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Therapeutic Drug Monitoring in Methadone Maintenance: Choosing a Matrix

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ABSTRACT. Methadone maintenance is the premier pharmacological treatment for opioid addiction, but it is rarely informed by evidence-based practice guidelines for dosage monitoring and adjustment. Such guidelines are crucial because the pharmacokinetics of methadone vary greatly among patients, and this variation may account for differences in treatment outcome. We review the pharmacokinetics of methadone and factors that may alter it (including drug interactions, disease states, and idiosyncratic differences among patients). Also reviewed are prospects for therapeutic drug monitoring (TDM) of methadone in plasma, urine, sweat, and saliva. Due to its ease of collection and its presumed representation of the bioavailable free-fraction of methadone, saliva may be a promising matrix. However, saliva methadone concentrations are influenced by salivary pH, and future studies are needed to determine how to control for that. Administrative, medical, and social implications of methadone TDM are briefly discussed. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com>]*

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THERAPEUTIC DRUG MONITORING (TDM) VERSUS DOSE IN METHADONE MAINTENANCE

An effective dose of methadone will prevent opioid withdrawal and craving, and will extinguish continued heroin use by blocking its euphoric effects. Multiple studies suggest a dose-response relationship with a threshold dose of 60-80 mg per day for optimal therapeutic efficacy as measured by treatment retention, increased abstinence, and decreased mortality.[1-3] Above this threshold, however, the dose-response curve is less clear.[4,5] In some cases, it may be smudged by the effects of concurrently administered psychosocial or behavioral interventions.[6-11] But in other cases, a seemingly adequate dose may be inadequate due to pharmacokinetic differences among individual patients.[12,13] This possibility is rarely considered in practice. Dose determination is either policy-driven, or speculatively based on clinical factors such as self-reported duration, quantity, and route of heroin use. These factors correlate poorly with dependence severity, as other environmental variables such as purity of available heroin influence the equation. Dose adjustments later in treatment are largely based upon behavioral determinants: continued opioid-positive urine screens, patient complaints of dose not ''holding,'' or physical evidence of opioid withdrawal. Guidelines for methadone dose determination through plasma levels were articulated by the Center for Substance Abuse Treatment.[14] These guidelines reflected the state of the art when they were published in 1993, but, as we discuss below, there have been subsequent advances in the use of plasma and other matrices. Unfortunately, even the 1993 guidelines seem rarely to be applied in clinical practice, leaving dose determination to the vagaries of staff or patient biases and resulting in treatment disparity.

Many medications (such as antimicrobials, digoxin, anticonvulsants, and lithium) are prescribed with routine therapeutic drug monitoring (TDM), to check patients' compliance and to maintain concentrations within therapeutic windows. This practice is necessary because, for these drugs, plasma levels do not depend solely on dose, but also on drug interactions, genetic or acquired differences in metabolism, and various medical conditions. Research increasingly suggests that TDM is also indicated for methadone treatment, as higher plasma levels predict better treatment outcome.[15-17] Some argue that, in compliant patients, plasma levels of methadone reliably correlate with dose[18] thus obviating the need for TDM in such patients. However, such a relationship is not always demonstrated; in one study, trough methadone plasma levels correlated more closely with rate of body clearance (r =

−0.697) than with daily dose (r = 0.502).[19] In another study, over 18 months, *mean* trough plasma levels correlated with mean daily dose (r = .947), yet at a given dose, the amount of variation was unacceptably high; in other words, the seemingly impressive correlation obscured a clinically-significant number of individual exceptions.[20] Some of this variability may reflect differences in pharmacokinetic disposition of methadone.

PHARMACOKINETICS OF METHADONE

Normal Pharmacokinetics of Methadone

Considering that methadone has had wide clinical use for decades, definitive information on its pharmacokinetics is surprisingly sparse in sources that most clinicians might initially consult. For example, the *Physician's Desk Reference* contains no such information, and a standard textbook of pharmacology[21] contains only minimal information. The paucity of pharmacokinetic data may be partly attributable to stigma from segments of the health-care community and lack of research interest from pharmaceutical corporations. Yet there are other impediments to a clear characterization of methadone's pharmacokinetics, such as wide variation across clinical populations. For example, the elimination rate of one methadone dose is slowest in methadone-maintained patients, intermediate in heroin users at initiation of methadone treatment, and most rapid in healthy non-opioid-using volunteers.[22]

The mean bioavailability of orally administered methadone (plasma AUC after oral versus intravenous administration) was 89% (SD 20%) on the first day of maintenance for 12 patients kept drug-free on a residential ward for 30 days; it decreased to 81% after a 24-day stabilization period.[23,24] In patients on long-term maintenance, the mean apparent volume of distribution was 6.7 L/kg;[18] peak plasma level (a doubling of trough concentrations) was reached in 2-4 hours.[22] The critical minimum trough level for clinical effectiveness has been suggested to be 150 ng/ml[25] (see page 64 for further discussion).

Plasma proteins act as a storage site for methadone, in equilibrium with the bioavailable free fraction. Typically, 86-89% is bound to plasma proteins such as albumin, globulin, and α_1-acylglycoprotein (α_1-AGP);[26-29] however, protein binding varies from 83% to 97%.[30] Some methadone is also stored in the liver and released unchanged into the bloodstream;[31] this may account for small secondary peaks in plasma levels sometimes observed 3-7 hours after oral dosing.[32,33]

Methadone's main metabolite is EDDP (2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine), which is believed to be inactive, though this has been questioned (de Vos, 1995).[13,19] *N*-demethylation of methadone to EDDP

occurs primarily in the liver via CYP3A4[34-37] with some possible minor involvement of CYP2C9 and CYP2C19.[34] Some authors have emphasized the role of CYP1A2[38] and CYP2D6[39,40] but recent evidence does not support this; in the case of CYP2D6, methadone appears to inhibit it without being a substrate for it.[34] In any case, the expression of CYP3A4 varies substantially among individuals[41] and there are sex differences in levels and anatomical distributions of many of the CYP enzymes.[42] Such differences may contribute to clinical heterogeneity in methadone metabolism.

Methadone's half-life ranges from 10 to 18 hours in healthy volunteers to 9-47 hours for opioid-tolerant patients at initiation of methadone maintenance, and 19-43 hours at steady-state maintenance.[18] Some of these estimates may be low due to inadequate sampling time: longer observations showed methadone's half-life to be 41 hours in healthy volunteers, and possibly longer and more variable in illicit-opiate users given a single dose of methadone.[22]

Methadone and EDDP are both eliminated by the kidney and the liver. The proportion of methadone eliminated by the kidney increases with dose, length of treatment, and urinary pH.[43] Mean oral clearance (i.e., whole-body clearance corrected for oral bioavailability) is slow: 115 ml/min in healthy volunteers, 53 mL/min in opiate users at first dose.[22] Elimination is slower in women than in men–a difference that could lengthen methadone's plasma half-life in women by approximately 7 hours.[19]

Alterations in the Pharmacokinetics of Methadone

Drug interactions: Drug interactions with methadone may occur through competition for metabolic pathways in the liver, competition at protein binding sites in plasma, and changes in urinary pH. Studies of drug interactions are difficult because they typically require subjects to remain under observation during at least 5 half-lives of the drug with the slowest elimination, calculated after expected changes. For example, if the half-life of methadone is estimated at 24-36 hours at initial dosing, baseline steady state is reached at 5-7 days. To study an interaction with a medication suspected to double methadone's half-life would require a period of at least 10 days (while on both medications) to reach a new steady state, then 2-3 days of serial blood levels taken at the same dosing schedule, followed by a washout period of 5-7 days on methadone only–and this if the interaction is expected to stop immediately upon discontinuation of the second medication, an unlikely scenario. It is likely that the cost of such studies (typically conducted on closed wards) in addition to other factors, such as stigma and prohibition, have curtailed the systematic evaluation of methadone's interactions. Consequently, only a few of the many possible interactions have been characterized systematically, and most have been documented by less than rigorous clinical reports. Some potential interactions are reviewed here and summarized in Table 1.

TABLE 1. Factors Altering Methadone Pharmocokinetics

Factors	Direction of Influence (Plasma Level)	Reference
Drug Interactions		
Prescribed Medications		
Ritonavir	Decrease	Iribarne et al. 1998
Nelfinavir	Decrease	Beauverie et al. 1998 Hsu et al. 1998 Geletko 2000
Zidovudine	Increase	Mckance-Katz et al. 1998
Fluconazole	Increase	Novick et al. 1985
Rifampin	Decrease	Cobb et al. 1998
Phenytoin	Decrease	Tong et al. 1981
Fluoxetine	Increase	Iribarne et al. 1998
Fluvoxamine	Increase	Alderman & Frith 1999
Tricyclic antidepressants	Decrease	
H_2 antagonists	Decrease	Charuvastra 1997
Drugs of Abuse		
Heroin	Decrease free fraction	Calvo et al. 1996
Cocaine	Decrease	Tennant & Shannon 1995
Nicotine	Increase	Kalow & Tang 1991 Kell 1995
Alcohol (Acute)	Increase (competition)	Cushman et al. 1978
Alcohol (Chronic)	Decrease (induction)	Kreek 1988
Disease States		
Liver Cirrhosis	Unstable, complex interaction	Kreek et al. 1976 Novick et al. 1985
Renal Failure	Unchanged	Kreek et al. 1980 Wolfert & Sica 1988
Diseases with changes in plasma protein	Alteration in free fraction	Wilkins et al. 1997 Abramson 1982 Craig & Stitzel 1990
Idiosyncratic Alterations in Methadone Pharmacokinetics	Increase or decrease	Nilsson et al. 1983 Dyer et al. 1999

Prescribed Medications

Protease inhibitors: Ritonavir inhibits CYP3A6 while inducing other enzymes. In an *in vitro* study of human microsomes, ritonavir (though not indinavir or saquinavir) inhibited methadone metabolism to a degree that seemed likely to have clinical significance.[44] In clinical studies, however, the opposite was found: ritonavir (and nelfinavir) *decreased* methadone plasma levels.[45,46]

Antinucleosides: A clinical report suggested that methadone increases zidovudine levels in HIV-infected injection drug users,[47] but no definitive effect as been documented.

Antibiotics and antifungals: Fluconazole and rifampin both affect methadone concentration and elimination.[12,48] Specifically, fluconazole increases methadone concentration [48] while rifampin accelerates methadone elimination through induction of CYP3A4.

Anticonvulsants: Phenytoin accelerates methadone elimination.[49]

Antidepressants: Fluvoxamine, and fluoxetine to a lesser extent, inhibit methadone metabolism.[44,50] Tricyclic antidepressant on the other hand accelerate methadone metabolism.

H_2 antagonists: Cimetidine, a potent inhibitor of CYP450 enzymes, increases plasma methadone levels.[51,52]

Interested readers can find a list of medications influencing CYP3A4, and thus potentially methadone metabolism, at the URL <www.urmc.rochester.edu/urmc/AAPCC/tables.html>

Drugs of Abuse

Illicit opiates: Chronic heroin users have elevated plasma α_1-AGP, which could reduce the free fraction of methadone.[53]

Cocaine: In a clinical setting, 72% of 67 cocaine users sampled 24 hours after their daily 100 mg dose of methadone had inadequate serum concentrations (< 100 ng/ml), suggesting an acceleration of methadone elimination by cocaine.[54]

Nicotine: Substances inhaled in cigarette smoke could induce CYP1A2.[55] However, as discussed above, the role of CYP1A2 in methadone metabolism has been questioned. Moreover, Kell[20] described a patient for whom heavy smoking (3 packs/day) seemed to *inhibit* rather than induce methadone metabolism: after abrupt smoking cessation, his plasma methadone decreased nearly 21% ($p < .05$) for at least 8 weeks, and he reported "not feeling right . . ." It is not clear to what extent his subjective complaints could be attributed to nicotine withdrawal itself.

Alcohol, acute intake: At high doses, alcohol is metabolized partly by

CYP450 enzymes; this could slow the metabolism of methadone through competition for those enzymes.[56]

Alcohol, chronic abuse: When chronic alcoholic methadone patients become abstinent, methadone elimination may be abruptly accelerated due to a sudden decrease in competition for chronically induced CYP450 enzymes, and also due to increased renal clearance.[26]

Disease and Physiologic States

The disposition of methadone is expected to be altered by pathology in any of the systems involved in its distribution, metabolism, storage, or elimination; only a few examples are reviewed here.

Liver cirrhosis: As mentioned above, the liver not only metabolizes methadone, but also, acting as a storage site, participates in prolonging its duration of action during steady state. In liver cirrhosis, the half-life of methadone is increased (possibly doubled) due to impairment in metabolism, yet plasma levels of methadone are generally low, due to impairment in the liver's ability to store and release methadone, and to produce albumin.[12,37] The decrease in plasma albumin results in alterations in protein binding, and the time-concentration curve flattens. Therefore, close monitoring and reduction in methadone dosage are indicated.[12]

Renal failure: No changes in plasma levels of methadone were observed in patients with end-stage renal failure on dialysis, and they remained within the expected range (0.09-0.68 microgram/ml) for the doses received (40-50 mg/day).[58,59]

States of decreased metabolism (hypothyroidism, congestive heart failure): These are likely to change methadone's volume of distribution, degree of protein binding, and elimination rate. No studies to date have evaluated these issues.

Diseases resulting in changes in plasma proteins: Several disease states alter drug kinetics via changes in protein binding.[60] Methadone's protein binding varies as a function of α_1-AGP levels, albumin levels, and their ratio.[61] Increased levels of α_1-AGP are found in cancer,[62] physiological stress (surgery, trauma), rheumatoid arthritis, and celiac disease.[63] Fluctuations in protein binding confound interpretation of total plasma levels, as only the free fraction is bioavailable and can access the CNS; in hypoalbuminemia, a seemingly small decrease in methadone plasma level may represent a larger absolute change in the free fraction. As already noted, the percentage of protein-bound methadone varied from 83.4% to 96.6% in an unselected group of methadone-maintenance patients.[30] Plasma protein levels also change in end-stage AIDS (wasting, cardiomyopathy, proteinuria), hepatitis C (a possible cause of increased IgG observed among intravenous drug users), liver insufficiency, protein malnutrition, congestive heart failure and nephrotic

syndromes. In such conditions, the ability to perform TDM of methadone appears to be crucial for clinical evaluation and dose adjustment, especially for the differential diagnosis of changes in mental status–yet overall plasma levels, by not reflecting the free fraction, could be misleading.

Pregnancy: Data suggest that late pregnancy seems to increase the apparent clearance of methadone because of a decrease in absorption.[64-67]

Idiosyncratic Alterations in Methadone Pharmacokinetics

In studies comparing methadone-maintenance patients who reduce or stop their illicit-opiate use versus those who do not, unexplained pharmacokinetic differences are sometimes found. Nilsson et al.[68] found that methadone's plasma half-life was shorter in ''therapeutic failures'' (persistent heroin users) than in ''responders'' (24.5 ± 2.6 vs. 34.0 ± 7.0 hrs). Similar rates of body clearance were reported for both groups (104 vs. 111 ml/min), but the ''therapeutic failures'' had a smaller volume of distribution (2.74 ± 0.96 vs. 4.20 ± 0.78 l/kg). Similarly, a more recent study[33] compared plasma levels of methadone in 9 ''nonholders'' (9 patients complaining of daily withdrawal symptoms) and 9 ''holders.'' Overall area under the curve did *not* differ between the 2 groups; in fact, trough levels were somewhat higher in nonholders than in holders. However, the nonholders showed a more rapid rate of decline in plasma methadone, and that rate of decline correlated with the severity of withdrawal symptoms ($r = 0.60$, $p < .001$). Therefore, both studies point to sharper daily fluctuations in methadone plasma levels in those unable to stop heroin use and in those complaining of withdrawal symptoms. In each study, the authors concluded that an appropriate response would be to shorten the dosage interval, a clinical decision that is rendered impractical given the restrictions imposed on methadone treatment throughout the last three decades.

WHICH BODY FLUID TO MONITOR?

In the preceding section we demonstrated the potential usefulness of TDM for determining the adequacy of an individual's methadone dose. We now discuss the properties of the different matrices available or in development for this purpose (see Table 2 for summary).

Plasma

As discussed above, measures of plasma methadone appear to differentiate treatment responders from nonresponders and predict pharmacological efficacy.[33,38,40] Weekly measures of trough methadone levels have been used to

TABLE 2. Methadone maintenance: perceived advantages and disadvantages of potential methods for TDM

Matrix	Advantages	Disadvantages
Plasma	Abundance of published data	Access to specimen can be difficult
	Basis for TDM recommendations	Aversive reactions
Urine	Easy access to specimen	Inference of plasma concentrations is technologically complex
		Clearance-dependent validity
		Specimen not always obtainable on demand
		Patients may view collection as invasive
Sweat	Easy access to specimen	Qualitative only
Saliva	Easy access to specimen	Concentrations subject to physico-chemical variations of milieu (wide variations)
	May reflect plasma free-fraction	

guide dose adjustments; dose increases for patients whose troughs were less than 200 ng/ml reduced or eliminated the use of heroin, benzodiazepines, alcohol, and stimulants, and increased patients' reports of subjective well-being.[69] Despite these results, the use of plasma for TDM has obvious drawbacks. It is impractical to obtain blood specimens from longstanding injection drug users with poor venous access. There are also psychological risks: the sight of blood may remind patients of drug-related activities such as "booting"[70] and "jacking";[71] the sight of syringes and needles may elicit conditioned craving or may result in aversive reactions. These drawbacks become even more salient in light of recommendations (cited on page 62) to measure methadone's *rate* of decline; if done in plasma, this would require serial venipunctures or several hours of monitoring with an indwelling catheter.[33] Consequently, even if relevant and helpful, it is unlikely that this strategy for TDM using plasma could be adopted by non-research methadone-treatment programs. Therefore, other avenues for TDM merit consideration.

Urine

Kell[43,72] showed that 24-hour trough methadone plasma concentrations can be estimated from urine samples. He described cases in which supple-

mentation with illicitly obtained methadone and other tampering procedures could be detected with estimates of plasma levels from urine. Kell[20] also showed that urine-estimated plasma levels of methadone can be reliable guides for dose adjustment. For a group of patients whose dose adjustments were made on purely clinical grounds (such as patient complaints), around 10-15% of urine samples remained positive for illicit opiates. For a group of patients whose dose adjustments were made on the basis of urine-estimated plasma levels, only 2-3% of urine samples remained positive for illicit opiates. Kell was thus able to calculate methadone's EC_{90} (90% effective concentration: the plasma trough at which 90% of urines were negative for illicit opiates) to be 80 ng/ml and the EC_{98} to be 600 ng/ml. (The mean and median daily *doses* that produced opiate-negative urines for 90 days were 73 mg and 80 mg, respectively.) Although encouraging, this method is complex and may not be "exportable" to a community setting: it requires fluorescent polarization immunoassay (FPIA) combined with software that accounts for sex, volume of distribution, urine pH and specific gravity. Furthermore, the method is not valid for patients with atypical clearance of methadone (e.g., patients with renal or hepatic disease).[24]

Sweat

Sweat is a noninvasive alternative to plasma monitoring that could serve to monitor compliance in treatment and probation programs.[73-75] A qualitative study showed concordance between sweat patches and urine tests for methadone and for illicit drugs, and showed that women preferred the sweat patches over urine tests.[76] A quantitative study of methadone concentration in sweat patches found no correlation with ingested methadone dose, but correlation with plasma levels was not reported,[77] limiting interpretation of the results. More studies are needed to determine the place of sweat patches in methadone TDM.

Saliva

Saliva may be an attractive matrix for TDM, for both theoretical and practical reasons. Its theoretical benefit is that, as a nearly protein-free ultrafiltrate of plasma, it should be accessible only to the plasma free fraction of methadone. (Although the free fraction could be determined from a plasma sample,[30] this is not routinely done, for reasons of cost; moreover, it would carry all the disadvantages of blood drawing.) Thus, a drug's saliva concentration could represent the true bioavailable portion of the drug that reaches the intended target tissue.[78] This approach has been exploited for phenytoin, whose salivary concentration correlates better with cerebrospinal fluid concentration than with serum concentration.[79]

However, there are 4 other physiochemical determinants of drug penetration into saliva: (1) molecular mass, (2) lipid solubility, (3) ionization in plasma (pKa), and (4) saliva pH (which increases with flow rate).[78] Methadone's small molecular mass and high lipid solubility are such that, indeed, if these were the only factors to consider, saliva methadone concentration would be a pure reflection of its free plasma concentration.[80] However, methadone is a basic drug with a high pKa (8.3-10.1),[81-83] so that small decreases in salivary pH can lead to dramatic increases in its saliva:plasma (S/P) ratio,[80] as was recently demonstrated in a sample of 10 methadone-maintenance patients.[83] This may explain some of the wide variations of methadone saliva:plasma ratio across studies: 10:1;[84] 4:1;[85] 1.3:1.0;[86] or even 0.5:1.0.[81] Before saliva can be used for methadone TDM, the first question to be answered is whether salivary methadone levels reliably predict free plasma levels across the therapeutic dose ranges, at a given salivary pH. If variation in saliva pH turns out to be problematic, it could be reduced through the use of candy-stimulated saliva specimens, whose pH is usually stable at approximately 7.0.[87] The second question is whether (once corrected for pH) saliva methadone level–the presumed free fraction–will better predict methadone's therapeutic effectiveness than plasma level.

If these questions are answered in the affirmative, the practical advantages of saliva collection would make it the method of choice for TDM in methadone-maintained patients. Many of these patients have poor venous access due to long histories of intravenous drug use, so a noninvasive and painless saliva collection would be more humane and acceptable. Saliva collection requires no specialized skills and (because saliva inhibits HIV replication) poses little risk of HIV transmission to clinic staff. Furthermore, saliva collection is unlikely to be hampered by patients' inability to produce specimens on demand.[78] Finally, serial saliva monitoring might be performed easily to evaluate methadone's rate of elimination.

TDM AND SOME LONGSTANDING ISSUES IN METHADONE MAINTENANCE

Patient-treatment matching: Due to constraints on the availability of resources, an ongoing challenge is the judicious allocation of intensive psychosocial interventions to the patients who need them most.[8] Refinement and standardization of methadone TDM could help determine which patients do require methadone dosage adjustments from those who require intensification of psychosocial or yet other therapeutic components.

Risk management: Individual differences in methadone metabolism and tolerance can lead to marked departures from the therapeutic range.[13,15,40,88] When this is suspected, objective confirmation would decrease the risk of

inadvertent overdose or withdrawal. Moreover, such documentation improves patient care, increases physician confidence in dose prescribed, and decreases physician liability.

Administrative issues: Surreptitious addition of methadone to urine samples by patients who divert and sell the majority of their take-home methadone has been suspected in several clinical settings.[89] This problem, if not addressed, could lead to loss of accreditation under the proposed regulations for methadone maintenance outside of specialized settings.

Forensic applications: By more accurately reflecting bioavailable drug levels at the time of sample collection, saliva may allow more specific assessment of the impairing potential of a substance; indeed, it has already been suggested that saliva be sampled for roadside drug tests.[90]

CURRENT CHALLENGES FOR TDM IN METHADONE MAINTENANCE

We suggest that TDM will become increasingly important, given upcoming changes in methadone treatment, and ongoing population changes among those seeking treatment, and that further investigation of TDM using saliva is necessary.

The rise of medical maintenance: Until now, in the U.S., methadone has been available solely through specialized clinics, subject to FDA regulation. It is now proposed that the Center for Substance Abuse Treatment oversee methadone treatment programs. Given the shortage of treatment slot availability relative to demand, it is hoped that methadone will then be dispensed in more varied clinical settings. The prospect of the medicalization of methadone and other opioid agonists for long-term treatment of opioid dependence prompts us to reassess current MMTP practices. TDM could help this process and have direct implications for the future acceptance of methadone treatment by the broader medical community and other entities, such as the insurance and health-care industries. The nonintrusive nature of saliva monitoring may be especially appropriate for office-based opioid-agonist maintenance; many private practitioners are reluctant to collect observed urines from their patients, perceiving it as a violation of the principles of the physician-patient relationship, which are based on trust and mutual respect.

Credentialing requirements: It is not yet known how treatment delivery will change under CSAT,[91] but it seems likely that credentialing organizations will seek to standardize treatment and improve quality of care on the basis of objective measures of treatment effectiveness. TDM will help validate quality of care as well as the need for ancillary behavioral or psychosocial interventions at methadone doses demonstrated to be within the effective therapeutic range.

The rise of polypharmacy: As the methadone-treated population ages,[92] patients themselves are increasingly likely to be on polypharmacy regimens for HIV/AIDS, HCV, tuberculosis, or other chronic health problems.[93] As discussed above, patients with chronic health problems require careful monitoring for both updated clinical evaluation and methadone dose and schedule adjustment.

CAVEATS ON THE USE OF TDM

The focus of this review is on the ranges and causes of individual differences in the pharmacokinetics of methadone, and on methods, available or in development, to monitor these differences. Clinical responses are also determined by psychological factors such as conditioned craving for opiates,[32] and by pharmacodynamic factors such as potentiation of methadone through concurrent use of benzodiazepines.[93-95] Therefore, pharmacokinetic data must be evaluated within their appropriate clinical context.

CONCLUSIONS

The practice of opioid-dependence treatment is changing. Factors affecting these changes include intercurrent infectious-disease epidemics, aging of the methadone-maintained population, multi-drug medical treatments, shifting prevalences of cocaine abuse, the increased availability of cheap, high-purity heroin leading to the prospect of a contingent of younger, highly tolerant opioid addicts,[96] and, finally, policy changes. Adopting practical and accurate analytical TDM methods will be desirable for the appropriate management of patients maintained on methadone.

For the present, plasma remains the best-studied matrix for TDM in methadone maintenance. However, the theoretical and practical benefits of saliva merit further investigation. The use of saliva for TDM has been advocated in the scientific literature over the past three decades, but its application to methadone maintenance has been scant, and there have been no systematic studies of the correlation among pH-corrected saliva methadone concentration, plasma free fraction of methadone, and treatment outcome. Such studies are needed to determine whether saliva assays can provide a convenient, cost-effective way to monitor the free fraction of methadone–the fraction of methadone that matters.

REFERENCES

1. Dole VP. Methadone treatment and the acquired immunodeficiency syndrome epidemic. JAMA. 1989;262(12):1681-2.

2. Caplehorn JR, Bell J. Methadone dosage and retention of patients in maintenance treatment. Med J Aust. 1991;154(3):195-9.

3. van Ameijden EJ, Langendam MW, Coutinho RA. Dose-effect relationship between overdose mortality and prescribed methadone dosage in low-threshold maintenance programs. Addict Behav. 1999;24(4):559-63.

4. Maddux JF, Esquivel M, Vogtsberger KN, Desmond DP. Methadone dose and urine morphine. J Subst Abuse Treat. 1991;8(4):195-201.

5. Maddux JF, Prihoda TJ, Vogtsberger KN. The relationship of methadone dose and other variables to outcomes of methadone maintenance. Am J Addict. 1997; 6(3):246-55.

6. Kreek M. Immnological function in active heroin addicts and methadone-maintained former addicts: Observations and possible mechanisms. NIDA Res Monogr. 1991;105:75-81.

7. Selwyn PA. Issues in the clinical management of intravenous drug users with HIV infection. AIDS. 1989;3(Suppl 1):S201-8.

8. McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The Effects of psychosocial services on substance abuse treatment. JAMA. 1993;269(15):1953-96.

9. Moolchan ET, Hoffman JA. Phases of treatment: A practical approach to methadone maintenance treatment. Int J Addict. 1994;29(2):135-60.

10. Silverman K, Higgins ST, Brooner RK, et al. Sustained cocaine abstinence in methadone maintenance patients through Voucher-Based Reinforcement Therapy. Arch Gen Psychiatry. 1996;53:409-415.

11. Silverman K, Wong CJ, Umbricht-Schneiter A, Montoya ID, Schuster CR, Preston KL. Broad beneficial effects of cocaine abstinence reinforcement among methadone patients. J Consulting Clin Psychology. 1998;66:811-24.

12. Novick DM, Kreek MJ, Arns PA, Lau LL, Yancovitz SR, Gelb AM. Effect of severe alcoholic liver disease on the disposition of methadone in maintenance patients. Alcohol Clin Exp Res. 1985;9(4):349-54.

13. Tennant FS, Jr. Inadequate plasma concentrations in some high-dose methadone maintenance patients. Am J Psychiatry. 1987;144(10):1349-50.

14. State Methadone Treatment Guidelines; 1993. (USDHHS, SAMHSA Center for Substance Abuse Treatment, ed. Treatment Improvement Protocol (TIP Series).

15. Horns W, Rado M, Goldstein A. Plasma level and symptom complaints in patients maintained on daily dosage of methadone hydrochloride. Clin Pharmacol Ther. 1975;17(6):636-49.

16. Holmstrand J, Anggard E, Gunne L-M. Methadone maintenance: Plasma levels and therapeutic outcome. Clin Pharmacol Ther. 1978;23:175-80.

17. Loimer N, Schmid R. The use of plasma levels to optimize methadone maintenance treatment. Drug Alcohol Depend. 1992;30(3):241-6.

18. Wolff K, Hay AW, Raistrick D, Calvert R. Steady-state pharmacokinetics of methadone in opioid addicts. Eur J Clin Pharmacol. 1993;44(2):189-94.

19. de Vos JW, Geerlings PJ, van den Brink W, Ufkes JG, van Wilgenburg H. Pharmacokinetics of methadone and its primary metabolite in 20 opiate addicts. Eur J Clin Pharmacol. 1995;48(5):361-6.

20. Kell MJ. Utilization of plasma and urine methadone concentration measurements to limit narcotics use in methadone maintenance patients: II. Generation of plasma concentration response curves. J Addict Dis. 1995;14(1):85-108.

21. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: A Goodman Gilman TR, AS Nies, P Taylor, ed. Goodman and Gilman's The pharmacological Basis of Therapeutics. 9th. ed. New York: Pregamon Press; 1996:521-55.

22. Wolff K, Rostami-Hodjegan A, Shires S, et al. The pharmacokinetics of methadone in healthy subjects and opiate users. Br J Clin Pharmacol. 1997;44(4):325-34.

23. Nilsson M-I, Änggård E, Holmstrand J, Gunne L-M. Pharmacokinetics of methadone during maintenance treatment: Adaptive changes during the induction phase. Eur J Clin Pharmacol. 1982;22(4):343-9.

24. Dole VP, Kreek MJ. Methadone plasma level: sustained by a reservoir of drug in tissue. Proc Natl Acad Sci U S A. 1973;70(1):10.

25. Dole VP: Methadone maintenance: Optimizing dosage by estimating plasma level. J Addict Dis. 1994;13(1):1-4.

26. Kreek MJ. Opiate-ethanol interactions: Implications for the biological basis and treatment of combined addictive diseases. NIDA Res Monogr. 1988;81:428-39.

27. Olsen GD. Methadone binding to human plasma proteins. Clin Pharmacol Ther.1973;14:338-343.

28. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. Clin Pharmacol Ther. 1987;41(4):392-401.

29. Eap CB, Cuendet C, Baumann P. Binding of d-methadone, l-methadone, and dl-methadone to proteins in plasma of healthy volunteers: Role of the variants of alpha 1-acid glycoprotein. Clin Pharmacol Ther. 1990;47(3):338-46.

30. Wilkins JN, Ashofteh A, Setoda D, Wheatley WS, Huigen H, Ling W. Ultrafiltration using the Amicon MPS-1 for assessing methadone plasma protein binding. Ther Drug Monit. 1997;19(1):83-7.

31. Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin-induced methadone withdrawal. N Engl J Med. 1976;294:1104-1106.

32. de Vos JW. Craving despite extremely high methadone dosage. Drug Alcohol Depend. 1996;40:181-84.

33. Dyer KR, Foster DJ, White JM, Somogyi AA, Menelaou A, Bochner F. Steady-state pharmacokinetics and pharmacodynamics in methadone maintenance patients: Comparison of those who do and do not experience withdrawal and concentration-effect relationships. Clin Pharmacol Ther. 1999;65(6):685-94.

34. Foster DJ, Somogyi AA, Bochner F. Methadone N-demethylation in human liver microsomes: Lack of stereoselectivity and involvement of CYP3A4. Br J Clin Pharmacol. 1999;47(4):403-12.

35. Iribarne C, Berthou F, Baird S, et al. Involvement of cytochrome P450 3A4 enzyme in the N-demethylation of methadone in human liver microsomes. Chem Res Toxicol. 1996;9(2):365-73.

36. Moody DE, Alburges ME, Parker RJ, Collins JM, Strong JM. The involvement of cytochrome P450 3A4 in the N-demethylation of L-alpha-acetylmethadol (LAAM), norLAAM, and methadone. Drug Metab Dispos. 1997;25(12):1347-53.

37. Rostami-Hodjegan A, Wolff K, Hay AW, Raistrick D, Calvert R, Tucker GT. Population pharmacokinetics of methadone in opiate users: Characterization of time-dependent changes. Br J Clin Pharmacol. 1999;48(1):43-52.

38. Eap CB, Finkbeiner T, Gastpar M, Scherbaum N, Powell K, Baumann P. Replacement of (R)-methadone by a double dose of (R,S)-methadone in addicts: Inter-individual variability of the (R)/(S) ratios and evidence of adaptive changes in methadone pharmacokinetics. Eur J Clin Pharmacol. 1996;50(5):385-9.

39. Bertschy G, Eap CB, Powell K, Baumann P. Fluoxetine addition to methadone in addicts: pharmacokinetic aspects. Ther Drug Monit. 1996;18(5):570-2.

40. Eap C, Bertschy G, Powell K, Baumann P. Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. J Clin Psychopharmacol. 1997;17:113-17.

41. Dahl ML, Johansson I, Bertilsson L, Ingelman-Sundberg M, Sjoqvist F. Ultrarapid hydroxylation of debrisoquine in a Swedish population. Analysis of the molecular genetic basis. J Pharmacol Exp Ther. 1995;274(1):516-20.

42. Beierle I, Meibohm B, Derendorf H. Gender differences in pharmacokinetics and pharmacodynamics. Int J Clin Pharmacol Ther. 1999;37(11):529-47.

43. Kell MJ. Utilization of plasma and urine methadone concentrations to optimize treatment in maintenance clinics: I. Measurement techniques for a clinical setting [see comments]. J Addict Dis. 1994;13(1):5-26.

44. Iribarne C, Picart D, Dreano Y, Berthou F. *In vitro* interactions between fluoxetine or fluvoxamine and methadone or buprenorphine. Fundam Clin Pharmacol. 1998;12(2):194-9.

45. Beauverie P, Taburet AM, Dessalles MC, Furlan V, Touzeau D. Therapeutic drug monitoring of methadone in HIV-infected patients receiving protease inhibitors [letter]. AIDS. 1998;12(18):2510-1.

46. Hsu A, Granneman GR, Bertz RJ. Ritonavir. Clinical pharmacokinetics and interactions with other anti-HIV agents. Clin Pharmacokinet. 1998;35(4):275-91.

47. McCance-Katz EF, Rainey PM, Jatlow P, Friedland G. Methadone effects on zidovudine disposition (AIDS Clinical Trials Group 262). J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18(5):435-43.

48. Cobb MN, Desai J, Brown LS, Jr., Zannikos PN, Rainey PM. The effect of fluconazole on the clinical pharmacokinetics of methadone. Clin Pharmacol Ther. 1998;63(6):655-62.

49. Tong TG, Pond SM, Kreek MJ, Jaffery NF, Benowitz NL. Phenytoin-induced methadone withdrawal. Ann Intern Med. 1981;94(3):349-51.

50. Alderman CP, Frith PA. Fluvoxamine-methadone interaction. Aust N Z J Psychiatry. 1999;33(1):99-101.

51. Dawson GW, Vestal RE. Cimetidine inhibits the *in vitro* N-demethylation of methadone. Res Commun Chem Pathol Pharmacol. 1984;46(2):301-4.

52. Charuvastra C, Gudeman D, Wilkins J, Ling Wa. Cimetidine may decrease opiate withdrawal symptoms in methadone patients. In: LS H, ed. College on Prob-

lems of Drug Dependence, 58th Annual Scientific Meeting: National Institutes of Health Rockville, MD; 1997: 136.

53. Garrido MJ, Aguirre C, Troconiz IF, et al. Alpha 1-acid glycoprotein (AAG) and serum protein binding of methadone in heroin addicts with abstinence syndrome. Int J Clin Pharmacol Ther. 2000;38(1):35-40.

54. Tennant F, Shannon J. Cocaine abuse in methadone maintenance patients is associated with low serum methadone concentrations. J Addict Dis. 1995;14:67-73.

55. Kalow W, Tang BK. Caffeine as a metabolic probe: exploration of the enzyme-inducing effect of cigarette smoking [see comments]. Clin Pharmacol Ther. 1991;49(1):44-8.

56. Cushman P, Jr. Alcohol and opioids: Possible interactions of clinical importance. Adv Alcohol Subst Abuse. 1987;6(3):33-46.

57. Kreek MJ. Medical Complications in methadone patients. Ann NY Acad Sci. 1978;311:110-34.

58. Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. Drug Alcohol Depend. 1980;5(3):197-205.

59. Charuvastra VC, Ouren J. Renal failure and treatment of a methadone maintenance patient. Med J Aust. 1977;2(13):433-4.

60. Reidenberg MM. Effect of disease states on plasma protein binding of drugs. Med Clin North Am. 1974;58(5):1103-9.

61. Romach MK, Piafsky KM, Abel JG, Khouw V, Sellers EM. Methadone binding to orosomucoid (alpha 1-acid glycoprotein): Determinant of free fraction in plasma. Clin Pharmacol Ther. 1981;29(2):211-7.

62. Abramson FP. Methadone plasma protein binding: alterations in cancer and displacement from alpha 1-acid glycoprotein. Clin Pharmacol Ther. 1982;32(5):652-8.

63. Craig C, Stitzel R. Modern Pharmacology. Vol. 3rd edition Boston: Little Brown and Company, 1990.

64. Pak RC, Ecobichon DJ. The effect of pregnancy and lactation on the elimination of methadone in guinea pigs. Drug Metab Dispos. 1981;9(2):170-1.

65. Szeto HH, Umans JG, Umans HR, McFarland JW. The relationship between maternal and fetal plasma protein binding of methadone in the ewe during the third trimester. Life Sci. 1982;30(15):1271-9.

66. Szeto HH, Umans JG, McFarland J. A comparison of morphine and methadone disposition in the maternal-fetal unit. Am J Obstet Gynecol. 1982;143(6):700-6.

67. Jarvis MA, Wu-Pong S, Kniseley JS, Schnoll SH. Alterations in methadone metabolism during late pregnancy. J Addict Dis. 1999;18(4):51-61.

68. Nilsson MI, Gronbladh L, Widerlov E, Anggard E. Pharmacokinetics of methadone in methadone maintenance treatment: Characterization of therapeutic failures. Eur J Clin Pharmacol. 1983;25(4):497-501.

69. Byrne A. Use of serum levels for optimizing doses in methadone maintenance treatment. J Maintenance Addict. 1998;1(3): 13-14.

70. Inciardi J. AIDS-a strange disease of uncertain origins. Am Behav Sci. 1990;33:397-407.

71. Ouellet L, Jimenez A, Johnson W, et al. Shooting galleries and HIV disease: Variations in places for injecting illicit drugs. Crime and Delinquency. 1991; 37: 64-85.

72. Kell M, Techman T. Rapid measurement of plasma methadone in a clinical setting using florescence polization immunoassay. J Addict Dis. 1996;15:69-83.

73. Cone EJ, Hillsgrove MJ, Jenkins AJ, Keenan RM, Darwin WD. Sweat testing for heroin, cocaine, and metabolites. J Anal Toxicol. 1994;18:298-305.

74. Kintz P, Brenneisen R, Bundeli P, Mangin P. Sweat testing for heroin and metabolites in a heroin maintenance program. Clin Chem. 1997;43(5):736-9.

75. Tsadik A, Oyler J, Cone E, Joseph R. Sweat testing for drugs of abuse I: Comparison of cocaine disposition in sweat collected with heated sweat patch device and the Pharmchek sweat patch.. The Society of Forensic Toxicologists and The International Association of Forensic Toxicologists (SOFT/TIAFT). Albuquerque, NM; 1998.

76. Taylor JR, Watson ID, Tames FJ, Lowe D. Detection of drug use in a methadone maintenance clinic: sweat patches versus urine testing. Addiction. 1998; 93(6):847-53.

77. Kintz P, Tracqui A, Marzullo C, et al. Enantioselective analysis of methadone in sweat as monitored by liquid chromatography/ion spray-mass spectrometry. Ther Drug Monit. 1998;20(1):35-40.

78. Haeckel R, Hanecke P. Application of saliva for drug monitoring. An *in vivo* model for transmembrane transport. Eur J Clin Chem Clin Biochem. 1996;34(3):171-91.

79. Troupin AS, Friel P. Anticonvulsant level in saliva, serum, and cerebrospinal fluid. Epilepsia. 1975;16(2):223-7.

80. Mucklow JC, Bending MR, Kahn GC, Dollery CT. Drug concentration in saliva. Clin Pharmacol Ther. 1978;24(5):563-70.

81. Kang GI, Abbott FS. Analysis of methadone and metabolites in biological fluids with gas chromatography–mass spectrometry. J Chromatogr. 1982;231(2):311-9.

82. Roerig DL, Dahl RR, Dawson CA, Wang RI. Effect of plasma protein binding on the uptake of methadone and diazepam in the isolated perfused rat lung. Drug Metab Dispos. 1984;12(5):536-42.

83. Bermejo AM, Lucas AC, Tabernero MJ. Saliva/plasma ratio of methadone and EDDP [letter]. J Anal Toxicol. 2000;24(1):70-2.

84. Lynn RK, Olsen GD, Leger RM, Gordon WP, Smith RG, Gerber N. The secretion of methadone and its major metabolite in the gastric juice of humans: Comparison with blood and salivary concentrations. Drug Metab Dispos. 1976;4(5):504-9.

85. El-Guebaly N, Davidson WJ, Sures HA, Griffin W. The monitoring of saliva drug levels: Psychiatric applications. Can J Psychiatry. 1981;26(1):43-8.

86. Wolff K, Hay A, Raistrick D. Methadone in saliva [letter]. Clin Chem. 1991; 37(7):1297-8.

87. Danhof M, Breimer DD. Therapeutic drug monitoring in saliva. Clin Pharmacokinet. 1978;3(1):39-57.

88. Anggard E, Gunne LM, Homstrand J, McMahon RE, Sandberg CG, Sullivan HR. Disposition of methadone in methadone maintenance. Clin Pharmacol Ther. 1975;17(3):258-66.

89. Galloway JH, Ashford M, Marsh ID, Holden M, Forrest AR. A method for the confirmation and identification of drugs of misuse in urine using solid phase extraction and gas-liquid chromatography with mass spectrometry. J Clin Pathol. 1998; 51(4):326-9.

90. Peel HW, Perrigo BJ, Mikhael NZ. Detection of drugs in saliva of impaired drivers. J Forensic Sci. 1984;29(1):185-9.

91. Zarkin GA, Dunlap LJ. Implications of managed care for methadone treatment. Findings from five case studies in New York State. J Subst Abuse Treat. 1999;17(1-2):25-35.

92. Choudhary S. Pharmacological issues in elderly patients on methadone. Pharm Alert. 1999;25(3):1-3.

93. Torrens M, Castillo C, San L, del Moral G, Gonzalez M, de la Torre R. Plasma methadone concentrations as an indicator of opioid withdrawalsymptoms and heroin use in methadone maintenance programs. Drug Alcohol Depend. 1998; 52(3):193-200.

94. Preston KL, Griffiths RR, Cone EJ, Darwin WD, Gorodetzky CW. Diazepam and methadone blood levels following concurrent administration of diazepam and methadone. Drug Alcohol Depend. 1986;18(2):195-202.

95. Tong TG, Benowitz NL, Kreek MJ. Methadone-disulfiram interaction during methadone maintenance. J Clin Pharmacol. 1980(Aug-Sep):506-513.

96. Schwartz RH. Adolescent heroin use: A review. Pediatrics. 1998;102(6):1461-6.