of Opioid Withdrawal (Abstinence Syndrome) & Overmedication

Overmedication Signs and Symptoms	Sedation ("nodding-off," drowsy), miosis (pinpoint pupils), itching/scratching, hypotension, respiratory depression (severe in overdose), depressed mental status, flushing, spasticity. Also, mild euphoria/invigoration (temporary).
Therapeutic Comfort Range	**No withdrawal or overmedication. Ultimately, no craving or illicit opioid use.**
Withdrawal Subjective Symptoms	Drug craving, anxious feelings, depression, dysphoria, irritability, fatigue, insomnia, hot/cold flashes, myalgia/arthralgia (aching muscles/joints), anorexia, nausea, abdominal cramps, restlessness.
Withdrawal Objective Signs	Illicit opioid use, mydriasis (dilated pupils), piloerection ("goose flesh"), diaphoresis (perspiring), muscle tremors/twitching (shaking), diarrhea, vomiting, lacrimation, rhinorrhea, sneezing, yawning, anxiety (outward signs), fever, tachycardia, hypertension.

Sources: Health Canada 2001; Leavitt et al. 2000; Strang 1999.

As the SML rises, objective signs of withdrawal disappear and subjective symptoms are a guide for further dose increases. At the optimal methadone dose, the SML stays in the therapeutic "comfort" range for that *individual patient* throughout the dosing period. If the methadone SML becomes too high, signs/symptoms of overmedication appear.

It is important to note that subtle effects of overmedication can include mild euphoria ("feeling good"), extra energy, staying up late to work, etc., which patients may perceive as falsely beneficial. The effects wear off and, then, patients may seek unnecessary and possibly harmful dose increases (Payte 2002).

Each patient poses a unique clinical challenge. Practitioners are cautioned against making the mistake of "treating SML test results" or dogmatically adhering to biased preconceptions of what is "enough" methadone, and thereby ignoring signs/symptoms as a guide to achieving optimal dosing (Leavitt et al. 2000).

The Importance of Tolerance

Methadone can be toxic to anyone who is not tolerant of opioids and a single dose can cause life-threatening respiratory depression (Harding-Pink 1993b). However, an opioid-tolerant person can function normally at doses that can be fatal to a non-tolerant person. Opioid tolerance is a complex process of neuroadaptation and even experienced opioid users can be at risk of toxic methadone effects (Strang 1999).

It is essential to estimate an individual's opioid-dependence, and associated tolerance, *prior to* initiating methadone treatment. Most methadone-associated deaths have been in persons with little or no tolerance to opioids (Buster and van Brussel 1996).

The traditional definition of tolerance is reduced response to one or more effects of a drug after repeated administrations (Kosten and George 2002; O'Brien 1996). Essentially, cells with opioid receptors become less sensitive to opioid stimulation and more drug is needed to achieve the same effects.

However, tolerance develops much more rapidly to some opioid effects than others. For example, tolerance develops quickly to the euphoric effects of opioids, while tolerance to gastrointestinal effects (e.g., constipation), sedation, or respiratory depression is slower to develop. This can be potentially fatal if users ingest increasingly greater amounts for euphoria (Harden 2002; White and Irvine 1999). In the case of methadone, tolerance development is incomplete (Kosten and George 2002), so respiratory depressant effects of other agents – e.g., alcohol, sedatives, opioids – or acutely excessive methadone may not be completely blocked even in persons at stabilized methadone-maintenance doses.

Dosing Stages & Safety

The outpatient MMT process moves through different phases, from start-up *induction* through stabilization on a *maintenance* dose (***Table 3***). Dose variations may be required throughout treatment in response to changing physiologic conditions and environmental influences affecting the patient.

Table 3: Phases of MMT

Phase	Objective
Initial Induction	Relieve withdrawal (abstinence) symptoms.
Early Induction	Reach tolerance level, reduce craving.
Late Induction Stabilization	Establish adequate dose (physical and emotional well-being)
Maintenance	Preserve desired effects (steady-state occupation of opioid receptors)

Sources: Leavitt 1999; Maremmani et al. 2003; Payte 2002

Starting Methadone

Starting methadone – induction – requires caution. Several risk factors have been noted: 1) initial dose quantity, 2) concomitant use of other drugs, and 3) general health of the patient (Humeniuk et al. 2000).

The risk of death during methadone induction has been calculated as nearly 7-fold greater than patients' risks of death prior to entering MMT (Caplehorn and Drummer 1999), and nearly 98 times greater for new patients than for patients who have been safely receiving methadone for more than two weeks (Karch and Stephens 2000). Deaths usually occur during the first 3 to 10 days of treatment (Payte 2000; Zador and Sunjic 2000; Wagner-Servais and Erkens 2003), at home during sleep, many hours after peak SML has occurred (Caplehorn 1998). Abnormal methadone metabolism or other factors in an individual can mean that methadone doses that would usually have been safe and appropriate can lead to potentially fatal overdose (Humeniuk et al. 2000).

A most critical aspect is the person's opioid tolerance at the time of initiating treatment, based on the patient's history of opioid type used, frequency, quantity, and route of administration (Payte and Khuri 1993; Strang 1999; Tenore 2003). However, tolerance level can be difficult to gauge.

For example, urinalysis may indicate illicit opioid use, but it does not indicate the dose, frequency, or time of last use (van Beusekom and Iguchi 2001). Some persons claiming to be regular opioid abusers may be either opioid naïve or occasional users, and infrequent opioid use does not engender tolerance with any certainty. Also, severity of withdrawal signs/symptoms alone, in the absence of other evidence, is *not* necessarily an indicator of tolerance or the need for higher starting doses. If any persons are started at methadone doses in excess of their established tolerance it can lead to overdose (Baden 1970).

Furthermore, U.S. federal regulations require that a complete physical examination, including all laboratory tests, must be completed for each patient within 14 days following admission to MMT (Federal Register 2001). However, considering the potential for physical disorders and adjunctive medications to interact with methadone, a physical examination, including a comprehensive history taking and cardiac health assessment, might be advised as part of the admission process. Researchers have reported deaths during induction associated with pre-existing physical illness, such as bronchopneumonia, hepatitis, or epilepsy (Drummer et al. 1992; Zador and Sunjic 2000). Any illness affecting respiratory health, drug metabolism or elimination, neurologic status, or cardiac function would be of special concern, suggesting closer monitoring of patients during induction and ongoing MMT.

Induction Dose Recommendations

The objective of the methadone induction process is to approximate the patient's opioid-tolerance level with methadone, thereby reducing withdrawal and opioid craving. A further aim is to diminish or eliminate other opioid use as rapidly as possible without sacrificing patient safety (Payte 2000).

Since there is no scientific formula for calculating opioid tolerance, the prudent methadone-dosing advice is to initially ***start low and go slow*** (Health Canada 2001). However, with an overly conservative approach to induction, the patient may self-medicate withdrawal symptoms with illicit substances (Humeniuk et al, 2000). Conversely, an overly aggressive strategy may result in methadone overdose or at least overmedication as peak SMLs rapidly rise (Health Canada 2001; Payte 2000).

Authorities in various countries have published guidelines for methadone induction dosing, and these are summarized in ***Table 4***. In general, care is needed in starting a dose toward the upper part of the indicated ranges; however, if a small dose is used (e.g., 10

Table 4: Induction Dosing Guidelines

Methadone Dose Range	Country (Ref)
Initial dose not to exceed 30 mg, or 40 mg total in first day.	USA (Federal Register 2001)
Initial dose 10-20 mg if tolerance is low or uncertain; 25-40 mg if opioid tolerance established.	UK (Strang 1999)
Initial dose 10-20 mg if opioid tolerance is low or uncertain; 25-40 mg if tolerance is high.	Europe (Verster and Buning 2000)
20-30 mg/d at first, more than 30 mg on first day only in patients with tolerance threshold known to be quite high.	EUROPAD Italia (Maremmani et al. 2002)
15-30 mg/d during the first 3 days (which represents time to 87.5% of steady state).	Canada (Health Canada 2001)
Initial dose 20-40 mg, based on estimated tolerance and documented drug use 3-days prior.	Australia (Humeniuk et al. 2000)

mg), further small doses (5-15 mg range) may be given based on the severity of *observed* withdrawal signs once peak SML has been reached (Payte et al. 2003).

The maximum of 40 mg allowed the first day by some guidelines might be considered excessive and require extra vigilance. Deaths during the first week of MMT in patients started at that dose have been reported by several sources (Humeniuk et al. 2000; Wagner-Servais and Erkens 2003; Zador and Sunjic 2000).

During methadone induction, patients may be in mild withdrawal toward the *end of the dosing interval*, so doses are *NOT* automatically increased based on how patients feel at 12 or more hours after dosing. Rather, patients are asked how they felt 3 to 8 hours after the last dose, and if they were relatively comfortable no increase is given (Payte 2000; Tenore 2003).

Some guidelines specify that, during the first week, doses should be increased by no more than 5 to 10 mg on any day and the total weekly increase beyond the starting day's dose should not exceed 20 mg (Verster and Buning 2000) or 30 mg (Strang 1999); although, some modifications of these limits might apply in special circumstances. At any dose, use of alcohol, sedatives, and/or short-acting opioids (e.g., heroin, oxycodone, hydrocodone) during induction significantly increases the risk of overdose death (Health Canada 2001; van Beusekom and Iguchi 2001).

There is no induction dosing protocol that has proved absolutely safe for all patients and, during the early days of induction, clinical observation of patients after dosing until peak SMLs are reached might be recommended. Methadone blood levels may rise up to 7-fold during the induction period with no change in dose, SMLs continue to rise for roughly 5 days after increasing a dose (Verebely et al. 1975), and toxic accumulation can occur even two weeks after treatment initiation (Health Canada 2001). If patients experience overmedication effects, their dose should be reduced or, at most, maintained an additional 5 to 7 days while more opioid tolerance develops (Tenore 2003).

The induction phase lasts until a steady-state methadone level is achieved (Payte et al. 2003). Payte (2000) has suggested a helpful checklist of induction safety tips, presented in ***Table 5***.

Achieving Stabilization

Once at a steady-state level, methadone should be present in sufficient concentration to maintain a therapeutic "comfort range" throughout the dosing interval (Payte et al. 2003). There is no clear relationship between prior "heavy" abuse of an opioid and the methadone dose ultimately required for stabilization (Health Canada 2001).

Initial research discovered that 80 to 120 milligrams of methadone for daily maintenance, on average, was sufficient for many patients (Dole et al. 1966). Due to individual patient factors (*Table 1*, above) some require significantly greater doses for treatment success, sometimes exceeding 200 mg/d (Leavitt et al. 2000; Payte et al. 2003).

Criteria for continued dose increases for stabilization include (Health Canada 2001):

- Signs/symptoms of withdrawal (objective and subjective);
- Persistent craving for opioids;
- The amount or frequency of opioid use not decreasing.

Dose adjustments during stabilization are usually in the 5 to 10 mg/d range – no more frequent than every 3 to 4 days (Health Canada 2001), or 5 days (Tenore 2003) – or a 20 mg/d total increase per week (Verster and Buning 2000). Some flexibility in this approach might be acceptable, provided there are no signs/symptoms of overmedication. Adequate dose cannot be determined by solely objective measures (including SMLs), and early withdrawal is purely subjective, so a consideration of patient self-reports is an important guide to continued dose increases (Payte and Khuri 1993; Verster and Buning 2000).

High doses of methadone are often necessary *and* safe, provided dose increases are modest and sufficient time elapses between escalations. However, patients with debilitating illness or who are sensitive to opioid effects may require longer intervals between dose increases and ultimately lower doses (Tenore 2003).

Table 5: Safety Tips During Induction

- ☐ Document all drug use, abuse, and addiction, noting drugs used, frequency, administration routes, and amounts. Include, to the extent possible, opioid-use patterns during 12 months, 30 days, and 24 hours prior to admission.
- ☐ Document the basis for determining opioid *physical* dependence (e.g., 2 or more objective signs plus subjective symptoms).
- ☐ An instant opioid urine screen is recommended.
- ☐ Adequacy of methadone dose during induction is based primarily on response at 3-8 hours after each dose, not at the end of dosing period (24 hours after last dose) when withdrawal is likely to be present.
- ☐ No further increase is required the following day if the patient was comfortable, without overmedication, during 3-8 hours after dosing.
- ☐ Any indication of overmedication during the 3-8 hour post-dose period is a basis for dose reduction, regardless of condition at 24 hours. (Reminder: overmedication can include feeling "good" with increased energy.)
- ☐ If a patient who was normal at 3-8 hours insists on the need for dose increase, give same dose as previous day and reassess the patient in 2-4 hours.
- ☐ Inform patient that peak blood levels of methadone increase daily even if the dose stays the same until steady-state is achieved. Patient may need *more time, not more methadone*.
- ☐ Remember: patients may provide false information at any time in a misguided attempt to get more methadone. Results can be fatal.
- ☐ Patients and their "significant others" (with permission) must be informed about signs/symptoms of methadone toxicity. Overmedicated patients are never allowed to "sleep it off" – help is needed immediately.

Modified from Payte 2000.

Ongoing Methadone Maintenance

Continued opioid use or relapse can be virtually eliminated in most patients via adequate methadone dosing practices (Eap et al. 2000). However, as Harding-Pink (1993a) once observed, **one person's methadone maintenance dose is another's poison, and vice versa**. Hence, the importance of *individualized* methadone dosing regimens for maintenance must be stressed.

What Is An Optimal Dose?

Over the years there have been many clinical trials comparing various doses of methadone for maintenance treatment. A consistently reported finding is that patients receiving higher methadone doses compared with those at lower doses exhibit superior outcomes; in terms of such variables as illicit-opioid abstinence, retention in treatment, and psychosocial rehabilitation (Eap et al. 2002; Leavitt 2003; Maremmani et al. 2003, Payte et al. 2003).

For example, in a review of 29 clinical studies examining methadone dosing in MMT – comparing average doses ranging from 0 mg/d (placebo) up to 250 mg/d (and 780 mg/d in one trial) – Maremmani et al. (2003) concluded that there is no evidence of lower doses being adequate for the vast majority of patients. Just how large a dose is "enough" depends on individual patient needs.

Clearly, while some patients thrive on doses well below 100 mg/d, others require hundreds of milligrams of methadone daily. For example, patients with high levels of emotional distress or psychiatric disorders often need increased methadone for stability (Maremmani and Shinderman 1999; Maxwell and Shinderman 1999; Verster and Buning 2000).

Vincent Dole (a developer of MMT), once observed: "There is no compelling reason for prescribing doses that are only marginally adequate. As with antibiotics, the prudent policy is to give enough medication to ensure success" (Dole 1988).

Also, Payte (2002) recently noted, "Arbitrary dose ceilings have no foundation in science or clinical medicine. Programs with 'dose caps' can expect problems with accreditation." Furthermore, such "caps" are not endorsed by the U.S. federal regulations or addiction medicine associations.

From a safety perspective, in a meta-analysis of methadone dosing studies, Caplehorn et al. (1996) found that patients having access to "high-dose maintenance" were at *reduced risk* of fatal heroin overdose during treatment compared with those at lower doses. Unfortunately, there have been no published studies directly examining effects of methadone maintenance dose amount on MMT patients' mortality.

The Utility of SMLs

Serum methadone levels (SMLs) are often of minimal clinical value, but they can be helpful in *special cases* to confirm a need for methadone dose increases and in identifying patients who may benefit from split daily dosing (Tenore 2003). On average, researchers have affirmed the benefit of a 150 to 600 ng/mL *trough* SML to suppress opioid craving and a trough level at or above 400 ng/mL to provide sufficient opioid blockade during methadone maintenance (Dole 1988; Eap et al. 2002; Leavitt et al. 2000; Payte et al. 2003). Clinical studies have demonstrated that methadone doses widely ranging from 50 mg/d to more than 900 mg/d may be necessary to achieve those optimal steady-state trough SMLs (Eap et al. 2000).

The goal is a trough level of 400 to 500 ng/mL and a peak of about twice that amount (e.g., 800-1000 ng/mL). Lower or much higher levels are acceptable if patients are illicit-opioid-free and exhibit neither withdrawal nor overmedication. Based on clinical experience, Tenore (2003) has divided trough SMLs into several ranges for interpretation (***Table 6***). However, the clinical presentation of the patient should *always* override serum level values (Gagjewski and Apple 2003).

A definitively toxic serum level of methadone for all persons is undetermined. SMLs reported in methadone-associated deaths commonly overlap those SMLs considered as therapeutic during MMT (Gagajewski and Apple 2003; Milroy and Forrest 2000; Sorg and Greenwald 2002). In review articles, methadone concentrations observed as fatal have ranged from 60 to 4,500 ng/mL (Mikolaenko et al. 2002; Wolff 2002). Therefore, monitoring patients for clinical signs/symptoms of overmedication is more critical than merely following trough or peak SML values.

Table 6: Interpreting Methadone SML Values

Trough Level	Clinical Effect
≤ 200 ng/mL	Subtherapeutic, withdrawal likely.
> 200-400 ng/mL	Sometimes little or no withdrawal, but opioid blockade probably incomplete.
> 400-500 ng/mL	Optimal, usually no withdrawal and opioid blockade achieved.
> 500-700 ng/mL	Withdrawal unlikely, but possible: monitor clinically for overmedication.
> 700 ng/mL	Withdrawal unlikely, examine other reasons for any discomfort (and monitor for overmedication)

Patient's clinical presentation should override SML values.

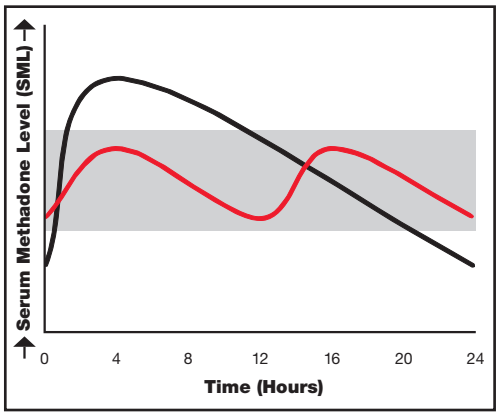
Source: Tenore 2003

Split Dosing

At any dose, if a patient is clinically overmedicated several hours after dosing but experiences withdrawal before it is time for the next dose – and/or the peak SML is more than twice the trough level (P:T ratio > 2.0) – splitting the daily methadone dose should be considered (***Figure 3***). In such cases, further once-a-day dose increases will not make the dose last longer and would only elevate the peak level, *not* the trough level. This results in greater overmedication during early hours but continued opioid withdrawal later (Payte and Khuri 1993; Payte 2002, Tenore 2003).

Figure 3: Splitting the dose (red line) keeps SML within the therapeutic range (gray zone), which corrects a high peak and low trough level (black line).

Adapted from Payte 2002.



Take-Home Doses

Take-home methadone doses for unsupervised self-administration are allowed under U.S. federal regulations (Federal Register 2001, ***Table 7***). However, individual state requirements may be more restrictive.

To qualify for more than a single day's take-home dose per week (if the clinic is closed for Sundays or a holiday), patients are expected to demonstrate capabilities of handling and taking methadone unsupervised, including: abstinence from unauthorized substances, regular clinic attendance, absence of behavioral problems or criminality, stability of home environment and social rela-

Table 7: Take-Home Methadone U.S. Federal Regulations	
Tenure in MMT	**No. of Day's Doses**
From start up (week 1+)	1 *(if clinic is closed on Sunday or holiday)*
First 90 days (0-3 mo. tenure)	1 added day/week *(2 days maximum)*
Second 90 days (3-6 mo. tenure)	1 added day/week *(3 days maximum)*
Third 90 days (6-9 mo. tenure)	1 added day/week *(4 days maximum)*
Fourth 90 days (9-12 mo. tenure)	2 added days/week *(6 days maximum)*
After 1 year (12+ mo. tenure)	Two-week supply *(14 days maximum)*
After 2 years (24+ mo. tenure)	One-month supply *(once/month visit)*
Tenure includes continuous participation in MMT while also meeting all requirements for take home doses. Presumably, a day's supply might include more than one dose in the event of split doses.	

tionships, assurance that methadone can be safely stored, and whether the rehabilitative benefits to the patient of decreased clinic attendance outweigh potential concerns regarding methadone diversion (Federal Register 2001).

Current U.S. federal regulations do not specify patient employment as a qualification for take-home methadone, nor are there restrictions on the dose amount in mg/d. Oral methadone may be distributed for take-home as liquid, solid tablets, or dispersible tablets (Federal Register 2001).

"Poison Cocktails"

Long ago, Roizin and colleagues (1972) called attention to the "poison cocktail" resulting from the intake of multiple psychotropic ("mind-acting") drugs, including methadone. Interactions can be *additive*, in which the net effect is the sum of the substances' individual harmful effects, or *supra-additive* (synergistic or potentiating) when total effects are greater than if just additive.

In cases of methadone-associated death, alcohol, benzodiazepines, and/or other opioids are frequently implicated (Zador and Sunjic 2000). In themselves, these other substances can be relatively moderate respiratory depressants, but when combined with each other and/or methadone the effects may be lethal (White and Irvine 1999). Numerous factors affect toxic drug interactions and their lethality, including: health status and pre-existing tolerance of the person, the number and type of drugs taken, and drug dosages (Roizin et al. 1972).

Patient Education is Essential

Educating patients, and their "significant others" (with permission), is essential for safety and treatment success. There are many myths and much misinformation surrounding methadone. Patients expecting MMT to quickly and easily solve their addiction problems are likely to be disappointed and uncooperative.

Among other things, patients need a basic understanding of how methadone works and what to realistically expect. They must appreciate that there is a delay of 2 to 4 hours before methadone has peak effect and there can be an accumulation of the drug after a dose increase.

Patients must be cautioned about the hazards of continued substance abuse or deceit about such practices. They, and those close to them, should be provided adequate information about signs/symptoms of methadone overmedication, which is especially critical during the induction stage.

Efforts to foster open, trusting relationships between patients and clinic staff will produce the most successful treatment outcomes. Patients need to feel that dosage adjustments, up or down, are for their comfort and safety; rather than rewards or punishments. Dosing decisions should always be made on clinical grounds, with patients involved in decisions and informed of the reasons – just as would be the case with other prescribed medications or medical procedures.

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