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OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Review Articles

Interpretation of Urine Drug Testing in Pain Patients

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Abstract

Background. Traditionally, urine drug screens have only been concerned with positive or negative results. Those results provide physicians treating patients for pain with chronic opioid therapy with information about medication compliance, use of nonprescribed medications, and use of illicit drugs. However, the analysis of urine for drugs offers additional information that, when compiled and accurately interpreted, may also be of great value to these doctors.

Purpose: The aim of this article was to discuss the interpretation of urine drug tests and their application to pain physician practices.

Method. We utilized a selection of recent articles on urine drug screening applicable to the pain patient population.

Results and Conclusions. The article provides pertinent information about interpretation of urine drug testing, which is separated into six categories: which drugs and metabolites to test for; which analytical cutoffs to use; pain medication metabolism; identification of alcohol use; determination of patient compliance; and which patient groups to consider for more frequent testing.

Key Words. Pain Medication; Urine Drug Testing; Drug Metabolism; Patient Compliance; Alcohol Use

Introduction

Chronic opioid therapy is commonly used in the management of patients suffering from chronic pain [1–5]. Opioid medications have a number of undesirable side effectsincluding sedation, dizziness, nausea, vomiting, and constipation [6–12], and have been associated with increased rates of opioid abuse and overdose death [13–16]. As a result, interdependent goals of therapy exist to provide effective analgesia while minimizing adverse effects and mitigating the risk of opioid abuse and overdose. Monitoring patient adherence to therapy is a critical component of long-term management of patients on chronic opioids.

Nonadherence to prescribed therapy is common among people with various diagnoses, including patients on chronic opioid therapy [17–20]. In fact, patients with chronic pain commonly modify their prescribed medication regimens [21,22]. Due to the variable nature of pain, patients may adjust their regimen based on the frequency or intensity of pain [23–47]. Published evidence has shown that adherence to opioid analgesics may be medication dependent, as demonstrated in Table 1.

Unfortunately, patients may not provide details regarding their medication-taking behavior or the modifications they have made [48–50]. Numerous tools exist to monitor patient adherence to therapy, including urine drug testing (UDT), prescription drug monitoring programs, and patient self-report [18–45]. However, patient self-report is often not reliable as a single measure of medication adherence and may provide information discordant with the prescribed regimen. Various screening tools, such as the Opioid Risk Tool (ORT) and the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), have also been described that predict aberrant behaviors in patients taking chronic opioid therapy [51]. UDT is one of the more commonly utilized tools in monitoring patients on chronic opioid therapy. Urine is currently the preferred matrix over blood [52] or saliva for monitoring drug or medication use because it is the most well-studied and accepted fluid for the analysis of these substances [53]. Recent publications have indicated that saliva may be useful for determination of medication

Table 1 Range of adherence

Opioid Medication	Adherence (%)
Methadone	92.2
Fentanyl	90.0
Oxymorphone	85.0
Morphine	83.5
Buprenorphine	82.8
Hydromorphone	80.4
Propoxyphene	77.6
Oxycodone	74.7
Hydrocodone	71.2
Tramadol	67.0
Meperidine	66.0
Tapentadol	65.8
Codeine	50.2

The table values are based on 290,627 specimens analyzed at Millennium Laboratories between September 2010 and November 2011. Percentages represent the number of reported medications detected over the total number of tests ordered for each medication.

adherence in part because the ease of collection and that the collection of the specimen can be witnessed by medical staff with reduced possibility of substitution and adulteration. The analysis can then be performed by immunoassay and by mass spectrometry [54–61]. Drug monitoring can reveal patterns of medication or illicit drug use. Research has demonstrated that some medications or substances are more commonly seen in the chronic pain population (Table 2) [62,63].

Numerous guidelines have recommended UDT for use in monitoring patients on chronic opioid therapy [1–3]. Additionally, published data has shown that frequent UDT may reduce illicit drug use [64,65]. However, use is not widespread [23,66,67]. Limited use of UDT may be due to a variety of factors, including inadequate physician knowledge regarding interpretation of results [68–70]. In fact, Levy et al. found a significant number of drug tests were susceptible to interpretation errors [71]. With adequate understanding and interpretation of the results, prescribers can use UDT to monitor use of prescribed medications, identify the use of nonprescribed medications, or use of illicit substances [21,23–46,72,73]. In general, a UDT result that is expectedly positive for a prescribed medication suggests medication adherence and an unexpected result (e.g., negative for prescribed medication, or positive for nonprescribed medication or illicit substance) suggests either nonadherence to the prescribed regimen or aberrant behaviors that should be further explored by the prescriber [1,2,29,43,66,67,70,74–82]. Unexpected results can be due to a variety of factors as results are driven by medication use factors such as dosing, dosing interval, and time of last dose. For example, an unexpected negative UDT result (e.g., negative for prescribed medication) may indicate that the patient has run out of the medication early or has been using a lower dose or less frequent dosing interval than is commonly prescribed [29]. A negative UDT result for a prescribed medication could also indicate that the patient is diverting the medication, which has much different implications [28,53,83].

Utilizing UDT to gain an understanding of the patient's medication-taking behaviors, potential aberrant behaviors, and to identify the risk of drug–drug interactions that may produce serious health risks, is critical for the treating physician to provide the best medical care [84].

Table 2 List of prescription and illicit drugs commonly used in the pain population

Drug Class	Analyte
Alcohol	Ethyl glucuronide
	Ethyl sulfate
	Ethanol (screen)
Amphetamines	Amphetamine
	Methamphetamine
	MDA
	MDMA
Barbiturates	Butalbital
	Phenobarbital
	Secobarbital
Benzodiazepines	Alpha-hydroxyalprazolam
	Oxazepam
	7-Amino-clonazepam
	Temazepam
	Nordiazepam
	Lorazepam
Buprenorphine	Buprenorphine
	Norbuprenorphine
Cannabinoids	Carboxy-THC
Carisoprodol	Meprobamate
	Carisoprodol
Cocaine	Benzoylecgonine
Fentanyl	Norfentanyl
	Fentanyl
Meperidine	Normeperidine
	Meperidine
Methadone	EDDP
	Methadone
Opiates	Hydrocodone
	Hydromorphone
	Oxymorphone
	Oxycodone
	Morphine
	Codeine
	6-Acetylmorphine
Phencyclidine	Phencyclidine
Propoxyphene	Norpropoxyphene
	Propoxyphene
Tapentadol	Tapentadol
Tramadol	Tramadol

EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine;
MDA = 3,4-methylenedioxyamphetamine;
MDMA = 3,4-methylenedioxymethamphetamine;
THC = tetrahydrocannabinol.

Optimizing outcomes through utilization of UDT results requires a clear understanding and ability to interpret those results. The following outlines six categories that the prescriber should be familiar with when interpreting UDT results: 1) medications/substances (including opioids) and relevant metabolites; 2) analytical cutoffs; 3) opioid analgesic metabolism; 4) interpretation of quantitative values; 5) monitoring concomitant alcohol use, and 6) testing frequency.

Medications/Substances (Including Opioids) and Relevant Metabolites

Historically, drug testing of the pain patient population followed a forensic model of testing using immunoassay screening followed by a confirmatory test for positive results, typically utilizing mass spectrometry. Immunoassay tests are commonly used despite many identified pitfalls of false-positive and false-negative results [85–95]. The advent of liquid chromatography tandem mass spectrometry (LC-MS/MS) has enabled a feasible, cost-effective advance in the monitoring of chronic opioid therapy. LC-MS/MS allows laboratories to provide both parent drug and metabolite information, and provides an expanded list of medications or substances that can be detected, yielding important advantages in determining medication adherence or substance use [96–98].

Point of care testing through immunoassay unfortunately is not conclusive in some cases. In fact, a common misconception is that an opiate screen (via immunoassay) will include all opiates and opioids. However, in general, opiate immunoassay screens will not reliably detect oxycodone, oxymorphone, meperidine, and fentanyl. Thus, confirmatory testing is often necessary.

To fully elucidate medication-taking behaviors and ensure accurate results, testing should include both parent compounds and metabolites. In some cases, such as with methadone, the parent compound may not be detected but the metabolite, i.e., 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), can be detected. UDT that does not include metabolites, such as EDDP could be inaccurately interpreted as an unexpected negative result, when in actuality, the patient is adherent to therapy. Prescribers should be familiar with the metabolic pathways of opiate medications in Figure 1 [72].

In considering a patient taking codeine, a review of the metabolic pathways demonstrates that morphine and hydrocodone are metabolites of codeine and that hydromorphone is a further metabolite of either hydrocodone or morphine [53,99]. Thus, an expected result in a patient on codeine can include a positive UDT result for codeine, morphine, hydrocodone, and hydromorphone.

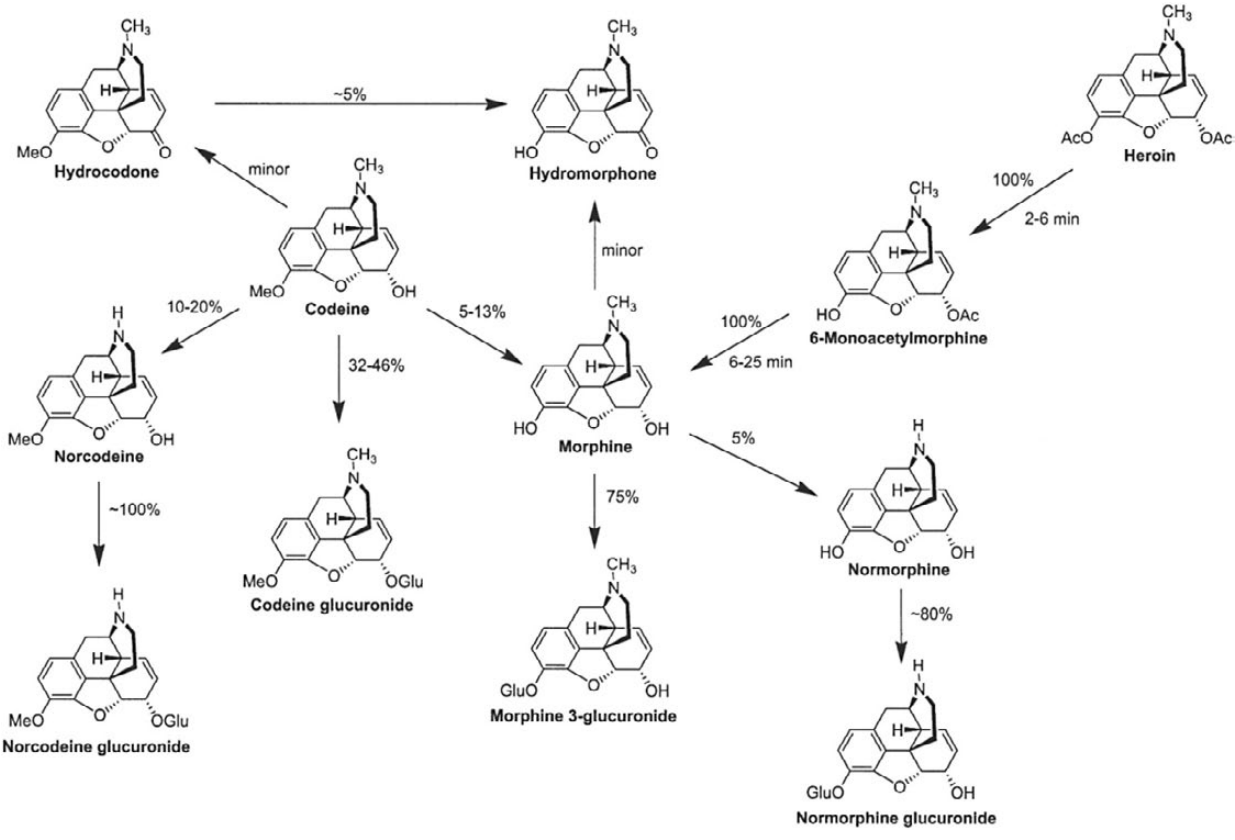

Figure 1 Metabolic pathways (morphine, codeine, heroin).

Over the past several years, a number of medications have been introduced or removed from the market. These changes include the removal of propoxyphene-containing medications [100] and the addition of a new medication class (tapentadol) [101], as well as the addition of hydromorphone and oxymorphone [102]. In the cases where the prescribed drug is the metabolite, such as hydromorphone and oxymorphone, the parent drug (morphine, oxycodone) should not be detected in UDT. Additionally, many point of care devices may not reliably detect medications that are metabolites of parent medications. The device's manufacturer's package insert typically provides further information regarding the ability of the device to detect these metabolites.

Unexpected UDT results may be due to a variety of causes, including pharmacogenetic variability, drug–drug interactions, false positives or false negatives, medication impurities, and patient medication-taking behaviors. Pharmacogenetic variability is common and often causes abnormal UDT results. In fact, approximately 7–10% of the Caucasian population lacks an active cytochrome P450 2D6 (CYP2D6) oxidizing enzyme, and thus are unable to metabolize codeine to morphine [103]. Thus, in a patient taking codeine as prescribed, UDT would reveal codeine but not the morphine metabolite. Drug–drug interactions may also significantly impact UDT results. For example, codeine is metabolized via cytochrome P450 2D6 primarily to morphine. Metabolism of codeine can be inhibited by P450 2D6 inhibitors, such as paroxetine (Paxil®) or bupropion (Wellbutrin®) [104], and thus UDT results may be negative for morphine in the presence of paroxetine or bupropion. False positive or false-negative results are most commonly problematic with point of care immunoassay testing. Prescribers should be familiar with the medications that may cause false positives. Some medications may also cause unexpected true positive results. For example, selegiline is metabolized to desmethylselegiline, l-amphetamine, and l-methamphetamine, and thus, selegiline use may be associated with an unexpected positive methamphetamine UDT result. Vicks® nasal inhaler contains l-methamphetamine as an active ingredient and thus, may also yield an unexpected positive methamphetamine result, as only a few labs can distinguish between the l-isomer and the street drug, the d-isomer. Some laboratories will differentiate between the two forms upon request. Due to the potential for true positives such as these, a complete medication history should be obtained, including over-the-counter and herbal products and other prescription medications.

Poppy seeds may cause true positive results on UDT for codeine and morphine. Although eating poppy seeds should be benign, avoiding their ingestion will simplify the interpretation of the UDT [105].

Impurities may exist in some opiate analgesic formulations and thus contribute to unexpected false positive results [106–109]. Identification of impurities has been made possible primarily due to the higher doses of opiate analgesics often times prescribed coupled with the 10,000-fold range of quantitation available with analysis using LC-MS/MS. Table 3 reviews known impurities in commercially available opiate analgesics [107].

Table 3 Known impurities in medication formulations

Formulation	Process Impurities	Allowable Limit (%)	Typically Observed (%)
Codeine	Morphine	0.15	0.01–0.1
Hydrocodone	Codeine	0.15	0–0.1
Hydromorphone	Morphine	0.15	0–0.025
	Hydrocodone	0.1	0–0.025
Morphine	Codeine	0.5	0.01–0.05
Oxycodone	Hydrocodone	1.0	0.02–0.12
Oxymorphone	Hydromorphone	0.15	0.03–0.1
	Oxycodone	0.5	0.05–0.4

Finally, patient aberrant behaviors may explain unexpected UDT results. Although this may include medication diversion, attempts to adulterate the urine sample may also cause unexpected results. For example, introducing codeine directly into the urine by shaving off parts of the tablet directly into the sample will yield an expected positive for codeine, but results will be negative for the morphine metabolite.

Analysis of opiate metabolites can also reveal information that explains or can predict clinical outcomes. Recently, the metabolites noroxycodone and norhydrocodone were shown to be important in identifying those patients who were rapid metabolizers of oxycodone or hydrocodone [110,111]. Rapid metabolizers may have shorter duration of action of hydrocodone and oxycodone. UDT focused only on the parent medications, oxycodone or hydrocodone, would fail to identify the patient-specific metabolic variation and potentially yield false-negative results.

Analysis of benzodiazepine metabolites is also clinically valuable. Alprazolam, clonazepam, and lorazepam each have one major metabolite; respectively these are alpha-hydroxyalprazolam, 7-aminoclonazepam, and lorazepam. In contrast, diazepam (Valium®) forms three measurable metabolites: nordiazepam, oxazepam, and temazepam. A brief description of the metabolic pathways of the benzodiazepines is presented in Figure 2 [112]. Accurate interpretation of UDT results for benzodiazepines relies on an understanding of the metabolic pathways. For example, a patient on diazepam will often test positive for oxazepam and temazepam. Failure to understand the metabolic pathway may lead to inaccurate interpretation of a positive oxazepam and temazepam UDT result, possibly concluding the patient is taking a nonprescribed benzodiazepine such as oxazepam (Serax®).

Other types of substances or medications, both new (Spice [synthetic cannabinoid] [113,114]) and old

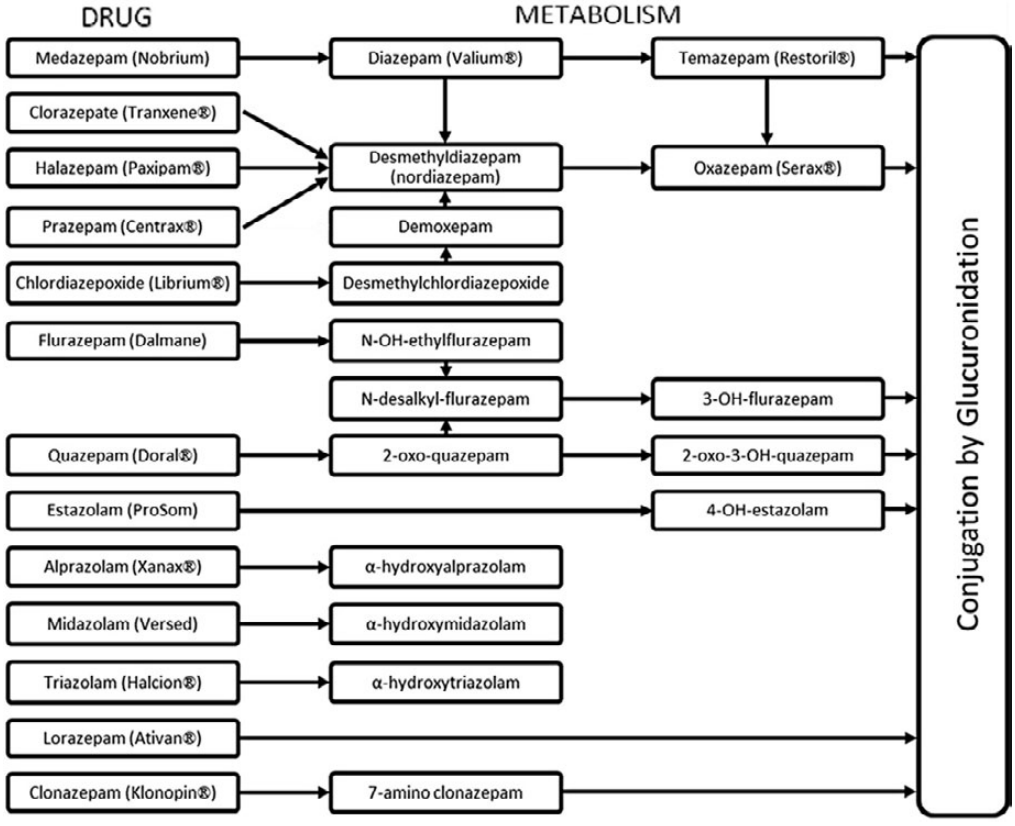

Figure 2 Metabolic pathways (benzos).

(quetiapine [Seroquel®] [115] and carisoprodol [Soma®] [116]), have potential for abuse as well and can typically be tested through LC-MS/MS.

Analytical Cutoffs

Cutoff concentrations are variable depending upon the analytical techniques used and the patient population for which they are used [117]. For example, hospital laboratories and small reference laboratories typically use analytical point of care devices and instrumentation with higher cutoffs (Table 4), which are often adequate for their purposes, such as identification of drug misuse or abuse and overdose cases [87,88,112,117–121]. However, these established cutoffs are often set too high to adequately monitor patients on chronic opioid therapy. Additionally, many of these tests are insensitive to certain opioids such as hydromorphone, hydrocodone, and oxycodone as well as certain benzodiazepines, including clonazepam and lorazepam, thus, increasing the likelihood of negative results for opiates in patients who are adherent with prescribed therapy.

Several studies have demonstrated that traditional analytical cutoffs used to detect opiates and benzodiazepines were set too high and were unable to identify the use of prescribed opiate or benzodiazepine therapy at typical dosing [85–87,112,119,120,122–124]. In general terms, the screening immunoassays would yield false-negative results for patients who were adherent to the prescribed therapy. For example, one study showed that in the case of the benzodiazepine clonazepam, only 28% of adherent patients were accurately identified [125].

Table 4 Standard cutoffs used in hospitals

Drug (Analyte)	Cutoff
Amphetamine	1,000 ng/mL
Barbiturates	300 ng/mL
Benzodiazepines	300 ng/mL
Cocaine	300 ng/mL
MDMA	500 ng/mL
Methadone	300 ng/mL
Methamphetamine	1,000 ng/mL
Opiates	2,000 ng/mL
Opiates300	300 ng/mL
Oxycodone	100 ng/mL
PCP	25 ng/mL
THC (marijuana)	50 ng/mL
Tricyclic antidepressants	1,000 ng

MDMA = 3,4-methylenedioxymethamphetamine; PCP = phencyclidine; THC = tetrahydrocannabinol.

Table 5 Best cutoffs

Drug	Analytical Cutoff (ng/mL)	Lower 2.5%	
		Estimated New Cutoff (Raw, ng/mL)	CR Normalized Cutoff (μg/g Creatinine)
7-Amino-clonazepam	10	19	15
Alpha-hydroxyalprazolam	10	15	11
Amphetamine	50	76	59
Buprenorphine	5	7	5
Carisoprodol	50	56	35
Codeine	25	29	15
Fentanyl	1	2	2
Hydrocodone	25	41	31
Hydromorphone	25	34	26
Lorazepam	20	30	25
Meperidine	25	88	28
Meprobamate	50	92	113
Methadone	50	89	74
Morphine	25	59	52
Oxycodone	25	45	46
Oxymorphone	25	44	38
Propoxyphene	50	60	42
Tapentadol	25	42	58
Tramadol	50	147	70

Laboratories providing services to pain management providers established lower cutoffs designed to more accurately identify the presence of opiate analgesics and other controlled substances, such as benzodiazepines. Recent studies have identified optimal cutoffs that allow identification of medications and illicit substances in 97.5% of the pain patient population [126,127]. Table 5 displays these medications and their associated cutoffs [126]. Cutoffs can vary by laboratory, thus, prescribers should be familiar with the cutoffs used when interpreting UDT results. Higher cutoffs may result in a greater incidence of false-negative results.

Opiate Analgesic Metabolism

Although immunoassays are not capable of identifying the presence of metabolites of opiate analgesics, analytical methods such as LC-MS/MS can identify both the parent compound and metabolites. Historically, common theory, related to metabolism of opiate analgesics and UDT, has suggested that both the parent medication and metabolite should be detected. This theory has led physicians to assume that a patient was nonadherent to prescribed therapy if both the parent compound and metabolite were not present. However, limited information or evidence is available regarding the true UDT profile for patients taking opiate analgesics [128–135].

More recently published evidence has begun to clarify the relationship between parent drug and metabolite in UDT. A study by Millennium Research Institute evaluated the urinary excretion patterns of 8,971 sequential specimens from patients being treated with opiate analgesics. Table 6 reviews the relationship between the parent drug and metabolites for several drugs. In some cases, as reviewed in Table 7, only the metabolite was present with no evidence of the parent medication.

Thus, for some medications, i.e., carisoprodol, buprenorphine, methadone, and propoxyphene, a negative result for the parent medication may be common and should not be interpreted as an unexpected or nonadherent UDT result. In other cases, only high concentrations of the parent medication are present in a urine specimen, with little or no metabolite identified. When the parent medication is identified with no metabolite present, the findings may be considered more suspicious for an attempt to deceive the test through "shaving" some of the parent medication into the urine sample. Table 8 reviews other common methods used to deceive a UDT.

Interpretation of Quantitative Values

Mass spectrometry techniques typically provide both a qualitative result (positive or negative) as well as quantitative results, which provide a specific quantitative level of medication, substance or metabolite, typically expressed in ng/mL. Urine excretion values depend upon the amount of drug that is metabolized. Data from patients administered carisoprodol, hydrocodone, morphine, methadone, and oxycodone demonstrated a wide range of values of the metabolic ratio calculated as metabolite divided by parent drug concentration, even within the same patient (S. Tse, D. Yee, N. Barakat, E. Leimanis & M. Hughes, personal communication; see Table 9). Despite this known

Table 6 Observations on the occurrence of parent drug and metabolite (concentration in ng/mL)

Drug	LC-MS/MS Cutoff	Metabolite	LC-MS/MS Cutoff	Percent of Times Metabolite Observed (%)	Median Drug Concentration When Metabolite Observed	Median Drug Concentration When Metabolite Not Observed
Methamphetamine	100	Amphetamine	100	88	6,589	701
Methadone	50	EDDP	50	97	2,269	355
Buprenorphine	10	Norbuprenorphine	20	97	65	131
Fentanyl	2	Norfentanyl	8	98	44	10
Carisoprodol	50	Meprobamate	50	98	457	174
Propoxyphene	100	Norpropoxyphene	100	97	624	362
Hydrocodone	50	Hydromorphone	50	69	1,540	341
Oxycodone	50	Oxymorphone	50	93	2,139	450

LC-MS/MS = liquid chromatography tandem mass spectrometry.

variability, attempts have been made to correlate the quantitative result back to a suggested dose of a prescribed medication in order to establish adherence with a prescribed medication regimen [136,137]. Using such an approach, approximately 40% of the patients could be considered nonadherent [47]. Nafziger et al., has criticized the attempted correlation of quantitative values to ingested doses and described the variances that occur in the metabolism of analgesics, including pharmacogenomic variability [138]. The authors stated that dosage calculations based on urine excretion measurements would have an excessively large range of potential values and should therefore not be used for clinical purposes. Carefully constructed clinical trials by Couto et al. were able to show that the variability in urinary drug excretion could be reduced and related to medication dosage [27,139] but further stated that these observations could not be used in the general population.

Table 7 Observation on the occurrence of metabolite without parent drug (concentration in ng/mL)

Metabolite	Drug	Percent of Times Metabolite Found Without Parent Drug (%)	Median Metabolite Concentration With Parent Drug	Median Metabolite Concentration Without Parent Drug
EDDP	Methadone	3.5	3,960	96
Norbuprenorphine	Buprenorphine	20	323	58
Norfentanyl	Fentanyl	7	304	18
Meprobamate	Carisoprodol	41	24,448	3,815
Norpropoxyphene	Propoxyphene	49	12,632	1,037

EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

Table 8 Deception

Type of Deception	Expectations
To dilute the urine	This will decrease the concentration of all drugs and some will be below the lower limit of quantitation. Validity testing of creatinine and specific gravity will detect this type of deception if the dilution is on the order of 10-fold or greater.
To "shave" some drug into the urine specimen	This usually results in very high values of parent drug without metabolite.
To add an adulterant to the urine that destroys the drugs	This method may deceive on an initial evaluation when the patient claims not to be on any medication, but cannot be used if the patient is being monitored for compliance.
To use urine obtained from a "clean" person	This form of deception requires that the perpetuator obtain urine with exactly their medication regimen. If they do not do so, the urine drug test will be classified as aberrant.

Table 9 Variability of urinary excretion of carisoprodol, hydrocodone, methadone, morphine, and oxycodone

	Intersubject		Intrasubject	
Medication and Metabolite	Mean Geometric MR	SD	Mean Geometric MR	SD
Carisoprodol and meprobamate	70.8	3.64	63.0	3.41
Hydrocodone and hydromorphone	0.61	3.34	0.15	2.35
Methadone and EDDP	1.71	2.08	1.68	1.63
Morphine and hydromorphone	0.008	2.3	0.007	1.6
Oxycodone and oxymorphone	0.48	—	0.41	—

The MR is the concentration of the metabolite divided by the parent drug.
EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; MR = metabolic ratio; SD = standard deviation.

However, published evidence has demonstrated that urinary drug excretion values can be compared with a "normal" population receiving a prescription for the same medication, and thus can identify results that could be considered abnormal [140] (see Table 10). However, "abnormal" results can be interpreted in various ways, some of which are discussed in Table 11.

Table 10 The 97.5 excretion percentiles of medications commonly used by patients in pain management expressed in micrograms per gram creatinine

Analyte	97.5 Percentile (μg/g Cr)
Alpha-hydroxyalprazolam	1,900
Amphetamine	41,900
Buprenorphine	600
Carisoprodol	7,300
Codeine	23,300
EDDP	37,400
Fentanyl	600
Hydrocodone	10,700
Hydromorphone	3,400
Lorazepam	6,900
Meprobamate	111,300
Methadone	22,000
Morphine	112,900
Norbuprenorphine	2,900
Nordiazepam	3,000
Norfentanyl	2,800
Norpropoxyphene	61,000
Oxazepam	9,700
Oxycodone	31,900
Oxymorphone	17,800
Propoxyphene	13,400
Temazepam	34,700
Tramadol	128,900

EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

Monitoring Concomitant Alcohol Use

In addition to monitoring adherence and the use of controlled substance, some physicians may also monitor concomitant alcohol use in patients being treated with chronic opioid therapy or other controlled substances. Reasons for monitoring concomitant alcohol use include concerns over potential interactions between alcohol and prescription opioid analgesics and the associated health complications and mortality [141].

The traditional method of detecting alcohol use by measuring urinary alcohol has significant limitations. Because alcohol is rapidly metabolized, it is not detectable unless it has been recently ingested. Thus, patients attempting to hide their alcohol use can avoid alcohol for 8–12 hours before the urine screen sample is collected and have a higher likelihood of a negative screen [142,143].

To overcome the short detection time, reference laboratories can also detect ethyl glucuronide (EtG) and ethyl sulfate (EtS), two alcohol metabolites that can be detected for days following alcohol ingestion [144–154]. The presence or absence of EtS and EtG provides the physician a more accurate indication of their patient's alcohol use [155], which can decrease the patient risk for morbidity and mortality. EtG and EtS appear in the urine within an hour of alcohol use and can be detected for 2–3 days depending on the amount of alcohol consumed [156–159].

When a UDT for alcohol is requested, alcohol is identified by a specific enzyme assay [160]. EtG is measured either by a screening immunoassay [161–163] or LC-MS/MS [162,164]. EtS is quantified by LC-MS/MS [165,166]. The screening immunoassay for EtG can have false positives; therefore, the mass spectrometry measurement is needed to confirm the result [166].

Table 11 Interpretation of unexpected urine drug testing results

Observation	Possible Interpretation	Possible Response
Prescribed drug not observed	Patient nonadherent (e.g., diversion, ran out of medication early, unable to fill medication due to cost, significant period of time since last dose)	Consultation with patient to determine underlying cause, changes in treatment regimen based on additional information gathered
Nonprescribed drug observed	Previously unidentified or unknown prescribed medication, medication obtained from friend/family, attempt to self-medicate symptoms	Consultation, possible referral to addiction specialist
Illicit drug observed	Illicit drug use, addiction	Consider referral to addiction specialist
Low creatinine, specific gravity	Over hydration, low body mass, attempt at deception by dilution, renal tubular dysfunction	Consultation with patient; Review medical and physical history
Parent drug only, no metabolite	Timing of dose (recent ingestion of parent medication without time for metabolism); metabolic variability (e.g., P450 2D6 deficient and unable to metabolize parent medication); attempt at deception	Consultation with patient; Review medication and dose taking history; consider oral or blood level to assure ingestion, consider pharmacogenomic test
Very high drug concentration	Metabolic variability (unable to metabolize parent medication to clear medication); unsanctioned dose increases, opiate abuse	Consultation with patient; review of prescription records, consider pill count
Low concentrations of unexpected drugs and/or metabolites	Remote use of unexpected substance/drug; *Note: Expected with benzodiazepines and methadone with long half-lives of weeks*	Monitor using creatinine corrected values, which should decline over time

EtG and EtS levels cannot be used to estimate the amount of alcohol consumed except in a very general sense [156,159]. For example, the presence of low levels of these metabolites in urine may be the result of excessive alcohol use days before collection, and high levels can be due to a person having consumed one to two alcoholic drinks the evening before collection [167].

Complicating the interpretation of the presence of ethanol in urine is the fact that in diabetic patients, urinary alcohol

Table 12 Scenarios for interpreting EtG and EtS results

A social drinker consuming two glasses of wine in the evening will have a negative urine alcohol test the next day but may have EtG levels above 10,000 ng/mL in the same urine specimen.
Typical urine drug testing observations and their interpretation include the following:

Scenario	Conclusion
Patient is positive for alcohol, ethyl glucuronide and ethyl sulfate.	Provided the patient is not diabetic (and the urine alcohol not the result of fermentation), patient had alcohol in their system at time of office visit.
Patient is positive for alcohol, negative for ethyl glucuronide, negative for ethyl sulfate.	Ethanol detected is probably the result of fermentation, not from the use of alcohol.
Patient is positive for ethyl glucuronide and ethyl sulfate.	Patient consumed alcohol within the last three days.
Patient is positive for ethyl glucuronide but not ethyl sulfate.	Probable alcohol use. About 5% of patients that use alcohol have only ethyl glucuronide in their urine. However consider bacterial contamination as a possible explanation.
Patient is positive for ethyl sulfate but no ethyl glucuronide.	Alcohol was consumed. However consider bacterial contamination as a possible explanation.

Table 13 Behaviors that may indicate opioid abuse and therefore require more frequent testing [74,177,178]

Behaviors More Indicative of Abuse	Behaviors Less Indicative of Abuse
Cannot tolerate most medications	Uses medications as prescribed
Requests medications with high reward	Makes most appointments
No relief with anything except opioids	Shows up for recommended evaluations
Admitted to seeking euphoria from opioids	Gives reasonable treatment recommendations a fair trial
Admitted to wanting opioids for anxiety	Rare or no medication incidents
Multiple dose escalations or other noncompliance with therapy despite warnings	Medication sensitivities and favorable responses not predictable by medication abuse liability
Frequent early renewal requests	Aggressive complaining about the need from more drug
Requested refills instead of clinic visit	Requesting specific drugs
Frequently misses appointments unless opioid renewal expected	Openly acquiring similar drugs from other sources
Urgent calls or unscheduled visits	Resistance to a change in therapy associated with "tolerable" adverse effects with expressions of anxiety related to the return of severe symptoms
Cannot produce medications on request	Drug hoarding during periods of reduced symptoms
Multiple episodes of prescription "loss"	Doses discussed at clinic visits
Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug	Has expected amount of medication left
Does not try non-opioid treatments	Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions
Stealing or "borrowing" drugs from others	Unapproved use of the drug to treat another symptom
Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber or after warnings to desist	Reporting psychic effects not intended by the clinician
Obtaining prescription drugs from nonmedical sources	No significantly altered consciousness
Prescription forgery	Stable or improving mood
Used additional opioids than those prescribed	Stable or improving sleep
Selling prescription drugs	Stable or improving pain
Injecting oral formulations	Stable or improving activity
Concurrent abuse of alcohol or illicit drugs	Improving relationships
Abnormal urine/blood screen	No alcohol or drug abuse
Intoxicated/somnolent/sedated	No withdrawal signs
Irritable/anxious/labile mood	Observers report appropriate use
Declining activity	Adopts self-management strategies (can demonstrate/discuss techniques)
Evidence of deterioration in the ability to function at work, in the family, or socially that appear to be related to drug use	
Increasing sleep disturbance	
Increasing pain complaints	
Withdrawal noted at clinical visits	
Observers report overuse or sporadic use	
Third part required to manage patients medications	
Was discharged from practice	
Overdose and death	

is often caused by fermentation of urinary glucose and not alcohol consumption [168]. EtG can be both produced and degraded in vitro as the result of bacterial contamination of the urine [169,170]. For this reason, the detection of EtG in the absence of EtS should be interpreted with caution. In contrast, EtS is stable, and the detection of both EtG and EtS provides strong evidence of alcohol exposure [154].

Sources of incidental exposure include alcohol containing hand washes, mouthwashes, and over-the-counter (OTC) medications [167,171–173]. A cutoff of 500 ng/mL for

both EtG and EtS has been suggested to eliminate positives that can occur with the normal use of these products. Some OTC medications such as Nyquil™ cough preparation contain up to 25% alcohol and may produce a positive result above this level [167]. We have provided several scenarios for interpreting EtG and EtS results in Table 12.

Testing Frequency [53]

An important consideration for any physician conducting urine drug screening is which patients to screen and how often to test. Published guidelines indicate that, prior to initiating opioids or other controlled substances, patients should be tested at baseline and then random testing should be conducted between two and four times per year unless an abnormal screen is observed or patient exhibits unusual behavior [2,3,22,53,174–176].

Patients who present with or display aberrant behaviors during therapy, or patients with greater risk factors for opioid abuse (e.g., personal history of addiction, family history of addiction), may require more frequent testing (see Table 13) [74,177,178]. In general, frequency of testing should be determined by the prescriber, based on published guidelines, patient behaviors, and medical necessity.

Conclusions

Managing chronic pain with chronic opioid therapy requires careful monitoring of medication adherence and patient behaviors. Adherence to prescribed therapy is variable and often impacted by patient-driven modifications to therapy. UDT is a key component in a comprehensive monitoring and risk mitigation plan. However, interpretation of UDT results can be difficult without adequate knowledge. Prescribers using UDT in their practice should be aware of the subtleties of opiate and opioid medication metabolism, individual cutoffs of UDTs, and the corresponding likelihood of false positive or false-negative results in order to properly interpret UDT results. Collaborating with laboratory toxicologists and clinical staff is also recommended to better understand the various test results. Concomitant monitoring of alcohol use can be helpful and is best accomplished by monitoring the ethanol metabolites EtG and EtS, which are most accurately measured by LC-MS/MS analytical procedures. Based on patient behaviors and risk factors, more frequent monitoring with UDT may be justified and has been documented to be cost-effective in reducing healthcare expenditures [179].

Patient compliance with medication regimens may vary depending on several factors. Therefore, physicians treating patients for pain should familiarize themselves with specific medications, their metabolites, and common adherence patterns so they are better prepared to discuss UDT results and formulate effective medication regimens for optimal patient care outcomes.

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