# The Use of the Methadone/Metabolite Ratio (MMR) to Identify an Individual Metabolic Phenotype and Assess Risks of Poor Response and Adverse Effects: Towards Scientific Methadone Dosing

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**Objectives:** Significant genetic variability of metabolism confounds reliable clinical use of methadone because physicians have no way of identifying individual patient metabolism. The methadone/metabolite ratio (MMR), the numerical ratio of serum methadone to its inactive metabolite ethylidine-dimethyl-diphenypyrrolidine (EDDP), represents the net expression of the genes controlling metabolism. The MMR has been adapted to four established pharmacogenetic metabolic categories: ultra-rapid (URM), extensive (EM, normal), intermediate (IM), and ultra-slow (USM).

**Methods:** This study reports on the analysis of 1700 paired peak and trough serum samples for methadone and EDDP. The MMR data were stratified by metabolic category. The reliability of these categories and the relationship of the MMR to 2 other laboratory assessments, a peak/trough ratio (PTR) and a methadone half-life, was tested. Additionally, peak and trough serum levels were analyzed by MMR category.

**Results:** Each category of MMR identified significantly different mean serum levels (peak and trough), peak/trough ratios, and half-lives. When serum levels were analyzed, evidence of subtherapeutic serum levels were found, predominantly in the URM and EM categories. Seventeen percent of peak serum levels were greater than 1000 ng (a level indicating potential toxicity) with a range up to 2384 ng, predominantly in the IM and USM categories.

**Conclusions:** The MMR measures an individual's phenotype for methadone metabolism. The data suggested underdosing in the URM category, as well as evidence of excessive dosing in IM and USM categories. The MMR provides a guide to safe and effective dosing, an alternative to the pharmacokinetically 'blind' dosing algorithms currently in use.

**Key Words:** biochemical phenotype, methadone dosing, methadone metabolism, methadone peak/trough serum level, methadone/metabolite ratio

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While methadone maintenance for opioid use disorder has certainly been proven effective, it is not consistently effective. Between 30% and 80% of patients receiving MMT are poor responders (Fonseca et al., 2011). While the reasons for poor response are multifactorial, a major reason relates to significant genetic variability of metabolism which confounds reliable clinical use. Slow metabolism and drug accumulation may cause untoward side effects or overdose deaths, or, conversely ultra-rapid metabolism and subtherapeutic concentrations may lead to withdrawal and/or drug use (Kharasch, 2017. Individual metabolic differences can result in a 17-fold variation in methadone serum levels for a given dose (Eap et al., 2002).

Since effective methadone doses vary considerably between patients and are not currently predictable, a trough plasma concentration of methadone, drawn prior to an AM dose, is the primary index for quantifying and determining individual responses to methadone (Yang et al., 2016). Over 30 years of research on effective dosing has led to a consensus that there is a 'therapeutic range' of trough serum levels. A range of 150 to 600 ng/ml was originally postulated by Dole (1988). Other studies have found effective trough levels of: 200 ng (Holmstrand et al., 1978), and between 250 ng and 400 ng (Eap et al., 2000). A recent study, measuring R-methadone concentrations as a more accurate assessment of the enantiomer active at the mu receptor, found more than 90% of patients with a good response, measured by negative urine testing, had R methadone levels between 80 and 250 ng/ml (corresponding roughly to racemic serum levels of 160–500 ng) (Mannaioni et al., 2018). Measurement of serum levels to guide dosing is not currently considered a standard

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clinical practice, although it is used in patients showing instability, such as withdrawal, drug use, or, perhaps sedation. An exception would be pregnancy, where profound metabolic changes across the perinatal period requires serum level monitoring to guide safe dosing (McCarthy et al., 2018).

A second laboratory test is the peak/trough serum ratio (PTR). The ratio of peak serum (drawn at 3–4 hours post dose) and trough levels (drawn before the next day's dose) has been shown to have clinical utility in detecting differences in patient metabolism. Those with a low PTR (<1.3) may benefit from lower methadone doses because they can maintain high serum levels throughout the 24-hour dosing period, while a high PTR (>2) can identify rapid metabolism and a need for split dosing to avoid excessively high peaks and withdrawal symptoms at the trough (Westermeyer et al., 2016). While a clinically effective range of trough levels has been established, no research could be found on the efficacy or safety of peak levels. In a small sample of 5 patients, Inturrisi and Verebeley found a mean peak of 860 ng with a range of 570 to 1006 (Inturrisi and Verebely, 1972). Kreek (1973), in a study of 9 patients providing 27 serum levels, found a mean 2-hour peak of 900 ng with a range of 460 to 1440. Neither study commented on the significance of high peak levels. However, peak levels greater than 1000 ng are commonly considered potentially toxic (Chugh et al., 2008).

A third laboratory aid in assessing individual metabolism is the serum methadone/metabolite ratio (MMR), measuring the rate of conversion of methadone to its inactive metabolite: ethylidene-dimethyl-diphenypyrrolidine (EDDP). The MMR reflects the individual's phenotypic expression of the multiple genes coding for the CYP 450 enzymes responsible for methadone metabolism. Enzymatic activity varies depending on the presence of different allele combinations (genetic polymorphisms) as altered by environmental factors, such as pregnancy, co-medications, or medical illness. The MMR has been adapted to the 4 established pharmacogenetic research categories: ultra-rapid metabolism (URM), extensive metabolism (EM, normal), intermediate metabolism (IM), and poor metabolism (PM) (Zanger and Schwab, 2013). This allows for four analogous phenotypic categories of MMR. In a study of the gene coding for the CYP2D6 enzyme applied to methadone metabolism, Fonseca et al. (2011) found the following distribution of metabolic categories in Spanish patients: URM (multiple copies of a functional allele) 5%, EM (at least 1 functioning allele) 85%, IM (2 decreased activity alleles) 5%, and PM (2 non-functional alleles) 5%. Although we have taken the terms for the 4 metabolic categories from pharmacogenetic research, in adapting them to clinical practice we have chosen to use the term 'ultra-slow' metabolism (USM) in place of 'poor' metabolism (PM), because USM, rather than reflecting a negative quality (ie, poor), actually confers the clinical advantage of achieving therapeutic blood levels with lower doses of methadone.

While methadone has been shown to have an average half-life of about 24 hours, Eap et al. (2002) reported a wide range of between 15 and 60 hours. Kapur (2012) found a range from 6.6 to 50 hours with a mean of 27.9 hours. Prescribing physicians, without access to methadone half-life calculations, can only presume a half-life of about 24 hours. Methadone dose adjustments are routinely done without any knowledge of the patient's actual metabolism. Most treatment programs use an algorithm that restricts dose increases to 5 to 10 mg, with about a week between dose increases. This limits risks of acute toxicity but does not monitor actual serum level changes that occur.

We previously reported on the use of the MMR in pregnancy to monitor perinatal changes in metabolism to improve safety and efficacy of dosing (McCarthy et al., 2018). We now report on a further application of the MMR to a large group of methadone patients whose physicians ordered peak/trough serum levels (PTR) for clinical reasons. In the interest of further exploring the clinical use of the MMR, the laboratory added the measurement of EDDP to all peak and trough serum samples. This study will report on this select population, using peak and trough plasma levels to generate the MMR, the PTR, and a calculated half-life. It is hoped that use of this new laboratory tool will improve outcomes and minimize adverse effects of dosing that is blind to individual pharmacokinetics.

## METHODS

San Diego Reference Laboratory is a nationally certified toxicology lab performing analyses required of certified methadone programs. In addition, the laboratory performs quantitative analyses of methadone serum samples ordered at the discretion of individual physicians. The samples for this study came from patients at 129 clinics across the United States. When PTR assessments are ordered, peak levels are drawn 4 hours after the AM dose and the trough is drawn 20 hours later. Submitted samples are accompanied by minimal information. No demographic data, dosing information, or indications for testing are included.

The numerical range for each category of the MMR was set by the laboratory as follows: URM <5, EM 5 to <12, IM 12 to <16, and USM 16 and above. The ranges were set based on the normal distribution curve for the whole MMR data set. The data was stratified into the 4 categories, which were statistically analyzed to determine their individual separation, and their relationship to the 3 other laboratory measures of clinical utility: peak/trough serum levels, the peak/trough ratio, and the calculated half-life.

Since we could find no research that supports the need for trough levels above 600 ng, we looked at the frequency of trough values exceeding 600 ng across the 4 metabolic categories. We also looked at the frequency of trough levels falling below either 150 ng or 400 ng, which are 2 standards previous research has associated with different rates of recovery, with 400 ng more likely associated with recovery (Eap et al., 2000). Finally, we looked at peak values exceeding 1000 ng, which would be especially relevant to risks of sedation or QTc prolongation that most likely occur at the peak.

Quantitative levels of both methadone and EDDP, analyzed using high pressure liquid chromatograph/triple quadrupole mass spectrometer (HPLC/MSS/MS), allows calculation of both the MMR and the PTR. The methadone half-life is calculated by the formula: 1/2 life = 20ln(2)/ln(peak/trough ratio). Statistical analysis was done using R, version 3.4.1. Anova post hoc *P* values were Bonferroni adjusted for

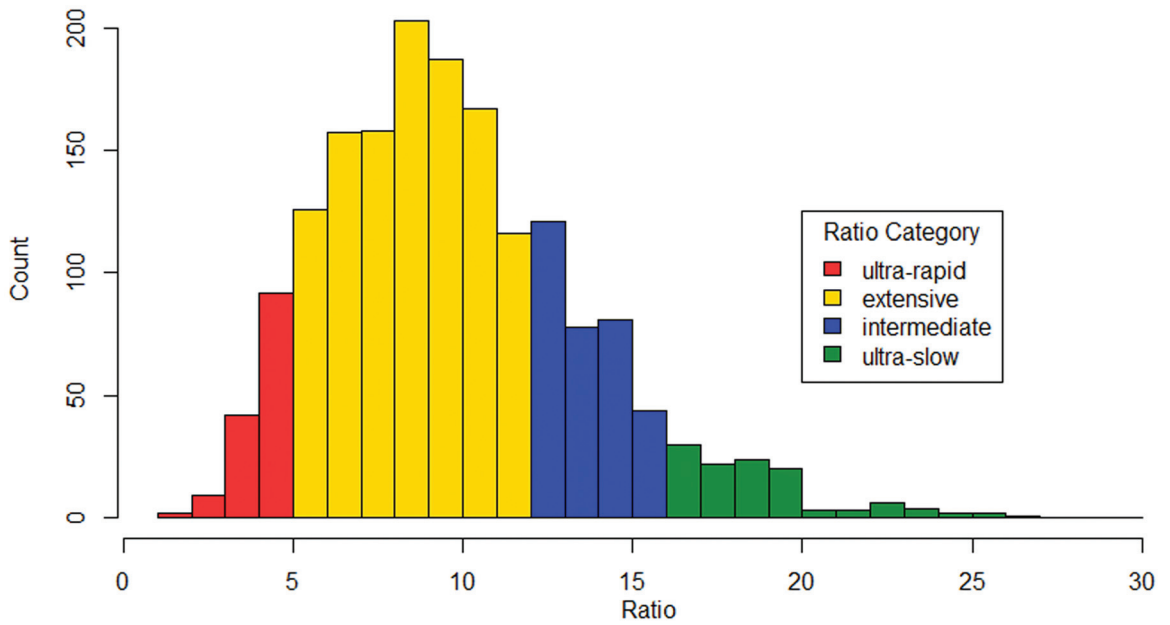


**FIGURE 1.** Distribution of methadone/metabolite ratio.

three comparisons. Some conclusions were checked with nonparametric tests when heteroskedasticity was at issue. Differences in proportions across MMR categories were tested for trend. All reported *P* values are 2 tailed.

The UC Davis IRB Administration reviewed this study and determined it was not research involving human subjects (FWA No: 00004557).

Joseph Graas, PhD, is the Director/Owner of San Diego Reference Laboratory (SDRL), which is a private for-profit laboratory specializing in methadone analysis. SDRL is the source of the data analyzed in this study.

## RESULTS

During calendar year 2018, the laboratory received 2194 paired methadone peak and trough plasma samples. Removed from the assessment were 221 samples where half-lives exceeded 50 hours, beyond which point calculations become erratic. Also removed were 273 samples where methadone or EDDP levels were below cutoff sensitivity (20 ng/ml). The final data set included 1700 paired samples (total serum samples 3400).

Using the MMR to stratify the data by metabolic category, we analyzed the following variables: distribution of the MMR in the total data set, peak and trough serum levels, calculated half-life, and the PTR. Figure 1 is a histogram of the distribution of the four metabolic categories for the 1700 samples: 8.5% URM (n = 145), 65.5% EM (n = 1114), 19% IM (n = 324), and 7% USM (n = 117).

Both peak and trough serum levels, stratified by category, are shown in Table 1. There was a wide range of peak and trough values within each category. The range of trough values (Table 1A) in each category was: 75 to 794 ng (URM),

**TABLE 1.** Methadone Serum Levels by MMR Category

**A. MTD Trough (ng/ml)**

| Category | n | Mean | St. Dev. | Minimum | Maximum | 95% Confidence Interval for Mean |
|---|---|---|---|---|---|---|
| Ultra-rapid | 145 | 271 | 155 | 75 | 794 | 245–296 |
| Extensive | 1114 | 419 | 192 | 113 | 1403 | 408–430 |
| Intermediate | 324 | 531 | 170 | 253 | 1255 | 513–550 |
| Ultra-slow | 117 | 603 | 174 | 334 | 1586 | 571–635 |

Anova $P < 2e\text{-}16$; Bonferroni adjusted: PM vs IM $P<0.001$, other comparisons $P < e\text{-}15$

**B. MTD Peak (ng/ml)**

| Category | n | Mean | St. Dev. | Minimum | Maximum | 95% Confidence Interval for Mean |
|---|---|---|---|---|---|---|
| Ultra-rapid | 145 | 553 | 272 | 163 | 1619 | 508–598 |
| Extensive | 1114 | 723 | 281 | 205 | 2270 | 707–740 |
| Intermediate | 324 | 846 | 239 | 386 | 1679 | 820–872 |
| Ultra-slow | 117 | 932 | 259 | 505 | 2383 | 885–980 |

Anova $P < 2e\text{-}16$; Bonferroni adjusted: PM vs IM $P < 0.01$, other comparisons $P < e\text{-}11$.

**TABLE 2.** Proportions of Troughs Over 600 and Peaks Over 1000

| Category | n | Trough level Over 600 ng/ml | Peak Level Over 1000 ng/ml | Peak Level Over 1000 ng/ml When Trough Level Over 600 ng/ml |
|---|---|---|---|---|
| Ultra-rapid | 145 | 4.8% | 7.6% | 100% |
| Extensive | 1114 | 14.5% | 14.4% | 80% |
| Intermediate | 324 | 24.4% | 24.5% | 72% |
| Ultra-slow | 117 | 33.3% | 33.3% | 70% |
| Test for Trend: | | $P < 4e\text{-}12$ | $P < 3e\text{-}16$ | $P = 0.03$ |

113 to 1403 ng (EM), 253 to 1255 ng (IM), and 334 to 1586 ng (USM). Mean trough values increased significantly across categories: 271 ng (URM), 419 ng (EM), 531 ng (IM), and 603 ng/ml (USM). The range of peak values (Table 1B) were: 163 to 1619 ng (URM), 205 to 2270 ng (EM), 386 to 1679 ng (IM), and 505 to 2383 ng (USM). Mean peak serum values were 553 ng (URM), 723 ng (EM), 846 ng (IM), and 932 ng (USM). The difference between IM and USM was significant at $P = 0.009$. All other comparisons were significant at $P < 0.0001$.

Table 2 shows the prevalence of trough levels greater than 600 ng and peak levels greater than 1000 ng, both potentially indicators of unnecessarily high dosing. Eighteen percent of trough values were greater than 600 ng: URM 5% (7/145), EM 14% (162/1114), IM 30% (96/324), and USM 43% (50/117). Seventeen percent of peak levels exceeded 1000 ng: URM 8% (11/145), EM 14% (161/1114), IM 24% (79/324), and USM 33% (39/117).

We further examined the frequency of trough levels that fell below either 150 ng or 400 ng respectively, 2 levels research has associated with recovery as measured by absence of drug use. Twenty-two percent (N = 32) of URM trough levels fell below the 150 ng threshold, with only 1% of EM, and no IM or USM, failing to meet this minimal efficacy level. When 400 ng was used as a measure of efficacy a total of 48% fell below this level, 84% (N = 122) of URM, followed by 54% (N = 599) of EM, 25% (N = 81) IM, and 6% (N = 7) of USM.

Table 3 shows the distribution of calculated half-lives by metabolic category. The means, by category, are: 20.4 hours for URM, 26.4 hours for EM, 31.03 hours for IM, and 33.12 hours for USM. The differences are significant between categories. The *P*-value is 0.021 for IM versus USM, and the other comparisons have $P < 2e\text{-}16$.

Table 4 shows the distribution of the PTR by metabolic category. Distribution of the means were: URM 2.19, EM 1.80, IM 1.62, and USM 1.56. These are in the expected range with only URM (defined by metabolite ratio) showing ultra-rapid metabolism (defined by PTR value). The Anova $P < 2e\text{-}16$ was highly significant. The IM and USM pairwise test had $P = 0.03$ (significant) whereas the other comparisons were highly significant at $P < 0.0000001$.

## DISCUSSION

To our knowledge, this is the largest published data set of patient methadone serum levels. We have tested and established clinically useful ranges for categories of methadone/metabolite ratios (MMRs) derived from the four pharmacogenetic categories of metabolism. This provides the physician with not only an expressed metabolic phenotype for each patient but also the general category of patient metabolism at the time of the test. Data analysis confirmed that the 4 metabolic categories were distinct from each other, in terms of identifying significantly different means of serum levels, peak/trough ratios, and calculated half-lives for each category. Although the mean values in each category were statistically distinct, there was overlap of values for these variables at the category boundaries. So, while the metabolic category alerts the physician to a patient phenotype, it provides only an estimate of a range of serum levels and should be interpreted together with a measured serum level. An MMR derived from a trough serum would give this information. The MMR, therefore, has a clinical value in alerting physicians about individual metabolism, as an aid to improving both efficacy and safety of methadone prescribing. This phenotype assessment can be achieved with one single blood draw, without the need for additional return clinic appointments for a second blood draw, and without the need for genetic testing for specific CYP 450 enzymes.

Our data found relatively high rates of metabolism slower than the EM norm (IM 19% and USM 7%). This is partially a function of how the ranges for the MMR were set by the laboratory, that is, to alert the physician to both ends of the normal distribution curve by identifying metabolism outside the EM norm. It is likely also an artifact of our non-random samples, which were presumably sent for analysis due to atypical clinical situations. At this point there is no normative MMR data in an unselected population with which to compare our findings.

**TABLE 3.** Distribution of Calculated Half-lives by MMR Category

| Category | n | Mean (hrs) | St. Dev. | Minimum | Maximum | 95% Confidence Interval for Mean |
|---|---|---|---|---|---|---|
| Ultra-rapid | 145 | 20.4 | 6.9 | 8.6 | 47.5 | 19.2–21.5 |
| Extensive | 1114 | 26.4 | 7.9 | 11.1 | 49.4 | 26.0–26.9 |
| Intermediate | 324 | 31.0 | 7.6 | 14.0 | 49.6 | 30.2–31.8 |
| Ultra-slow | 117 | 33.1 | 7.2 | 18.3 | 49.9 | 31.8–34.4 |

Anova $P < 2e\text{-}16$; Bonferroni Adjusted: PM versus IM $P = 0.03$, other comparisons $P <$ e-16.

**TABLE 4.** Distribution of Peak/Trough Ratios by MMR Category

| Category | n | Mean | St. Dev. | Minimum | Maximum |
|---|---|---|---|---|---|
| Ultra-rapid | 145 | 2.19 | 0.59 | 1.34 | 5.04 |
| Extensive | 1114 | 1.80 | 0.34 | 1.32 | 3.47 |
| Intermediate | 324 | 1.62 | 0.21 | 1.32 | 2.68 |
| Ultra-slow | 117 | 1.56 | 0.16 | 1.32 | 2.14 |

Anova $P <$ e-16; Bonferroni Adjusted: PM versus IM P = 0.25 non-significant, other comparisons $P <$ e-12.

When the MMR is calculated from a trough serum, that level can be compared to established efficacy standards. The assessment of trough serum levels at 2 established ranges for efficacy (150 ng and 400 ng) found that only 3% of samples fell below 150 ng (virtually all URM), while 48% of samples fell below the more effective 400 ng cutoff (including 84% of URM and 54% of EM samples). If continued drug use was the reason for physician ordering of serum levels, our data indicates that underdosing may be a significant problem, especially with the URM, but also EM, phenotypes.

Although there is no evidence of efficacy above trough levels of 600 ng, we found that 18.5% of the 1700 samples were above this level, with 29.6% of IM and 42.7% of USM samples exceeding this therapeutic value. Further, trough levels >600 were significantly associated with peak serum levels greater than 1000 ng. Using 1000 ng as a starting point for discussion of potential toxicity seems reasonable (Chugh et al., 2008). Many patients were receiving doses of methadone that resulted in high peak serum levels. Risks were especially prominent in IM (mean peak 846 ng and maximum 1679 ng) and USM (mean peak 932 ng and maximum 2380 ng) categories.

These levels likely occur gradually, since common dosing algorithms limit risks of acute overdose by allowing sufficient time between dose increases for tolerance to occur. It seems also likely that dosing was not correlated with the patient's actual pharmacokinetics. The risks of pharmacokinetically 'blind' dosing is that some patients can become gradually tolerant to higher and higher serum levels without any awareness on the part of the physician. The rate of decline of serum levels from peak to trough has been found to be twice as rapid in patients reporting withdrawal (Dyer et al., 1999) suggesting that single doses of methadone were not suitable for up to one-third of patients. Westermeyer et al. (2016) demonstrated that simply raising single doses of methadone in patients reporting withdrawal increased only the peak without effecting the trough, potentially worsening the rate of decline. Dividing the dose reduces the peak and the rate of decline. While speculative, it is possible that the high levels in our data represent repeated attempts to manage patient complaints of instability by merely raising single doses, rather than dividing doses.

Our calculated half-live range was from 8 to 49 hours. Longer half-lives were associated with higher serum levels, seen especially in the IM and USM categories. Daily dosing of a medication with a measured half-life significantly longer than 24 hours poses questions about medication accumulation and side effects which, while important, are beyond the present study.

When we looked at the PTR stratified by phenotypic category, we found the URM phenotype was, as expected, correlated with a higher mean PTR of 2.19. However, since the MMR provides useful information on all 4 categories of metabolism, not merely URM, it would seem that the MMR is a better screening tool, especially if a trough level is used to generate the MMR. A PTR could then be used if there are concerns about toxicity at the peak. The finding of very high peak levels, from 1366 ng to 2383 ng across the 4 phenotypic categories, indicates the importance of further study of peak levels as related to toxicity risks which include falls, seizures, QTc prolongation, respiratory depression, and other morbidities (Westermeyer et al., 2016).

The MMR is a static snapshot of metabolism that can be very dynamic depending upon enzyme induction or inhibition secondary to environmental changes. It can provide important information when done serially, such as in pregnancy when it can alert the physician to increased metabolism during pregnancy and rapid reversal of induction post-partum (McCarthy et al., 2015). And it can provide documentation of changes due to effects of co-medications. The regulatory default for methadone dosing is single daily doses and there are major regulatory barriers to providing methadone in divided doses when needed, such as in pregnancy. Regulations should be adapted to newer pharmacokinetic information that dictates the need for physician flexibility in determining a methadone dose regimen suited to the individual patient's metabolism. The MMR could be used, if further validated, to help justify to regulators the need for split dosing.

## LIMITATIONS

This study presents pharmacokinetic data on a convenience sample of methadone maintenance patients referred for peak/trough serum levels. It cannot be uncritically extended to a normal population of methadone-maintained patients for which we have no comparison data. It is likely that our sample is skewed by overinclusion of patients suspected of rapid metabolism (the most likely reason for PTR testing to be ordered) or patients with poor response to treatment and/or requirement for unusually high doses. Some patients tested likely experienced environmental alterations of metabolism (perinatal metabolic changes or medications that induce or inhibit methadone metabolism). Further research should establish normative MMR data on patient populations free from environmental factors known to alter CYP 450 genetic expression. Alternatively, a cohort of unselected patients, with information on dose, dose regimen, co-medications, and conditions altering gene expression, could be used to establish normative data on MMR categories and distribution.

Additionally, the timing of the first MMR test depends on when the ratio becomes a stable predictor of patient metabolism. This may be as early as the second day of dosing where it could guide an individualized induction and perhaps help avoid oversedation in USM patients. This hypothesis, however, would have to be specifically tested.

## CONCLUSIONS

We have added to the evidence for the clinical utility of methadone/metabolite ratios in determining ranges of serum levels and half-lives in a subset of methadone patients. Our comparison of the MMR with the PTR found that the MMR provides more clinically useful information. We have demonstrated that low serum levels, potentially associated with treatment failure, were predominantly in the URM and EM categories, and that high serum levels, potentially associated with safety risks, were associated with IM and USM category. Given the established variability of methadone metabolism which can confound clinical dosing decisions, a case can be made for use of MMRs as a baseline in all patients, and certainly in patients requiring high doses. This patient phenotyping would move methadone dosing in a more science-based direction, improving both efficacy and safety over the current state of algorithmic dosing in general use.

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# Potential for Precision Medicine in Methadone Treatment of Opioid Use Disorder

*Andrew J. Saxon, MD*

The paper by McCarthy et al. (2019) opens a potential new opportunity to apply precision medicine to the use of methadone to treat opioid use disorder (OUD). McCarthy and colleagues analyzed data from 1700 blood specimens provided by patients receiving methadone maintenance treatment for OUD and sent to a single clinical laboratory for assays of serum methadone concentrations. This analysis found that the ratio of serum methadone concentration to the concentration of its inactive metabolite ethylidine-dimethyl-diphenypyrrolidine (EDDP) could be used to divide the samples into 4 categories closely corresponding to the 4 categories of metabolic activity classically defined in the pharmacokinetic literature to describe the human variation in metabolism of a given pharmacologic compound: poor metabolizers (called ultra-slow metabolizers in the paper), intermediate metabolizers, extensive metabolizers, and ultra-rapid metabolizers.

The analysis further showed significant associations between these categories and the methadone serum concentration peak to trough ratio which already has recognized clinical utility and is obtained when patients demonstrate a poor response to methadone, particularly when patients complain of pre-dose withdrawal symptoms no matter how high the daily dosage goes. Patients with this clinical profile and a peak to trough ratio greater than 2 are presumed to be extensive or ultra-rapid metabolizers in whom methadone has a short half-life, and who will therefore require split dosing, having their total daily dosage divided into 2 separate administrations, to keep the trough serum level above the range at which withdrawal symptoms supervene.

For background and as briefly noted by McCarthy et al, the metabolism of methadone is quite complex and not yet fully elucidated. Current understanding indicates that multiple CYP 450 enzyme systems, including CYP3A4, CYP2B6, CYP2C19, CYP2D6, CYP2C9, and CYP2C8, likely contribute to N-demethylation of methadone to EDDP, and so metabolic pathways might be different across different individuals (Volpe et al., 2018). CYP 450 enzyme activities are determined largely by genetics with some contribution by environmental effects, for example enzyme inhibition or induction by various substrates. The science of understanding genetic effects on methadone metabolism remains in its infancy, but preliminary data suggest that polymorphisms in CYP2B6 may indeed contribute to rate of metabolism, whereas polymorphisms in CYP2D6 appear not to do so (Victorri-Vigneau et al., 2019). When one considers the plethora of enzymes involved, the number of potential polymorphisms that could contribute to alterations in methadone metabolism, and the potential interactions between different genetic influences in a single individual, it seems quite apparent that clinically useful genetic testing to place patients receiving methadone in 1 of 4 metabolizer groups described above is not on the current horizon. Thus, a simpler biomarker that could serve a similar function, such as the methadone/EDDP ratio propounded by McCarthy et al, holds considerable allure.

What clinical advantages might such a biomarker offer? McCarthy et al point out that, to the best of our current awareness, extensive and ultra-rapid metabolizers make up at most about 10% of the population of individuals receiving methadone treatment for OUD. Thus, during ongoing routine clinical care the vast majority of patients can be well managed without obtaining serum methadone levels or any other biomarker and simply using clinical judgment to determine a therapeutic methadone dosage when withdrawal signs and symptoms are absent, use of illicit opioids has ceased, craving for opioids is eliminated, and side effects are minimized.

However, McCarthy et al argue that if the methadone/EDDP ratio can accurately identify the roughly 10% of extensive and ultra-rapid metabolizers who might need split dosing, it could replace the use of peak to trough ratio which requires 2 separate blood draws rather than a single draw. A single draw could have some modest logistical advantages because obtaining a peak level requires the patient to remain in the clinic for 3 to 4 hours after ingesting the day's methadone dose and going for the blood draw in the correct timeframe.

McCarthy et al also suggest that the methadone/EDDP ratio could be applied at the outset of an episode of methadone treatment, as early as day 2 to predict which patients are poor

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(ie, ultra-slow) metabolizers. If this potential to predict poor metabolizers from a single, readily available biomarker were conclusively demonstrated, it could have wide clinical application to make precision medicine for methadone treatment a reality. Individuals with opioid use disorder already have considerably increased risk for mortality compared to the general population, but the initial weeks of methadone maintenance treatment represent a time of even more heightened risk (Sordo et al., 2017). Because of methadone's average long half-life, some of these deaths have occurred iatrogenically when the daily dosage of methadone was titrated upward too rapidly (Caplehorn, 1998), presumably in poor metabolizers in whom, because of its long half-life, methadone can accumulate over sequential doses until steady state has been achieved. Given this serious risk and our current inability to distinguish poor metabolizers, all patients starting methadone treatment must undergo a slow, painstaking, stepwise increase in dosage that often requires 4 to 6 weeks to reach a therapeutic dosage. The bulk of the patients who are not poor metabolizers could probably tolerate a more rapid titration, over a week or 2. While patients wait many weeks to arrive at a stable dosage, they continue to experience withdrawal, and many continue illicit opioid use, which in itself increases risk for overdose and death. The long wait to achieve stability most likely also contributes to early treatment dropout because patients understandably fall prey to the misapprehension that the treatment is not working. If a single biomarker could indeed identify poor metabolizers, we could then apply this precision to individualize the initial titration of methadone doses, by titrating only poor metabolizers slowly and titrating the other patients more rapidly, making this early component of treatment safer and more effective for everyone. However, McCarthy et al's hope that the methadone/EDDP ratio could serve as such a biomarker as early as day 2 of treatment demands considerably more rigorous study before it could come into regular clinical use, as McCarthy et al acknowledge.

Overall McCarthy et al do an excellent job of conveying the limitations of their current work which mainly revolve around the fact that no clinical information was available on the patients who provided the serum specimens for analysis. So, what further work might support the application of methadone/EDDP ratio to routine clinical care? Clearly, studies are needed that examine methadone/EDDP ratio in the context of full sets of clinical information including patient demographics, medical and psychiatric history, concurrent medications, methadone dosage, electrocardiograms to assess the QT interval, indices of liver and kidney health, and urine drug screen results. Longitudinal studies that investigate the stability of methadone/EDDP ratio over time, particularly comparisons of this biomarker during the first few days in treatment with methadone to the interval when a stable, effective dose has been reached. Since future work on the genetics of methadone metabolism will likely occur, it would be ideal to collect methadone/EDDP samples in that context.

It is worth noting that, in addition to its use in treatment of OUD, because of its long half-life and its effects on N-methyl D-aspartate receptors (Inturrisi, 2005) and on serotonin and norepinephrine reuptake (Codd et al., 1995), methadone has considerable utility as an analgesic in the palliative care setting. A biomarker such as methadone/EDDP ratio that could help to predict safe and adequate dosing could also serve a valuable function in that context.

While much work remains to be done, McCarthy et al deserve praise for bringing the methadone/EDDP ratio to the attention of the field as a possible biomarker that conceivably might allow us to treat our patients with OUD with more precise, individualized, scientific exactitude.

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