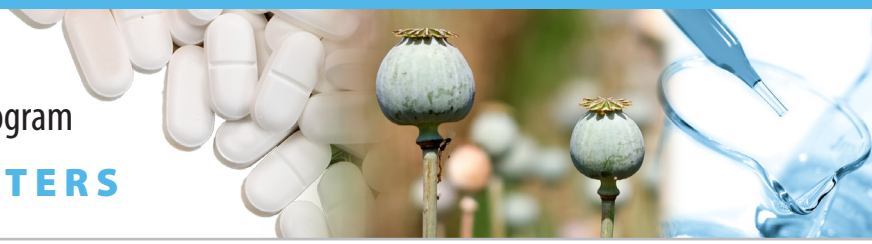
National Laboratory Certification Program
DRUG TESTING MATTERS



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An Essential Medicine and Drug of Abuse: Prevalence and Pharmacology of Methadone

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In April 2019, Heidi's law (HR 2285) (1) was introduced to Congress. The bill urges the Secretary of the Department of Health and Human Services (HHS) to revise the Mandatory Guidelines for Federal Workplace Drug Testing Programs to include methadone. In this installment of Drug Testing Matters, we provide a summary of methadone information, including pharmacology, prevalence, and expected concentrations in different matrices.

Historical Background and Use

Methadone [(RS)-6-(dimethylamino)-4,4-diphenylheptan-3-one] is a synthetic opioid with analgesic effects similar to morphine. First discovered by German scientists in 1939, it was originally referred to as VA 10820 or Amidon. It was approved for use in the United States in 1947 under the name methadone. For pain management and opioid addiction treatment, methadone is administered orally or parenterally and supplied as a 10 mg/mL solution, 5 to 40 mg tablets or 40 mg diskettes (2). While methadone is included on the World Health Organization's (WHO's) list of essential medicines (3), it also has potential to produce adverse effects, including addiction, respiratory depression, sedation and lightheadedness (4).

Pharmacology and Effects

Methadone is a racemic mixture, with similar effects and potency to morphine (5). Of the two enantiomers, levomethadone is a much more potent μ-opioid agonist than dextromethadone. Antagonist activity of the N-methyl-D-aspartate (NMDA) receptor is also thought to contribute to the analgesic properties of methadone (6).

Methadone's long half-life of 15 to 55 hours is a key reason for its use in medication-assisted treatment (MAT) for opioid addiction; however, it can also lead to methadone accumulation in the body, resulting in sedative effects. Given its mechanism of action, it is not surprising that an extensive literature review revealed that methadone was one of 15 medications associated with increased risk of a motor vehicle crash (7). Between 2010 and 2014, methadone was detected in 1% (11 positive results) of fatally injured motor vehicle drivers in Kentucky (8). In Fatality Analysis Reporting System (FARS) data for fatal two-vehicle crashes (1993–2016), methadone was detected in 14.3% of drivers testing positive for prescription opiods (9).

As demonstrated in Figure 1, the major metabolic transformation of methadone is demethylation and subsequent cyclization to form 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrroline (EDMP). Methadone, EDDP, and EDMP are excreted in urine, with EDDP as the major metabolite. EDDP and EDMP do not have pharmacological effects (2).

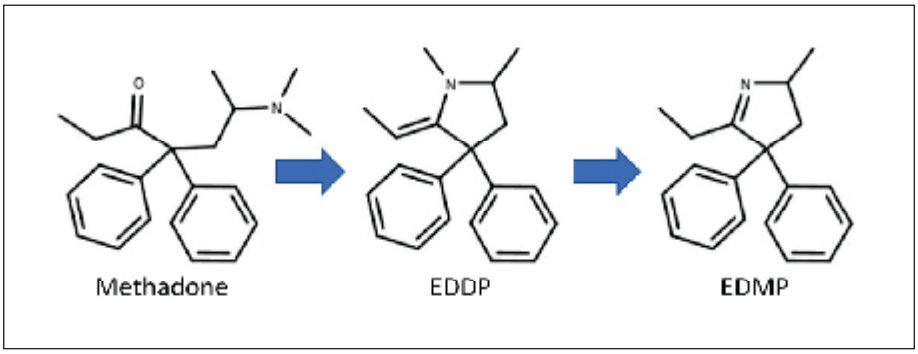

Figure 1. Metabolic Scheme with Structures

Prevalence

Between 2002 and 2006, methadone prescriptions for pain management increased by 25.1% per year on average, however, they decreased by an average of 3.2% per year after 2006 (10). Methadone is not excluded from contributing to the opioid epidemic; overdose deaths rose from 784 in 1999 (4.7% of total overdoses) to 5,518 in 2007 (15.3%), followed by a slow decrease to 2,740 (3.9%) in 2019 (11).

Trends in methadone abuse can also be estimated using data from the Drug Enforcement Administration's (DEA's) National Forensic Laboratory Information System (NFLIS), which collects drug chemistry analysis results from local, state, and federal forensic laboratories. National estimates of methadone reported to NFLIS increased from 4,967 reports in 2003 to 10,774 reports in 2009 (12, 13), followed by a steady decrease to 1,839 cases in 2019 (14).

Concentrations in Urine

As seen in Table 1, urinary concentrations of methadone and EDDP have been studied in several different populations. In 7,962 specimens from chronic pain patients (15), the median methadone and EDDP concentrations were 3.0 mg/g creatinine (cr) and 5.3 mg/g cr, respectively. Assuming a creatinine concentration of 130 mg/dL (16), this corresponds to 2,300 ng/mL and 4,100 ng/mL for methadone and EDDP, respectively.

Unsurprisingly, somewhat higher concentrations have been reported in patients undergoing treatment for substance abuse (including MAT). Urinary concentrations of methadone and EDDP were semi-quantitatively determined by immunoassay (i.e., cloned enzyme donor immunoassay, CEDIA) in 729 specimens from 27 patients in the maintenance phase of methadone maintenance therapy (17). The median methadone and EDDP concentrations were 6,200 and 4,500 ng/mL, respectively. In a smaller study (n = 64) (18) using gas chromatography/mass spectrometry (GC-MS), mean trough concentrations of 8,200 and 7,400 ng/mL were reported for methadone and EDDP, respectively. Interestingly, in 21 specimens collected 4 hours after administration, the mean urine concentrations were higher: 12,400 ng/mL (150% of trough) and 14,700 ng/mL (200% of trough) for methadone and EDDP, respectively.

A study on prison inmates in Norway (19) measured methadone, EDDP, creatinine, and pH in 1,539 methadone-positive urine specimens. Most specimens had a pH between 5 and 7.9. The average methadone concentration dropped from around 5 µmol/mmol creatinine at pH 5 to about 1 µmol/mmol creatinine at pH 7.9, while average EDDP concentrations were stable at around 5 µmol/mmol in the same pH interval.

Table 1. Concentrations of Methadone and EDDP in Urine

Study	N	Population	Methadone Median (Q1–Q3) ng/mL	EDDP Median (Q1–Q3) ng/mL
Leimanis 2012 (15)	7,962[a]	Chronic pain	3,900[b] (1,600–8,100)	6,100b (3,200–13,300)
Preston 2003 (17)	729[c]	MAT	6,200 (3,200–12,800)	4,500 (3,200–6,600)
Diong 2014 (18)	64[d]	MAT	Mean 8,200 [range 100–32,000]	Mean 7,400 [range 66–27,000]
Bernard 2007 (19)	1,539	Prison inmates (MAT)	8,400 [range 220–80,000]	12,000 [range 0–68,000]

[a] Methadone and EDDP ≥ 100 ng/mL and creatinine ≥ 20 mg/dL; [b] Calculated from values as mg/g cr assuming 130 mg/dL creatinine (16); [c] used CEDIA for quantification. Methadone ≥ 300 ng/mL (14 negative) and EDDP ≥ 100 ng/mL; [d] Methadone ≥ 300 ng/mL (14 negative) and EDDP ≥ 100 ng/mL.

Information collected in 2019 from HHS-certified laboratories performing non-regulated workplace testing revealed that most laboratories used an initial cutoff 300 ng/mL for methadone, with one laboratory reporting a cutoff of 100 ng/mL for EDDP. Confirmation cutoffs ranged from 25 to 300 ng/mL for methadone and/or EDDP using GC-MS; gas chromatography/tandem mass spectrometry (GC-MS/MS); and liquid chromatography/tandem mass spectrometry (LC-MS/MS). The positivity rate in non-regulated specimens for methadone and/or EDDP ranged from less than 0.5% to 6%. Based on this information, it was estimated that approximately 0.2% of federal workplace specimens would test positive for methadone and/or EDDP (20).

When confirming methadone and EDDP using GC-MS, a low injector temperature should be used, and laboratories should verify that methadone is not converted to EDDP during analysis. One study found that 2.5% of a 5,000 ng/mg methadone spike was converted to EDDP using an injector temperature of 260°C. A lower temperature showed less conversion (21).

Concentrations in Oral Fluid

Oral fluid concentrations of methadone have been studied in different populations (i.e., chronic pain patients (22), MAT patients (23-26), and drivers (27)) using various analytical methods (Table 2). Three of the six studies reported median concentrations of around 200 ng/mL (24, 25, 27), while the others reported median concentrations of 64, 51, and 570 ng/mL, respectively (22, 26, 28). First quartile data were available in five studies and ranged from 21 to 210 ng/mL. The results were also supported by Gray et al. (23), who reported that 96% of specimens from pregnant women in a maintenance program contained more than 20 ng/mL of methadone.

EDDP concentrations were reported in all but one of the studies. In general, they were lower and showed less variability. Median concentrations range from 17 to 70 ng/mL (n=6) and first quartile concentrations from 10 to 45 ng/mL (n=5).

Two studies analyzed paired oral fluid and urine specimens to study relative detection rates. In patients with buprenorphine prescriptions (5,060 specimens), West et al. reported a higher detection rate in oral fluid compared to urine (1.6% vs. 1.0%) (26). Methadone was more frequently detected in oral fluid compared to urine (1.0% vs. 0.8%), while the opposite was true for EDDP (0.2% vs. 1.0%) (26). Interestingly, Vindenes et al. reported identical detection rates (46%) and correlation between urine (limit of detection [LOD] 300 and 62 ng/mL in screening and confirmation, respectively) and oral fluid (LOD 15 ng/mL) when analyzing 164 paired specimens from 45 patients treated with either buprenorphine or methadone (29).

Table 2. Concentrations of Methadone and EDDP in Oral Fluid

Study	n	Population	Device	Methadone median (Q1–Q3) ng/mL	EDDP median (Q1–Q3) ng/mL
Gray 2011 (23)	414[c]	MAT	Salivette	95.7% > 20 [range 5.2–78,000]	[range 1.0–1,800]
Cooper 2005 (24)	104[d]	MAT	Cozart Rapiscan	~180 (70->180)[e]	21 (17–44)
Heltsley 2011 (22)	462[a]	Chronic pain	Quantisal	64 [range 2.1–240,000]	29 [range 1.0–3,400]
Martins 2008 (25)	60	MAT	Salivette	190 (110–390)[f]	32 (29–35)[f]
West 2018 (26)	79	MAT (buprenorphine)	Quantisal	51 (21–250)[b]	17 (10–21)[b]
Herrera-Gomez 2018 (27)	2,656	Roadside	Unknown/ possibly multiple	200 (60–410)	N/A
Cone 2007 (28)	998	Mixed legal/ MAT/workplace	Intercept	570 (210–1,300)	45 (22–140)

[a] n = 400 for EDDP; [b] concentrations recalculated to account for 1:4 dilution of oral fluid in collection device (Quantisal); [c] n = 368 for EDDP; Specimens from 16 patients; [d] n = 10 for EDDP; [e] 50% of specimens reported as > 180 ng/mL for methadone, median is approximate; [f] reported as sum of enantiomers; [g] Cutoff recalculated to account for 1:3 dilution of oral fluid in collection device (intercept).

Concentrations in Hair

Over the last 20 years, methadone and EDDP have mainly been measured in hair from patients treated with methadone, with varying results, as can be seen in Table 3. Median concentrations of methadone varied from 2,700 to 19,000 pg/mg,30-33 which might be attributed to differences in the methodology used.

Table 3. Methadone and EDDP in Hair

Study	n	Population	Methadone median (Q1–Q3) pg/mg	EDDP median (Q1–Q3) pg/mg
Lucas 2000 (30)	8[a]	MAT (pregnant)	19,000 (7,000–30,000)	3,400 (1,400–5,100)
Musshoff 2005 (31)	41	MAT	2,700 [range 250–13,000]	430 [range 50–2,200]
Paterson 2003 (32)	60	MAT	15,000 (8,000–27,000)	N/A
Girod 2001 (33)	26[b]	MAT	5,000 (3,900–8,900)	1,300 (1,000–2,300)

[a] n = 7 for EDDP; [b] n = 13 for EDDP.

Conclusions

Methadone is an important therapeutic drug, but the potential for both abuse and impairment can be a safety issue. Inclusion of methadone in workplace drug testing programs may therefore be warranted. Methadone and its main metabolite EDDP have been quantified in urine, oral fluid, and hair at concentrations that should be achievable with analytical methodology available to most drug testing laboratories.

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