When "Enough" Is Not Enough:

New Perspectives on Optimal Methadone Maintenance Dose

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Abstract

Some methadone maintenance treatment (MMT) programs prescribe inadequate daily methadone doses. Patients complain of withdrawal symptoms and continue illicit opioid use, yet practitioners are reluctant to increase doses above certain arbitrary thresholds.

Serum methadone levels (SMLs) may guide practitioners' dosing decisions, especially for those patients who have low SMLs despite higher methadone doses. Such variation is due in part to the complexities of methadone metabolism. The medication itself is a racemic (50:50) mixture of 2 enantiomers: an active "R" form and an essentially inactive "S" form. Methadone is metabolized primarily in the liver, by up to five cytochrome P450 isoforms, and individual differences in enzyme activity help explain wide ranges of active R-enantiomer concentrations in patients given identical doses of racemic methadone.

Most clinical research studies have used methadone doses of less than 100 mg/day [d] and have not reported corresponding SMLs. New research suggests that doses ranging from 120 mg/d to more than 700 mg/d, with correspondingly higher SMLs, may be optimal for many patients.

Each patient presents a unique clinical challenge, and there is no way of prescribing a single best methadone dose to achieve a specific blood level as a "gold standard" for all patients. Clinical signs and patient-reported symptoms of abstinence syndrome, and continuing illicit opioid use, are effective indicators of dose inadequacy. There does not appear to be a maximum daily dose limit when determining what is adequately "enough" methadone in MMT.

Key Words: Methadone, therapeutic dose, serum methadone levels, pharmacokinetics, metabolism, clinical implications.

Introduction — Shaping Clinical Intuition

PATIENTS IN METHADONE MAINTENANCE TREATMENT (MMT) programs frequently complain of withdrawal symptoms and continue their high-risk behaviors. They protest, "My dose isn't holding me"; "I have drug cravings at night"; or "I wake up sick every morning" (1). Yet practitioners may be reluctant to increase methadone doses above certain thresholds, believing patients are already receiving "enough" of the medication (1). Payte and Khuri (2) have defined "enough" methadone as "the amount required to produce the desired response for the desired duration of time, with an allowance for a margin of effectiveness and safety." However, the issue of optimal methadone dosing during maintenance therapy — what is "enough" under various circumstances — still seems unresolved.

Vincent Dole, a co-developer of MMT in the mid-1960s, advised that (3) "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." However, MMT programs may prescribe inadequate daily doses of methadone more for philosophical, moral, or psychological reasons than for sound pharmacological and clinical ones (4). Many clinicians also assume that lower doses automatically prevent toxicity and eventually engender opioid abstinence (5).

Some researchers have recommended routine therapeutic drug monitoring using serum methadone levels (SMLs) as a diagnostic tool for guiding dosing decisions (4), and have noted a correlation between "poor performance" in MMT and lower methadone serum levels (6). Others have concluded that the determination of such serum levels is not likely to be of practical value in MMT programs (7), and that many patients

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have subtherapeutic SMLs despite "high" methadone doses (7,8).

There are indications that SMLs can be useful when the clinical picture does not agree with the typical or expected response to a given dose of methadone (1), but they must be used and interpreted cautiously. Regardless of a particular serum level reading, the patient may not be getting enough daily methadone (9). Clinical signs and patient-reported symptoms of abstinence syndrome and illicit opioid use can often be the most effective indicators of dose inadequacy.

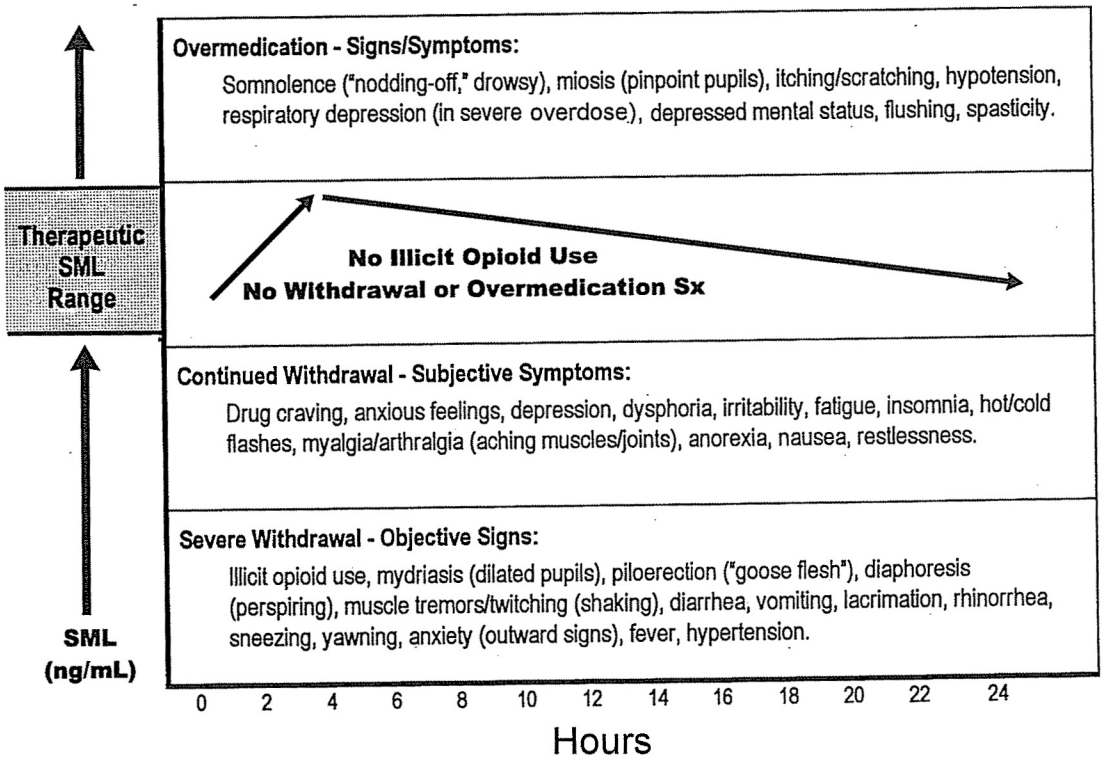
For several reasons discussed in this paper, higher methadone dosing and correspondingly higher SMLs than previously considered necessary or advantageous may be desirable. An understanding of methadone's pharmacokinetics and pharmacodynamics can enhance clinical intuition and assist practitioners in prescribing reliably effective and safe doses that will result in better MMT outcomes.

Traversing Peaks and Troughs

Methadone, administered daily at a steady dose, should be present in the blood at levels sufficient to maintain an asymptomatic state over a 24-hour period, with no periods of opioid overmedication or withdrawal (1, 4). As with any opioid, methadone withdrawal (abstinence syndrome) involves a constellation of clinical signs and symptoms (2, 3, 9, 10–12) (see Table 1). It is important to note that patients may experience subjective symptoms in the absence of observable signs (3), and the onset and severity of withdrawal in methadone-maintained patients are variable, depending on the patient's metabolism of the medication, among other factors.

Table 1

Signs/Symptoms of Opioid Withdrawal (Abstinence Syndrome) and Overmedication (2, 3, 9-12)



SML+ serum methadone level
As the serum methadone level rises, the objective signs of abstinence syndrome disappear and the clinician uses subjective symptoms as a guide for further dose increases. At the optimal methadone dose, the serum methadone level stays in the therapeutic range throughout the 24 hour period. If the methadone dose is too high, signs/symptoms of overmedication appear

The elimination half-life of methadone averages 28 hours or less, but may range from as low as 4 hours to a high of 91 hours. The clearance rate of methadone from the body can vary from individual to individual by a factor of almost 100 (5, 13). Measuring levels of methadone in the blood via SMLs — in nanograms per milliliter (ng/mL) — is helpful in determining just how much of the medication is circulating in the patient's system at the time of testing. Typically, the blood level reaches a high point, or "peak," about 3 to 4 hours after taking the dose, and there is a gradual decline over the remainder of the 24-hour period to a low point or "trough" level before the next dose (1). Although a strong correlation between methadone dose and concentrations in plasma ($r = 0.82$, $p < 0.001$) has been noted (14), the relationship may not be linear. Moreover, there is a need to account for the high degree of inter-individual variation (5, 15–17).

Payte and Zweben have suggested (1) that the peak SML at 3 to 4 hours post-dosing should be no more than twice the trough level, giving an ideal peak/trough ratio of 2 or less. A trough SML alone, although of some use, does not indicate the rate at which the serum level changes over the time-course of a dose (1). However, in everyday clinical practice, measuring peak and trough levels can be time-consuming and invasive, due to necessary multiple phlebotomies (5). In lieu of this, physically evaluating patients for signs/symptoms of overmedication (Table 1) about 3 hours after a dose increase can help to assess whether the peak/trough ratio is appropriate (16).

Researchers have affirmed the need for a trough SML of 150–600 ng/mL to suppress drug craving (1, 3, 4), and a trough level at or above 400 ng/mL to provide adequate opioid cross-tolerance which makes ordinary doses of IV heroin ineffective (non-reinforcing) during MMT (1, 2). Today, many practitioners consider an SML of 400 ng/mL (trough) as adequate therapy for stabilized methadone maintenance. However, Eap et al. (13) have observed that "no study so far has clearly demonstrated the existence of such a threshold [i.e., minimally adequate SML]," and Hiltunen and colleagues (10) noted that recommended SML ranges have not been validated against self-reported clinical symptoms in patients. An optimal trough SML may range from 400 mg/mL to values much higher, and efforts to set methadone ceiling doses and commensurate SMLs by policy or regulation are not based on scientific, clinical, or laboratory evidence (1).

Broad SML Ranges

Patients taking the same methadone doses have SMLs which vary significantly. Bradbury and Paris reported on 55 patients evaluated for ongoing problems with their methadone dose and opiate withdrawal signs/symptoms (15). Average patient time in treatment was 46 months and mean methadone dose was 98 mg/d (range 30–160 mg; mode 100 mg). Trough methadone plasma levels were obtained for all patients upon entry into the study (Table 2).

SMLs ranged from 10–530 ng/mL, with some patients well below adequate trough levels at each methadone dose. Moreover, as Table 2 demonstrates, there was no apparent correlation between methadone dose and SML. More than a third of the patients also were being prescribed psychotropic medications — e.g., antipsychotics, antidepressants, benzodiazepines, anticonvulsants — and this was positively correlated with continued opioid abuse. The authors speculated that there may be limitations in the psychosocial coping mechanisms in such patients influencing continued opioid abuse (15). However, as others have found, there could also have been metabolic interactions of methadone with the prescribed psychotropic medications, and SMLs below therapeutic thresholds for those particular patients (1, 9, 13, 18).

SMLs are generally more appropriate for confirming inadequate dose than for determining the optimum dose, and they should be interpreted within the context of the patient's overall clinical presentation. Bradbury and Paris provide some telling examples (15):

> A woman transferred from an MMT program where she was having difficulties but was told that her 100 mg/d dose was "enough." At the

TABLE 2
MMT Patients Evaluated for Dose/Withdrawal Problems (15)

n	Dose mg/d;	SML — mean ± (SD) mg/mL	SML — range ng/mL
2	30	70 (42.4)	40–100
1	40	20	—
1	50	320	—
4	60	95 (65.6)	10–170
4	70	132.5 (58.5)	100–120
4	80	332.5 (205.7)	150–530
1	90	350	—
20	100	236.4 (122.4)	90–520
2	110	115 (134.4)	20–210
10	120	212.4 (142.4)	10–440
3	140	271.2 (123.6)	130–360
3	160	243.3 (181.5)	50–510

new clinic her dose was raised to 120 mg/d but the plasma level was still fairly low (130 ng/mL). The dose was titrated upward to 180 mg/d, relieving her withdrawal symptoms.

A patient taking several psychiatric medications and 80 mg/d of methadone was experiencing severe withdrawal symptoms. Her trough SML was non-detectable. However, at 140 mg/d she experienced sedation soon after taking her methadone, and opiate withdrawal at night (peak/trough ratio apparently high). Splitting the dose — 70 mg in the morning and 70 mg at night — eliminated both sedation and withdrawal symptoms.

A male patient was stable and free of illicit drugs at 100 mg/d, but insisted on a dose reduction. At a lower dose he soon developed withdrawal symptoms. His blood level tested at 100 ng/mL, convincing him he needed to return to the original dose.

As in the last example, many patients have concerns about needing higher methadone doses and may minimize reported withdrawal symptoms or deny the extent of continued opioid abuse. SMLs can be used as a tool to address those fears, objectively demonstrating when the dose is too low to provide an adequate therapeutic blood level of the medication. And for patients taking co-medications or with organic dysfunctions such as liver or kidney disease, which might interact with methadone metabolism, SMLs can help confirm a need for higher dosing or split doses to achieve desired therapeutic levels (15).

Nuances of Methadone Metabolism

Methadone's peak-trough-average SMLs and its rate of elimination (half-life) may be influenced by several factors, such as poor absorption, metabolism, changes in urinary pH, concomitant medications or drug abuse, diet, physical condition, pregnancy, and even vitamins (1, 15, 18). Considerable flexibility in dosing is required to stabilize patients whose methadone pharmacokinetics may be affected by so many factors.

Methadone itself is a more complex substance than many appreciate. The formulation universally used in MMT is a 50:50 racemic mixture of two molecular forms, or enantiomers, specified as "R" (also called *levo-* or *l-methadone*) and "S" (*dextro-* or *d-methadone*). These two enantiomers have the same chemical composition but different spatial arrangements and kinetics: only R-methadone has clinically significant mu-receptor agonist activity, while the S form is essentially inactive as an opioid agonist. R-methadone also has a higher clearance rate (13).

These differences in methadone structure and action have been known since the earliest days of MMT. In their original 6 patients, Dole (3) tried switching from the usual racemic R/S mixture to S-methadone and noted the gradual appearance of abstinence symptoms. Unaware of the switch, patients reported that they "seemed to be getting the flu." When returned to a mixture also containing the R-enantiomer, the patients again became functionally normal.

Methadone metabolism is largely a function of liver enzyme activity involving cytochrome P450 isoforms (CYP450 enzymes). Drugs that induce these enzymes can accelerate methadone metabolism, abbreviate the duration of its effect, lower the SML, and precipitate abstinence syndrome. Other drugs can inhibit this enzyme activity and slow the rate of methadone metabolism, thereby raising the SML, and extending the duration of methadone's effects (1, 13).

Recent research has demonstrated that several CYP450 isoforms — CYP3A4, CYP2D6, and to a smaller extent CYP1A2, and also possibly CYP2C9 and CYP2C19 — are involved in methadone metabolism (13, 19). Eap and colleagues have reported on genetic and environmental factors acting on these enzymes, leading to a high degree of inter-individual variation in methadone pharmacokinetics (13).

First, the CYP2D6 isoform selectively metabolizes the R-methadone enantiomer. A genetic polymorphism has been described for this enzyme, which is virtually absent in a small portion of the population, resulting in decreased metabolism of methadone. Another segment of the population has very high CYP2D6 activity due to duplication or multiplication of the CYP2D6 gene, and such persons might require very high SMLs of methadone for optimal effect, since there is an increased metabolism of the active R-enantiomer (13).

Second, there is more than a 40-fold inter-individual variation in activity of the CYP1A2 isoform, although it is not genetically polymorphic. CYP1A2 appears to be involved in metabolizing both R- and S-methadone but, overall, plays a relatively minor role. Of interest, tobacco smoking enhances the enzyme's activity, leading to faster methadone metabolism (13, 17).

Third, CYP3A4, the most abundant CYP isoform in the liver, is also expressed in the gut. While there is no genetic polymorphism, there is up to a 30-fold inter-individual variability of its existence and activity in the liver, and up to an

11-fold variability in the gut. CYP3A4 is also involved in the metabolism of many medications, such as selected benzodiazepines, antidepressants, anticonvulsants, antibiotics, and antivirals (including interferon and HIV protease inhibitors), that MMT patients may be taking. These and others can interact to raise or lower the methadone SML (see Table 3). In some cases, such as when MMT is initiated, methadone itself may induce increased CYP3A4 activity (13).

Finally, a very recent *in vitro* study suggests that two other CYP enzymes — CYP2C9 and CYP2C19 — may be involved in methadone metabolism (19). However, their relative clinical importance still needs confirmation by *in vivo* investigations.

In sum, individual differences in the activity of CYP1A2 and CYP3A4, in addition to the genetic polymorphism of CYP2D6 and the possible involvement of CYP2C9 and CYP2C19, help account for wide variances in methadone metabolism. As a result, in patients given exactly the same dose of racemic methadone, corrected for body weight, concentrations of the active R-enantiomer can vary from 1- to 17-fold even in the absence of potentially interacting co-medications (13). Such phenomena help explain clinical cases of so-called "fast metabolizers" who repeatedly complain, "My methadone dose is not enough to hold me."

The Glass Ceiling

Past research over the years raises the question: How high is a "high" methadone dose? Dole observed long ago (3) that 100 mg/d may fail to hold methadone blood levels within a therapeutic range for many patients. Despite this, a 100-mg dose has become accepted as a "glass ceiling" of sorts, rarely to be penetrated, and in practice much lower thresholds are maintained.

TABLE 3
Some Drugs That Affect Methadone Metabolism (1, 2, 18)*

↓ Reduce SML**	↑Increase SML
Phenytoin	Cimetidine
Carbamazepine	Ketoconazole
Rifampin	Fluconazole
Barbiturate sedatives/hypnotics	Amitriptyline
Certain antivirals	Diazepam
Urinary acidifiers, ascorbic acid	Fluvoxamine maleate
Ethanol (chronic use)	

Contraindicated Drugs — Precipitate Opioid Withdrawal
Opioid antagonists (naloxone, nalmefene, naltrexone), tramadol, buprenorphine, butorphanol, dezocine, nalbuphine, pentazocine

*Note: List is not inclusive of all drugs that may interact with methadone
**SML=serum methadone level

An extensive survey conducted in 1988 by the University of Michigan Institute for Social Research found that nearly 70% of U.S. clinics maintained patients at an average dose of 50 mg/d or less (20). This was well below an 80–120 mg/d range recommended by Dole and others (1–3, 21), which would average about 100 mg/d, with significant numbers of patients above and below the range. This situation seems to have improved only slightly since 1990, as informal surveys found that the U.S. average methadone dose was 56.6 mg/d in 1993 and 69.4 mg/d in 1998 (22).

Clinical researchers continue to evaluate low methadone doses. Although several often-quoted studies found that "higher" doses were more beneficial in terms of less continued opioid abuse, the doses studied averaged only in the 40–50 mg/d range (23–25). One randomized trial explored the relative merits of 50, 20, and 0 mg/d, predictably finding that opiate-positive urines increased as dose decreased (26). None of the studies explored doses exceeding the 100 mg/d barrier, even though opioid addicts who are not receiving adequate doses of methadone might be expected to respond poorly to treatment, just as would any patients prescribed deficient pharmacotherapy for any other chronic medical condition (20).

Strain et al. (27) recently reported a trial enrolling 192 MMT patients randomized to receive daily methadone in a defined "moderate" dose range of 40–50 mg/d or a "high" dose of 80–100 mg/d. Over the course of 30 weeks, the "high-dose" group had statistically significant lower rates of opioid-positive urines than the "moderate-dose" group (53% vs. 61.9% respectively, $p = 0.047$). However, this difference in illicit opioid use outcomes between the two dosage levels, with an absolute risk reduction of only 8.9%, was remarkably modest.

In this study (27), both the "moderate" dose (mean 45.8 mg/d) and the "high" dose (mean 89.5 mg/d) were clearly subtherapeutic for many patients. The authors conceded that "it is possible that dosages in excess of 100 mg/d may be required for optimal benefit in some patients."

As a further example, Magura et al. prospectively followed for up to three years in treatment more than 1000 patients newly admitted to New York City MMT clinics (28). Three groups were identified in terms of dosing levels established within the first 3 months: 42% were at "low dosage" (mean = 34 mg/d); 39.4% received "medium dose" (mean = 58 mg/d); 18.4% were considered "high dose" (mean = 84 mg/d). Nei-

ther health status and concurrent use of prescribed medications nor SMLs were assessed.

This investigation found no association between methadone dose level and continued heroin abuse. The authors noted that continued heroin use resulted in patients receiving increased methadone doses, although they acknowledged that "it may be that such upward dosage adjustments [were] simply not high enough to achieve their aim." Indeed, the average methadone dose level for the entire sample population was 52 mg/d (±20 SD) with only 3% of patients averaging 90 mg/d or higher.

To explore the question of just what might constitute more appropriately "high" methadone dosing, Maxwell and Shinderman (9) identified a group of 164 patients who, despite methadone doses of up to 100 mg/d, had high rates (87%) of continuing illicit opioid use. These patients, assigned to a "high dose" (HD) condition, received clinically guided dose increases, resulting in a mean dose of 211 mg/d (range 120–780 mg). This cohort was compared to a randomly selected control group receiving an average dose of 69 mg/d (range 10–100 mg), drawn from a clinic population of 1100 patients.

Group characteristics differed in two significant ways. Prescription psychotropic medications were being taken by 63% of the HD group compared to only 28% of the control patients ($p < 0.001$). Also, the HD group reported taking larger amounts of daily heroin, spending more money on their addictions, than control subjects prior to entering treatment (mean $153/day vs. $87/day; $p < 0.001$).

The fraction of opioid-positive urine samples decreased from 87% to 3% in the HD group compared to a decrease from 55% to 36% in the control group. Furthermore, the one year or more retention-in-treatment rate for the HD group was 86%, compared to 35% for the general clinic population, a 51% absolute risk difference in favor or higher doses.

SMLs were performed on most of the HD group patients; when the trough levels were less than 200 ng/mL, patients exhibited objective signs of abstinence syndrome. As methadone dose was increased and the SML rose, objective signs disappeared, but some patients still reported subjective symptoms of withdrawal. This is consistent with a report by Loimer and Schmid (4) which calculated that even patients with trough plasma levels exceeding 600 ng/mL may complain of withdrawal symptoms. Further increases in methadone dose, reaching a therapeutic SML range, alleviated all symptoms and continued heroin abuse abated (see Table 1).

Maxwell and Shinderman noted (9) that SMLs were somewhat helpful in confirming inadequate methadone dose, but were not useful for determining optimal dose. "Although 400 ng/mL is the lowest SML that is usually considered effective in alleviating objective signs and subjective symptoms of [abstinence syndrome]," they wrote, "some HD group patients had SMLs of 800–1200 ng/mL when titrated to doses resulting in no signs of opioid [overmedication], no symptoms of withdrawal, and no illicit substance use."

The higher-than-expected SMLs necessary for optimal dose in the HD group might have been predicted from their larger heroin habits prior to MMT and their greater intake of prescription psychotropic medicines, some of which might have interacted to accelerate methadone metabolism overall or to selectively reduce levels of the active R-enantiomer. Testing for serum R/S-enantiomers would have been enlightening, but this test is not yet available in most laboratories. In lieu of this, Maxwell and Shinderman proposed that (9) "medical evaluation of objective signs and subjective symptoms is a sensitive, reliable, and cost-effective method of dose titration." Furthermore, this study concludes that (provided the clinical picture does not suggest opioid overmedication) there does not appear to be a maximum limit for optimal methadone dose.

Treating Patients, Not Test Results

There is no way of prescribing a single best methadone dose to achieve a specific blood level as a "gold standard" for all patients. In clinical practice, when faced with continued illicit drug use or patient-reported withdrawal or craving complaints, serum levels may confirm what is happening to methadone in the patient's system. SMLs can be an educational aid for encouraging a fearful patient to accept a more adequate methadone dose or for assuring a less experienced colleague, a wary relative, a reluctant insurance company, or a circumspect regulatory agency, that a dose increase is justified.

Since SML results are not reliable for determining optimal dose, clinical symptoms and signs become particularly important as a dosing guide, as this final example illustrates:

> A 33-year-old woman was initially titrated to a methadone dose of 100 mg/d (trough SML 680 ng/mL), but she continued heroin use. After 6 weeks at that dose and ongoing psychotherapy in the MMT program, her heroin use continued and a repeat trough SML was performed. At

> the time of phlebotomy, the patient was diaphoretic, restless, yawning, pupils 7 mm, and complaining of severe drug cravings — the SML was 810 ng/mL. Her dose was titrated upward to 400 mg/d, at which time she reported abstinence from illicit opioids and relief from cravings, with no clinical signs of opioid overmedication. After 5 months of continued opioid abstinence and patient-reported feeling [of] "normal" at this dose, her trough SML measured 1800 ng/mL; peak SML was 3400 ng/mL. The patient has been successfully maintained on 400 mg/d of methadone with continued illicit drug abstinence for more than three years.

In this case, the final peak/trough ratio of 1.9 (3400/1800) was within a desirable range (1), although the SMLs might seem excessive. Given the inter-individual variances of methadone metabolism observed by Eap et al. ([13] described above), only a fraction of this woman's serum methadone might have been the active R-methadone enantiomer; however, enantioselective testing was unavailable to establish this. Although this case may seem a rare example, it strongly demonstrates the importance of being guided by clinical signs and symptoms in dosing decisions. The first SML reading of 680 ng/mL mistakenly suggested the patient was getting "enough" methadone, but a 400 mg/d methadone dose and very much higher SML proved necessary to achieve optimal therapy.

Dole has stressed (3), even when the means for repeated measurements of SMLs are available, that any rigid set of dosing guidelines would be misleading. "Fortunately, this laboratory support is not needed," he wrote. "An experienced clinician can judge the adequacy of the dose from [the] effects." He advised, as did Maxwell and Shinderman, that adequate methadone dosing can be readily identified by listening to patient-reported symptoms, considering their timing in relation to daily dose, noting the patient's response to a change in dose, and evaluating his or her emotional stability.

Dole believed (3) that "the patient's clinical state is correlated reliably with the blood level and the degree of tolerance." Similarly, Hiltunen and colleagues found (10) that patient-reported subjective withdrawal symptoms correlated significantly with SMLs, and that patients may still experience and complain of such symptoms in the absence of any objective signs.

Dole's classic advice of "listen to the patient" seems all the more apropos in view of recent discoveries about the individual differences in methadone metabolism discussed above. However, pharmacokinetics do not explain everything, and there may be interacting pharmacodynamic host factors, such as the potential role of psychosocial influences (15). In addition, new research suggests genetic variations at the opioid or the dopamine receptors in the brain (29).

Finally, environmental factors also need consideration, as the drug scene has greatly changed. Over the years, street heroin has become purer in quality and lower in price, making it more economically accessible. A report of the U.S. Drug Enforcement Agency noted that from 1980 to 1995, the price of a milligram of street heroin decreased from $3.90 to $1.04, while its purity increased from 3.6% to 39.7% (30). Purity levels exceeded 60% in New York, Philadelphia, and Newark (31).

Higher-purity street heroin has led to its increased use, since it can be smoked, snorted, or otherwise inhaled without the need for hypodermic injection. This has attracted many new users among young, working, white, and middle-class populations (31). Those who snort or smoke heroin increased from 55% of users in 1994 to 82% in 1996 (32). All of this suggests that today's increasing numbers of opioid addicts often have more refractory drug dependencies, which will require higher doses of methadone during MMT.

There have been cases of patients requiring in excess of 2000 mg of daily methadone, possibly due to the metabolic interactions with other medications or organ dysfunction. However, in this era of HIV/AIDS, hepatitis C, tuberculosis, and other widespread infectious diseases among substance-abusing populations, the "exceptional" MMT patient requiring exceptionally high doses may become more of a "rule" than presently imagined.

Conclusion

There is no scientific rationale for maintaining patients at lower than optimal methadone doses, yet some MMT practitioners and researchers seem philosophically committed to dosing regimens that expose countless patients to unnecessary abstinence syndrome and illicit opioid use each day. Dole (3) has written "the results are generally poor, [since] limiting or withholding medication that reduces drug hunger increases the need for illicit narcotics."

Therapeutic drug monitoring tests can play a useful role in MMT programs. However, a basic precept of sound medical practice is to trust clinical findings — withdrawal signs/symptoms, drug

craving, and continuing opioid abuse — as indicators of inadequate versus adequate dose. Each patient presents a unique clinical challenge. Practitioners are cautioned against making the mistake of "treating test results" or dogmatically adhering to biased preconceptions of what is "enough" methadone, and thereby ignoring patients' needs for optimal methadone doses.

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