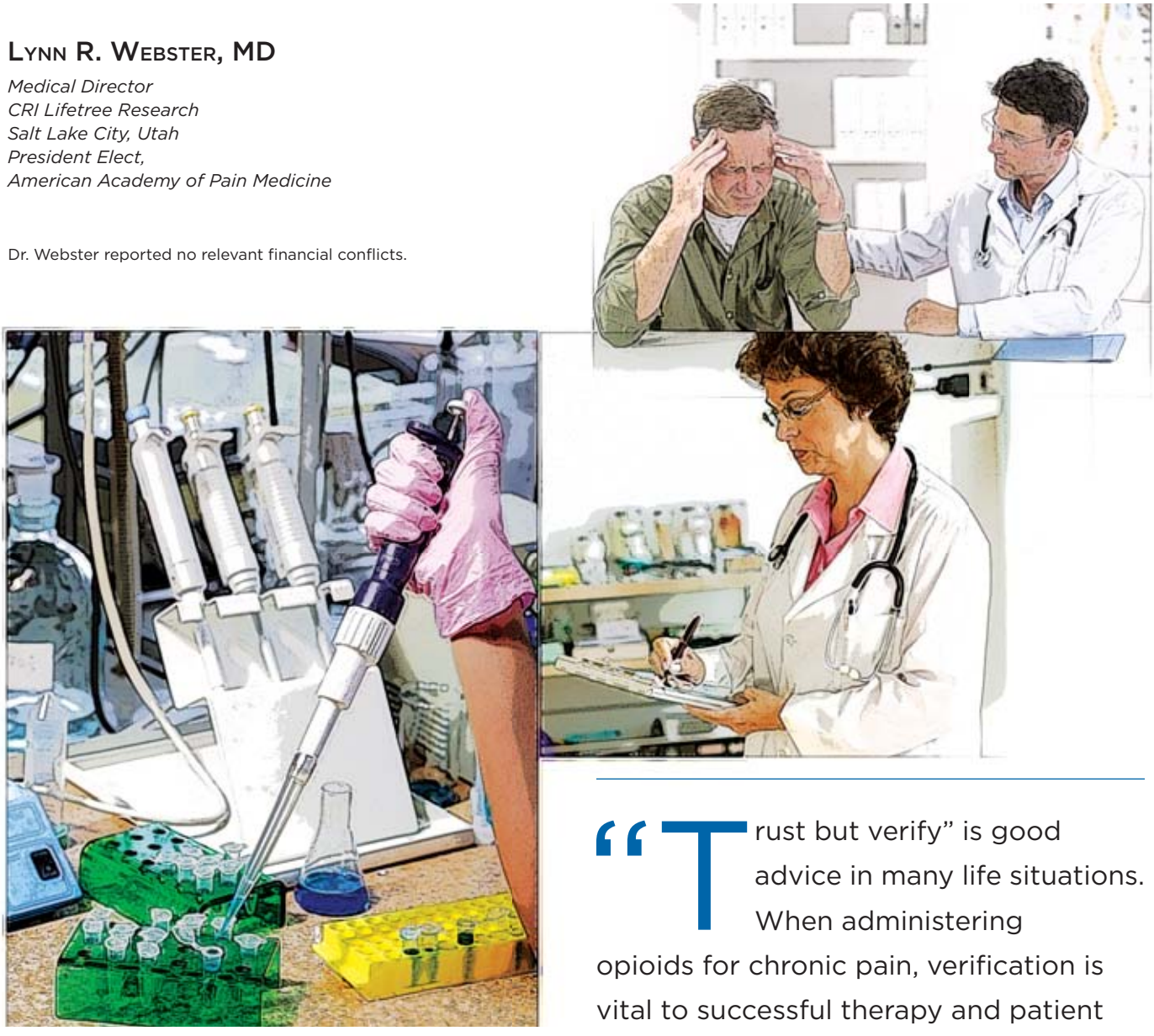
The Role of Urine Drug Monitoring In Pain Management

Lynn R. Webster, MD

Medical Director
CRI Lifetree Research
Salt Lake City, Utah
President Elect,
American Academy of Pain Medicine

Dr. Webster reported no relevant financial conflicts.



"Trust but verify" is good advice in many life situations. When administering opioids for chronic pain, verification is vital to successful therapy and patient safety. This is because studies show discrepancies between medical direction and actual adherence to medication regimens among patients on opioid therapy.[1-3]

Table 1. Potential Benefits of Urine Drug Monitoring

Identify unauthorized substances, whether illicit street drugs or nonprescribed medications (ie, signs of drug abuse or possible addiction).
Detect the presence of prescribed medication as evidence of regimen adherence (absence may indicate diversion or hoarding, although caution must be used in drawing conclusions due to test limitations).
Assist with diagnosis and therapeutic decision making.
Corroborate the patient's self-report of adherence.
Provide documentation for the patient for workplace or legal requirements.

Of 470 patients treated in an urban pain management setting, 45% were retrospectively found to have abnormal urine screens, defined as the absence of a prescribed opioid, the presence of illicit substances or unauthorized prescription medications, or an adulterated urine sample.[1] Further research has shown that physicians are easily fooled by actors posing as patients.[4] Some nonadherence may be unintentional, and some may reflect serious problems with use that stem from causes such as abuse, addiction, diversion for illegal sale, or inappropriate use due to mental health comorbidities or life stress.

Urine drug monitoring (UDM) can help inform clinical decisions. Although a valuable tool, UDM cannot be used as a sole determinant of adherence, and its limitations should be clearly understood by physicians.[5] Most evidence suggests that UDM is best used in concert with other clinical monitoring tools, such as checks of the state prescription database and ongoing assessments of the patient's pain relief, function, quality of life, and psychosocial indicators.

Need for Better Medication Management in Chronic Pain

The wide prevalence of chronic pain in America is confirmed in a recent report from the Institute of Medicine (IOM), which found more than 100 million individuals with chronic pain, costing up to $635 billion annually in medical treatment and lost productivity.[6] Few of these individuals will need long-term opioid therapy, but certain patients whose moderate to severe pain has not responded to earlier interventions do achieve meaningful, long-term pain relief on opioid therapy.[7] For these patients, initial assessment and ongoing monitoring of progress toward clinical goals is necessary. Poor adherence puts patients at risk for overuse or underuse of medication and also puts the public at risk for increased availability of opioids to abuse through diversion. Federal statistics show that most opioids diverted for nonmedical use came from home medicine cabinets. Data from the National Survey on Drug Use and Health (2009-2010) showed that 70% of America's 2.4 million first-time prescription drug abusers got the drugs from family and friends.[8] There are clinical and societal consequences when opioids are misdirected away from their medical purpose and end up in the wrong hands.

Reasons for Urine Drug Monitoring

For pretreatment assessment and regular ongoing monitoring, UDM is relatively quick and easy to perform. Potential benefits of UDM are listed in Table 1.

Patients Who Would Benefit From Urine Drug Monitoring

Most patients to be initiated on chronic opioid therapy should have an initial screen in keeping with "universal precautions," which are modeled on the infectious disease paradigm.[9] Periodic follow-up testing is recommended. Certain patient characteristics observed clinically suggest the need for adherence testing and

Table 2. Validity Testing of a Urine Specimen[14,15]

Urine Specimen Is Reported As	When
Diluted	Creatinine concentration ≥2 mg/dL but <20 mg/dL, and specific gravity >1.001 but <1.003
Substituted	Creatinine concentration <2 mg/dL and specific gravity ≤1.001 or ≥1.020
Adulterated	pH <3.0 or ≥11, nitrite concentration ≥500 Qg/mL; chromium (VI) concentration ≥50 Qg/mL; presence of a halogen (eg, from bleach, iodine, fluoride), glutaraldehyde, pyridine, surfactant

include aberrant drug-seeking behavior, refusal of a full diagnostic workup, and substance abuse history. However, consensus guidelines on opioid prescribing jointly endorsed by the American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) state that patient risk factors can be poor predictors of adherence, leading to missed problematic behavior by other patients.[10] The APS/AAPM guidelines suggest random rather than scheduled testing as a better measure of true patient behavior.

Efficacy Data

Although evidence is lacking for improved clinical outcomes with UDM, it is apparent that the presence of unauthorized substances or the absence of prescribed substances could point to problems that would interfere with safe and effective opioid therapy.[10] Using several monitoring measures in combination may be best. One study showed that 45% of patients with previously demonstrated aberrant drug-related behaviors were able to adhere to their medication regimens after management with UDM in combination with signed treatment agreements and multispecialty care.[11]

Issues in Testing

Use of Patient Agreements

Monitoring for regimen adherence in patients receiving opioid therapy should be an expected part of therapy. This monitoring is comparable to checking for the effects of medications to regulate diabetes, cardiovascular irregularities, and other chronic medical conditions.

Treatment agreements that lay out the goals, expectations, responsibilities, and parameters of the selected course of therapy can be useful[9] and, if used, should be signed by provider and patient. Up-front agreements can reduce the stigma of UDM that exists in some patients' minds and make clear that adherence monitoring is a routine part of medical practice.

Types of Tests

In contrast to forensic testing, which is concerned with locating illegal use of substances, clinical testing seeks to establish adherence. For that reason, 2 types of tests are usually necessary: initial (qualitative) testing and confirmatory (quantitative) testing. Initial testing consists of a radioactive or enzyme-mediated immunoassay test, which can show whether or not certain drug classes are present but typically cannot isolate specific opioids.[12] Confirmation testing is done via high-performance liquid chromatography or combination techniques, such as gas chromatography/mass spectrometry, which can detect actual molecular structures of specific drugs and their metabolites.[12]

Initial immunoassays traditionally have screened for amphetamines, cocaine, opiates, marijuana, and phencyclidine.[13] Newer initial tests also can test for most drugs prescribed for pain. If results are positive, confirmatory testing should follow. Specific drugs to test for include the following:

- morphine
- hydrocodone
- hydromorphone
- oxycodone
- oxymorphone
- fentanyl
- buprenorphine

Point-of-care tests are administered outside of laboratory settings and are read visually by clinic personnel.[12] Offering quick turnaround, they are only used for initial screening. Clinic staff must be trained to follow precisely all protocols established by the test's manufacturer. Test accuracy and cutoff scores vary, and it is recommended that positive results be sent for confirmation in a laboratory before therapeutic decisions are made based on results.

Validity Testing

Patients may tamper with urine samples by adding adulterants, diluting the sample, or substituting another individual's sample for their own; or they may attempt to influence test outcome by ingesting excess water or diuretics prior to giving a sample.[12] Testers should record the temperature of urine within 4 minutes of voiding, with temperatures outside the range of 90°F to 100°F suggesting substitution. Three tests of specimen validity with federally mandated criteria for interpretation are for urinary creatinine, specific gravity, and pH (Table 2).[14,15] For comparison, know that a randomly collected adult urine sample (with some exceptions) should include the following:

- 15 to 400 mg/dL creatinine;
- a specific gravity of 1.002 to 1.030; and
- pH in the range of 4.5 to 8.0.

Cutoff Scores and Other Laboratory Issues

Results may be reported using terms that indicate only whether a substance is present. Cutoff scores indicate levels of a drug necessary for detection or a positive result. In some instances, the drug may be present but the level is too low to be read as positive. Physicians should communicate with labs to ensure reporting methods are consistent with the needs of clinical practice.

Issues in Interpreting UDM Results

The most important limitation is that a UDM result cannot determine exposure time, dose, or frequency of drug use and certainly cannot be used to diagnose addiction. Test results should not in themselves dictate therapeutic decisions but should be interpreted in the context of additional clinical signs and should be discussed with the patient.

When interpreting UDM results, physicians should consider the possibility of false-negatives or false-positives as influenced by opioid drug metabolism, pharmacokinetics, lab limitations, and other factors. A false-negative occurs when a drug is actually present but the test returns a result below the cutoff score or does not detect that particular analyte. A false-positive indicates a substance is present when it is not.

Factors that could give rise to false-negatives or false-positives include the following:

Cross-reactivity. Cross-reactivity is possible with foods, over-the-counter (OTC) medications, and prescribed drugs.[12] A well-known false-positive result is possible for opiates with the ingestion of poppy seeds. Other substances that have been reported to cause false-positives include quinolone antibiotics (for opiates), the antipsychotic quetiapine (for methadone), the antidepressants trazodone (for fentanyl) and venlafaxine (for phencyclidine), diet pills such as clobenzorex and fenproporex (for amphetamine), promethazine used to treat allergies, agitation, nausea, and vomiting (for amphetamine), and l-methamphetamine OTC nasal inhaler (for amphetamine). To avoid false-positives, lab personnel should be informed of all prescribed and OTC medications a patient is taking that could interfere.

Limited Windows of Detection. Most drugs can be detected via UDM for 2 to 3 days after use.[16] However, misunderstood dosing directions and the speed at which an individual metabolizes opioids due to genetic factors can influence results.

Lab Error or Test Insensitivity. Some immunoassays are not sufficiently sensitive to detect a drug at a given level, particularly opioids at therapeutic levels. If a result is inconsistent with the clinical picture, it should be confirmed that the lab's assays can detect the drug in question.

Drug Metabolism

Individuals who metabolize opioids more quickly than what is considered typical may return a result that shows a medication is absent although it was actually consumed.

Some unexpected substances may be present as metabolites of the prescribed drug or even byproducts of the manufacturing process (Figure).[17] For example[13,17]:

- Codeine is metabolized to morphine.
- Morphine is not metabolized to codeine, but small amounts of codeine may be a manufacturing byproduct.
- Codeine is partially metabolized to hydrocodone.
- Hydrocodone is metabolized to hydromorphone.
- Morphine can produce the minor metabolite hydromorphone.
- Heroin is metabolized to 6-monoacetylmorphine and morphine.

The following steps help avoid errors in interpretation:

- Take a complete history of all medication and other substance usage prior to administering the test.

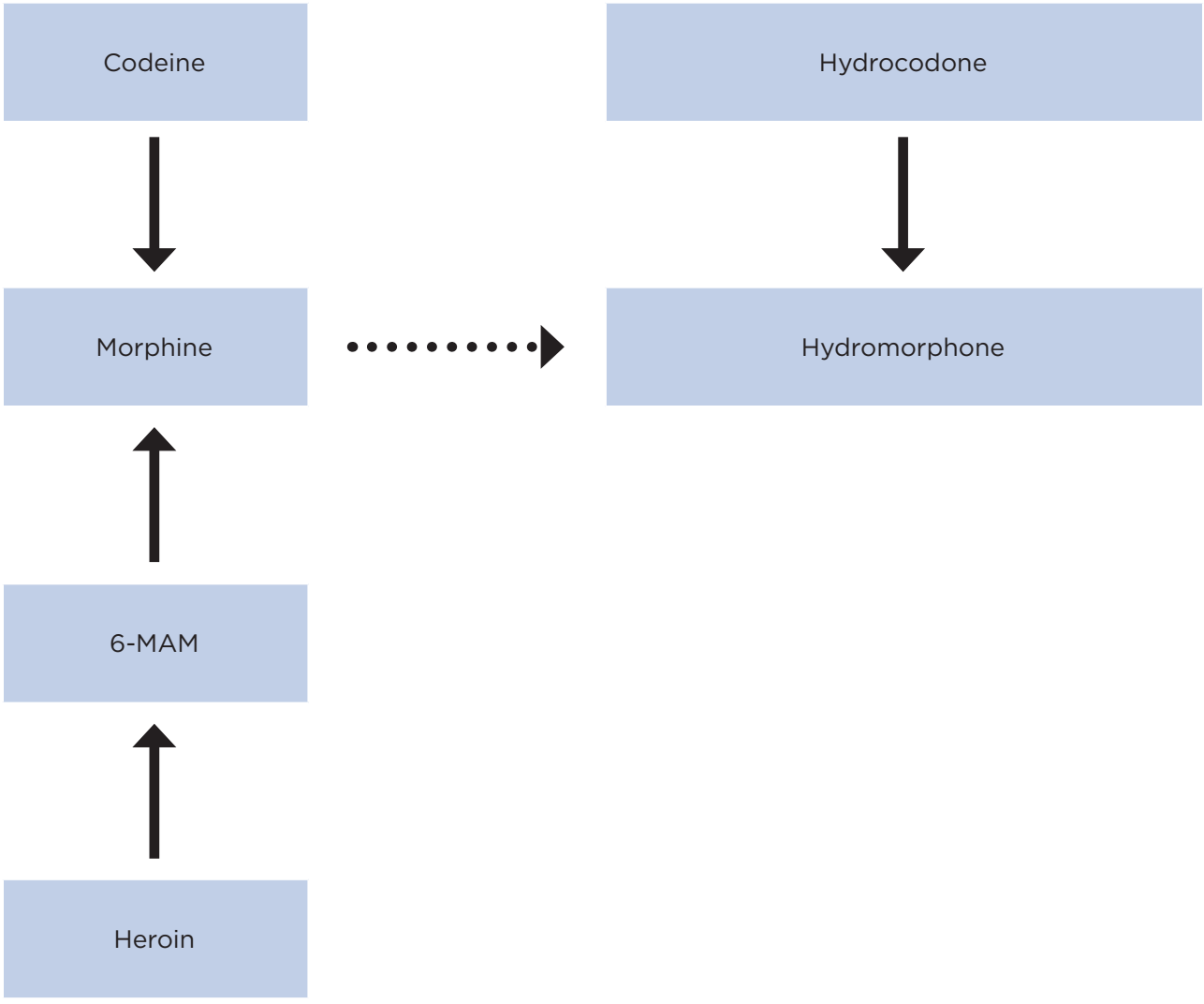


Figure. Example of opioid metabolism.[a,17]

6-MAM, 6-monoacetylmorphine

[a] Not comprehensive pathways, but may explain the presence of apparently unprescribed drugs.

- Be familiar with the metabolites common to opioid metabolism.
- Understand that the absence of prescribed opioids does not in itself prove diversion, hoarding, or binging.

Conclusions

Urine drug testing is part of the ongoing monitoring process of patients on chronic opioid therapy. It is used to confirm the presence of prescribed medications and to detect the presence of unauthorized substances. Being widely available, it is considered a valuable tool to track progress toward treatment goals and to guard against nonmedical use and diversion. However, issues with individual and drug metabolism, test reliability, interpretation difficulties, and physician knowledge limit the conclusions that can be drawn. False-negatives and false-positives are possible. Although results must be cautiously applied to clinical care, they should be broached with the patient and documented in the medical record, and may indicate the need for treatment adjustments.

References

1. Michna E, Jamison RN, Pham LD, et al. Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings. *Clin J Pain.* 2007;23(2):173-179.
2. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res.* 2006;6:46.
3. Quest Diagnostics Health Trends™. Prescription drug misuse in America: laboratory insights into the new drug epidemic. *Health Trends: Prescription Drug Monitoring Report 2012.*
4. Jung B, Reidenberg MM. Physicians being deceived. *Pain Med.* 2007;8(5):433-437.
5. Christo PJ, Manchikanti L, Ruan X. Urine drug testing in chronic pain. *Pain Physician.* 2011;14(2):123-143.
6. IOM (Institute of Medicine). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington, DC: The National Academies Press; 2011.
7. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010;20(1):CD006605. Review.
8. Pizzi D. Federal agencies highlight the good, bad and ugly of prescription drug epidemic. *Pain Medicine News.* 2012;10(6):1,18,22.
9. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med.* 2005;6(2):107-112.
10. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130.
11. Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med.* 2007;8(7):573-584.
12. Hammett-Stabler CA, Webster LR. *A Clinical Guide to Urine Drug Testing.* Stamford, CT: PharmaCom Group Ltd; 2008.
13. Webster LR, Dove B. *Avoiding Opioid Abuse While Managing Pain: A Guide for Practitioners*. North Branch, MN: Sunrise River Press; 2007.
14. Bush DM. The US Mandatory Guidelines for Federal Workplace Drug Testing Programs: Current status and future considerations. *Forensic Sci Int.* 2008;174(2-3):111-119.
15. Substance Abuse and Mental Health Services Administration. Department of Health and Human Services. Mandatory guidelines for federal workplace drug testing programs. *Fed Regist.* 2004;69:19643-19673.
16. Caplan YH, Goldberger BA. Alternative specimens for workplace drug testing. *J Anal Toxicol.* 2001;25(5):396-399.
17. Gourlay D, Heit HA, Caplan YH. Urine drug testing in clinical practice: dispelling the myths & designing strategies. Stamford, CT: PharmaCom Group, Inc.; 2006.

Acknowledgment: Medical writer Beth Dove of Dove Medical Communications, Salt Lake City, Utah, assisted in the preparation of this manuscript.