Urine Drug Testing for Pain Management

Urine drug testing (UDT) is an important safe prescribing practice for all controlled substances. For patients with chronic pain and chronic opioid therapy, UDT is one component of the initial and ongoing risk assessment.

The Wisconsin Medical Examining Board (MEB) opioid prescribing guideline recommends a UDT prior to initiating chronic opioid therapy and at minimum once yearly; more frequent UDT is recommended for higher risk patients.

Immunooassay (IA) urine drug tests are qualitative screening tests that identify presence or absence of drug classes. IA tests rely on the binding of an antibody designed to detect a specific chemical or group of closely related chemicals. IA tests can be performed in a lab or as a point of care test.

Variables that can influence the test result include test specific drug cutoff levels (minimum concentration of a drug or metabolite that must be present to produce a positive result), cross-reactivity within the drug class of interest, cross-reactivity of unrelated drugs, drug dose, dosing frequency and timing related to testing, metabolism (patient pharmacokinetics), urine dilution and urine pH.

Advantages of IA:
- Simultaneously screen for multiple drugs
- Fast results, inexpensive

Disadvantages of IA:
- In general, specific drugs are not detected within a drug class (for example opioid IA test detects several opioids in the class, not just morphine, codeine, etc.)
- Variable sensitivity and specificity by test manufacturer; review of product insert is helpful
- A drug with concentration below the drug class cutoff will be reported as negative (the drug or metabolite in the class is present, just not detected); a false negative test if the goal is to detect presence of any concentration of drug in the class
- Polypharmacy may not be detected (for example morphine and hydromorphone are prescription drugs that could be taken concurrently, yet not separately identified by any opiate IA drug test)

Gas Chromatography and Liquid Chromatography-Mass Spectrometry (GC-MS/LC-MS) urine drug tests are quantitative, confirmatory tests identifying specific drugs and their metabolites and their respective concentrations.

Advantages of GC-MS/LC-MS:
- Highly specific (few false-positives); highly sensitive (few false-negatives) due to lower cutoff levels for detection
- Results are definitive for specific measurable substances
- Can detect multiple drugs within the drug classes, assisting interpretation (many drugs within a class, such as opioids will be reported if detected above the measuring limit)

Disadvantages of GC-MS/LC-MS:
- Results take 2-3 days; the test is typically run at an outside lab due to the need for specialized equipment
- More expensive (but may be more cost effective depending on the drug information needed)
Why Urine Drug Testing?

- Provides objective data regarding compliance with the pain treatment plan
- Aids in the evaluation of aberrant behaviors, unexplained symptoms, or unexpected responses to treatment. Is the patient taking illicit drugs? Is the patient taking prescription medications from other sources? Has the patient stopped taking their medication?
- Improves patient safety by identifying dangerous medication combinations from non-prescribed sources that can increase the risk of overdose
- **Important note:** A positive drug test will not provide a diagnosis of a substance use disorder nor does a negative test result rule out a substance use disorder.

Patient Preparation and Education

- Use a controlled substance treatment agreement (CSTA) that explicitly outlines expectation for UDT.
- Explain to patient that UDT is part of universal precautions. Patients are more likely to accept UDT as part of the treatment plan when they know they are not being signaled out or suspected of abusing drugs.
- **Patient education tip:** “Opioids are dangerous medications when not used appropriately. In order to provide you safe and effective treatment for your chronic pain, I am required to conduct UDT periodically. This is done for all patients receiving long-term opioid medication.”

Interpretation of Immunoassay (IA) Urine Drug Test Results

Interpretation of IA test results requires an understanding of which drugs are included in the drug test panel, test specific drug cutoff levels, which drugs or drug metabolites will be detected, window of detection, and potential cross-reactivities for specific drugs. **Contact the laboratory when looking for specific drugs to make sure the correct test is ordered.** Clinicians should have access to a copy of the lab manual for the drug test panel(s) used in their clinic.

Definitions:

- “Expected” test result is positive for the patient’s prescribed medication, but negative for all other unexpected substances
- “Unexpected” test result could be negative for the prescribed medication, positive for unexpected substance(s), or both

Opioid Metabolic Pathways

It is important to understand basic metabolism of opioids for accurate IA test interpretation. For example, codeine metabolizes to morphine and to a lesser extent hydrocodone, therefore, all three substances may be present in urine.

Responding to unexpected NEGATIVE results for prescription opioids:

- Take a thorough medication history including date of last use and quantity of use during the preceding 2-3 days
  - Patients on low dose PRN medication may result negative
  - Did the patient run out of medication early due to increasing the dose or frequency of use? Rule out poorly controlled pain versus substance misuse/abuse.
  - Is the patient not taking the full prescribed dose? Rule out patient hoarding of drug for future use versus diversion?
- Is the testing outside the window of detection for the expected prescribed drug?
- Is the drug testing panel specific to the expected prescribed drug?
- Clinical conditions that could produce negative results:
  - Induced enzyme levels from smoking causing more rapid metabolism/elimination of the drug
  - Shortened GI tract from surgery reducing absorption of the drug
- Did the patient consume excessive fluids causing diluted urine? Check the specific gravity of the sample.
- Has the specimen been adulterated or substituted?
- Consider retesting; consider possibility of diversion or non-use of medication.
- The rate of false negative results with IA is rare; typically confirmatory testing is not needed for negative results. Consider confirmatory testing if the patient adamantly reports taking the medication in question.

Responding to unexpected POSITIVE results for prescription opioids:

- Take a thorough medication history, including OTC medications, to assess for potential cross-reactivities; include in the history where medication was obtained to assess for non-prescribed source
- Review the PDMP to check for other sources of prescribed medication
- Some opioids are normally metabolized into other opioid substances. The presence of other opioid substances may indicate appropriate use of the prescribed opioid.
- Consider confirmation testing to rule out cross reactivity. See table Urine Drug Testing – Prescription Medications.

Follow-up of unexpected positive results for ILLICIT DRUGS:

- See table - Drugs of Abuse Testing – Illicit Drugs
- Avoid making significant treatment decisions based solely on UDT results. All unexpected results require further evaluation and can indicate a wide spectrum of aberrant behaviors from chemical coping to substance use disorder. Treatment decisions should be based on all relevant data including UDT, patient interview, ePDMP review, and the behavioral and physical assessment.
Treatment planning

- All unexpected results require further evaluation.
- IA positive results should be considered presumptive until confirmed by GC-MS/LC-MS, although it is not always necessary to confirm all positive results. Talk with the patient about possible cross-reactivities related to medications or food; send for confirmation if the patient’s self-report is not consistent with the test result.
- When in doubt, consult with a clinician knowledgeable in UDT interpretation e.g. pain management specialist or a colleague managing higher risk pain patients.
- Discussing test results with a patient can be difficult. Patients need clear explanation of the test results in terms they can understand and what it means for them and the treatment plan. Straightforward, nonjudgmental communication is essential.
- Follow-up may include counseling, increased frequency of office visits and UDT, limiting quantity with opioid prescription, evaluation for mental health and substances use disorders with referral to Behavioral Health or Addiction Medicine as appropriate, and/or discontinuing the opioid medication.
- Consider referral to a comprehensive pain management specialist in the context of uncontrolled pain that is difficult to manage by the primary care provider, especially if the patient feels the need to seek outside substances to control pain. Patient should be advised that the purpose of the referral is to look at alternative treatment options that may or may not include prescribing of opioid analgesics.


Interpretation of Confirmatory Urine Drug Test Results

Positive IA results should be considered presumptive until confirmed by gas or liquid chromatography-mass spectrometry (GC-MS/LC-MS), although it is not always necessary to confirm all positive results. GC/LC-MS provides highly-specific results through identification and quantification of the individual drugs or metabolites within a specimen. GC/LC-MS also provides highly sensitive results due to lower cutoff levels for detection.

Correct interpretation of confirmatory test results requires a more comprehensive understanding of metabolic pathways, particularly for opioids and benzodiazepines, in order to understand which metabolites will be present and which metabolites should not be present, based on the patient’s prescribed medication.
Understanding confirmatory urine drug test results:

1. Metabolites should be present; absence suggests potential adulterated sample (SAMHSA, 2012)
2. Opioids are metabolized in a linear sequence
   a. Heroin is rapidly converted to 6-MAM and then to morphine; there is minimal metabolism to hydromorphone. Rarely will heroin or 6-MAM be present due to heroin’s very short half-life.
   b. Codeine is metabolized to morphine; therefore, both substances may be present after codeine use.
      i. Codeine alone is possible because a small proportion of patients (<10% of caucasians) lack the enzyme needed to convert codeine to morphine.
      ii. Codeine may be metabolized to small quantities (generally <15%) of hydrocodone; this should not be interpreted as hydrocodone use when high concentrations of codeine are present.
   c. Morphine is metabolized to 3-morphine-glucuronide and 6-morphine-glucuronide and to a small extent (< 5%) to hydromorphone.
      i. Morphine does not metabolize to codeine; presence of morphine only is consistent with use of morphine or heroin.
   d. Hydrocodone may be metabolized to small quantities of hydromorphone; this should not be interpreted as hydromorphone use when high concentrations of hydrocodone are present.
   e. Synthetic opioids e.g., oxycodone, methadone, and fentanyl, have limited metabolism.
      i. Oxycodone is metabolized to noroxycodone and oxymorphone. If the concentration of oxycodone is greater than oxymorphone, use of oxycodone is likely.
      ii. Oxymorphone does not produce any metabolites that could be mistaken for another
opioid.

3. Benzodiazepine metabolism is complex; providers should refer to metabolic pathways for anticipated metabolites.

4. THCA quantification can demonstrate abstinence through decreasing levels.
   a. May be present in urine for more than 3 months in chronic high users
   b. Levels may increase if a patient has lost significant weight despite being abstinent
   c. Passive smoke inhalation does not produce appreciable amounts of THCA in a urine specimen to explain positive marijuana results

5. Amphetamines are minimally metabolized but frequently cross react; therefore, confirmatory testing is needed to identify which substances are present.

6. A methamphetamine positive result requires chiral analysis to differentiate between two isomers: d-methamphetamine and l-methamphetamine
   a. Any d-methamphetamine present is from an illicit source.
   b. If 100% of the isomer is l-methamphetamine (aka l-desoxyephedrine), the source is likely from a Vicks inhaler or a metabolite of selegiline.

7. Confirmatory tests provide quantitative concentrations of drugs and their metabolites; however, there is currently no broadly accepted, scientifically validated relationship between the concentrations reported in the urine and the doses taken of any drug.
   a. Interpretation of quantitative concentrations is difficult and requires more specialized training
   b. Providers with questions about interpretation should speak with a pain or addiction specialist experienced with interpretation.

8. Confirmation of all positive IA results is not clinically indicated and not cost effective.
   a. If a patient admits drug use when informed of a positive test result, a confirmatory test is generally not needed.
   b. If the IA test is highly specific to a drug with limited cross-reactivities e.g., cocaine, confirmation is generally not needed.
   c. Refer to the tables Drugs of Abuse Testing – Illicit Drugs and UDT – Prescribed Medications to help determine when confirmation is necessary.

Confirmatory testing with chromatography and spectrometry of positive urine drug testing by IA is complicated and contains many opportunities for miscommunication and misunderstanding. This guide is intended to provide a broad overview of the most common pitfalls that providers are likely to encounter. Any questions can be referred to a pain or addiction specialist experienced with interpretation and clinical application of findings.

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References:

