



New High-Resolution Targeted Opioid Screen

Superior Sensitivity and Specificity to Evaluate Adherence to Prescribed Opioid Therapy

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Disclosures

- None

Objectives

- Describe the clinical utility and limitations of the following urine drug tests used to support pain management/monitoring of controlled substances:
 - Traditional opiate immunoassays
 - Mass spectrometry-based targeted screening assays
- Define the metabolic profiles of opioids commonly used in pain management and discuss how to interpret screening/definitive test results.

Opioid Crisis in America¹

- Sale of opioid pain relievers (OPR) quadrupled between 1999 and 2010
- Enough OPR were prescribed in 2010 to medicate every American adult around the clock (every 4 hours) for a month
- Large number of patients (>40%) still report inadequate treatment of pain
- Medical examiner reports also continue to show an increase in opioid related fatalities
- Chronic pain costs up to \$635 billion/year in medical treatment and lost productivity



Why Do Clinicians Use Urine Drug Tests (UDT) to Monitor Opioids?

- Clinical Practice Guidelines:
 - American Society of Interventional Pain Physicians (ASIPP) Guidelines^{2,3}
 - Urine drug testing (UDT) must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy (Evidence: Good)
 - Verify adherence or compliance to prescribed medications
 - Identify undisclosed drugs
 - Discourage drug misuse, abuse, diversion

2016 CDC Recommendation for UDT

- When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.⁴

Why Do Clinicians Use Urine Drug Tests (UDT) to Monitor Opioids?

- Clinical Practice Guidelines
- Financial Reasons⁴:
 - Nonadherence to opioid therapy leads to increased healthcare utilization and costs
 - Early monitoring of opioid adherence using UDTs may provide substantial cost savings associated with health care issues incurred in nonadherent chronic pain patients

Why Do Clinicians Use Urine Drug Tests (UDT) to Monitor Opioids?

- Clinical Practice Guidelines
- Financial Reasons⁴
- Regulatory Scrutiny (State and Federal Regulations)⁵:
 - State Level:
 - Physicians can prescribe controlled substances w/ state board issued medical license.
 - Some states may require additional registration
 - Most states also have a regulation, guideline, or policy statement for prescribing opioid analgesics for pain
 - Some states discourage or prohibit physicians from prescribing opioids to patients whom they know or should know are using controlled substances for nontherapeutic purposes
 - Federal Level:
 - Must first satisfy state requirements of licensure and registration
 - DEA issues a federal controlled substances registration
 - Federal laws/regulations do NOT prohibit the use of opioids to treat pain if a patient is abusing controlled substances

Types of UDTs

- Screening assays
 - Identify drugs and/or drug metabolites with variable specificity often by drug class
 - Typically immunoassay-based
 - POC or laboratory-based
 - Economical
 - Quick TAT (<24 hours)
 - Qualitative results
 - Limited sensitivity and specificity
 - Higher cutoffs
- Definitive assays
 - Identify and/or quantify the drug and/or drug metabolite with high specificity
 - Typically GC-MS or LC-MS/MS
 - Laboratory-based
 - More labor intensive (higher cost)
 - Longer TAT (2-7 days)
 - Qualitative or Quantitative results
 - Optimal sensitivity and specificity
 - Lower cutoffs

Screening Assays

- Types:
 - Traditional screening assays
 - Point-Of-Collection Tests (POCT)
 - Laboratory-based (commercial immunoassays)
 - Targeted screening assays
 - Laboratory-developed-tests (LDT) using TOF-MS or other MS/MS analyzers

Test	Advantages	Disadvantages
POCT	Fastest TAT	Limited sensitivity
	CLIA-waived versions available	Higher cutoffs
	Instant result to review/discuss with patient	Limited specificity
	Great if patient resides far from care	Maintain inventory/regulatory compliance
Immunoassay-lab based	Good for high-risk patient	Higher cost
	Automated	Limited sensitivity
	CLIA environment	
	Most economic	Limited specificity
Targeted screen	Larger test menu	
	Better sensitivity	Limited availability
	Better specificity	
	Broadest test menu	

Cross-Reactivity Issues with Immunoassays

- Urine opiate immunoassay target
 - Morphine
- Concentration required to trigger a “positive” opiate result

Drug	ng/mL Equivalent to 300 ng/mL Morphine	Approximate % Cross-reactivity
6-acetylmorphine	386 ng/mL	78%
Dihydrocodeine	510 ng/mL	59%
Codeine	224 ng/mL	134%
Hydrocodone	1,086 ng/mL	28%
Hydromorphone	1,425 ng/mL	21%
Oxycodone	>75,000 ng/mL	<0.4%
Oxymorphone	>100,000 ng/mL	<0.3%

Limitations of Immunoassays⁶

Drug	Immunoassay	Immunoassay cutoff	LC-MS/MS cutoff	Samples missed
Codeine	Opiates	300 ng/mL	50 ng/mL	~30%
Hydrocodone				~23%
Hydromorphone				~69%
Morphine	Oxycodone	100 ng/mL	50 ng/mL	~12%
Oxycodone				~5%
Oxymorphone				~10%
Alprazolam (alpha-hydroxyalprazolam)	Benzodiazepine	200 ng/mL	20 ng/mL	~53%
Lorazepam				40 ng/mL

High-Resolution Targeted Opioid Screen TOSU / Targeted Opioid Screen, Urine

- Features and Benefits:
 - Uses high-resolution accurate mass spectrometry to identify 33 different opioids and/or metabolites where immunoassays are not adequate
 - Lower detection limits (improved sensitivity)

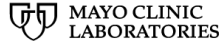
Drugs Detected in the High-Resolution Targeted Opioid Screen

Analyte	Cutoff	Analyte	Cutoff	Analyte	Cutoff
Buprenorphine	5 ng/mL	6-acetylmorphine	25 ng/mL	Naloxone	25 ng/mL
Norbuprenorphine	5 ng/mL	Fentanyl	2 ng/mL	Naloxone-3-β-glucuronide	100 ng/mL
Norbuprenorphine glucuronide	20 ng/mL	Norfentanyl	2 ng/mL	Propoxyphene	25 ng/mL
Codeine	25 ng/mL	Oxycodone	25 ng/mL	Norpropoxyphene	25 ng/mL
Codeine-6-β-glucuronide	100 ng/mL	Noroxycodone	25 ng/mL	Tapentadol	25 ng/mL
Morphine	25 ng/mL	Oxymorphone	25 ng/mL	N-desmethyl-tapentadol	50 ng/mL
Morphine-6-β-glucuronide	100 ng/mL	Noroxymorphone	25 ng/mL	Tapentadol-β-glucuronide	100 ng/mL
Hydrocodone	25 ng/mL	Oxymorphone-3-β-glucuronide	100 ng/mL	Tramadol	25 ng/mL
Norhydrocodone	25 ng/mL	Methadone	25 ng/mL	O-desmethyl-tramadol	25 ng/mL
Dihydrocodeine	25 ng/mL	EDDP	25 ng/mL		
Hydromorphone	25 ng/mL	Meperidine	25 ng/mL		
Hydromorphone-3-β-glucuronide	100 ng/mL	Normeperidine	25 ng/mL		

High-Resolution Targeted Opioid Screen: TOSU / Targeted Opioid Screen, Urine

- Features and Benefits:
 - Uses high-resolution accurate mass spectrometry to identify 33 different opioids and/or metabolites where immunoassays are not adequate.
 - Lower detection limits (improved sensitivity)
 - Improved test utilization without compromising turn-around-times
 - Significantly reduced need for confirmatory testing required with traditional immunoassay screens
 - Ability to detect “spiked” samples
 - Available with enhanced reports with interpretative comments

Example of Enhanced Report



1-800-533-1710

TOSU

Targeted Opioid Screen, Urine

Patient ID SA00122417	Patient Name SAMPLE REPORT, TOSU	Birth Date 1990-08-08	Gender F	Age 29
Order Number SA00122417	Client Order Number SA00122417	Ordering Physician CLIENT,CLIENT	Report Notes	
Account Information C7028846 DLMP Rochester		Collected 22 Aug 2019 08:00		

List prescribed opioids

Hydrocodone

ADDITIONAL INFORMATION

Accuracy and completeness of declared medications on reports solely dependent on information submitted by client.

Opioid Interpretation

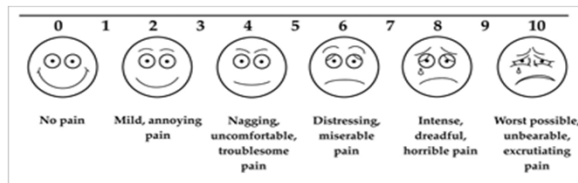
Test detected the presence of hydrocodone and several of its metabolites (hydromorphone, dihydrocodeine, norhydrocodone). Suspect use of hydrocodone within the past three days.

Drug	Result	Cutoff	Drug	Result	Cutoff
Hydrocodone <i>Lorab, Norco, Vicodin; Also a very minor metabolite of codeine and impurity (<1%) of oxycodone.</i>	Present	25 ng/mL	6-monoacetylmorphine <i>Metabolite of heroin</i>	Not Detected	25 ng/mL
Norhydrocodone <i>Metabolite of hydrocodone</i>	Present	25 ng/mL	Hydromorphone-3-beta-glucuronide <i>Metabolite of hydromorphone</i>	Not Detected	100 ng/mL
Dihydrocodeine <i>Metabolite of hydrocodone</i>	Present	25 ng/mL	Oxycodone <i>Endocet, Percocet, Oxycotin</i>	Not Detected	25 ng/mL
Hydromorphone <i>Dilaudid, Exalgo; Also a metabolite of hydrocodone and a minor (<5%) metabolite of morphine.</i>	Present	25 ng/mL	Noroxycodone <i>Metabolite of oxycodone</i>	Not Detected	25 ng/mL
			Oxymorphone <i>Namorphes, Opans; Also a metabolite of oxycodone.</i>	Not Detected	25 ng/mL
			Oxymorphone-3-beta-glucuronide <i>Metabolite of oxymorphone</i>	Not Detected	100 ng/mL
			Noroxymorphone <i>Metabolite of oxymorphone</i>	Not Detected	25 ng/mL
			Fentanyl <i>Actiq, Duragesic, Fentora</i>	Not Detected	2 ng/mL
			Norfentanyl	Not Detected	

Clinical Case Study

Comparison of Traditional Immunoassay Screens with Confirmation Testing vs High-Resolution Targeted Opioid Screen Only

- Case History:
 - 38 year-old-male
- Medical History:
 - Chronic lower back pain
- Medications:
 - Hydrocodone (10-mg bid)
 - Tramadol (50-mg prn)
- Clinical Evaluation:
 - VAS: Originally 6/10, Now 3/10
- Compliance Assessment:
 - Patient admits taking meds as prescribed; last dose was in the AM



Clinical Case Study Continued

Using Conventional Approach with Immunoassays and Reflex to Confirmation Tests

- Goal: Verify adherence to hydrocodone and tramadol using UDT

Screening Test	Urine Cutoff	Result
Amphetamine/ Methamphetamine	500 ng/mL	Negative
Barbiturates	200 ng/mL	Negative
Benzodiazepine	200 ng/mL	Negative
Cocaine Metabolite	300 ng/mL	Negative
Methadone	300 ng/mL	Negative
Opiates	300 ng/mL	Presumptive Positive
Definitive Test	Urine Detection Limit	Result
Codeine	100 ng/mL	<100
Hydrocodone	100 ng/mL	2,153 ng/mL
Hydromorphone	100 ng/mL	1,780 ng/mL
Morphine	100 ng/mL	<100
Oxycodone	100 ng/mL	<100
Oxymorphone	100 ng/mL	<100

Clinical Case Study Continued

Using Conventional Approach with Immunoassays and Reflex to Confirmation Tests

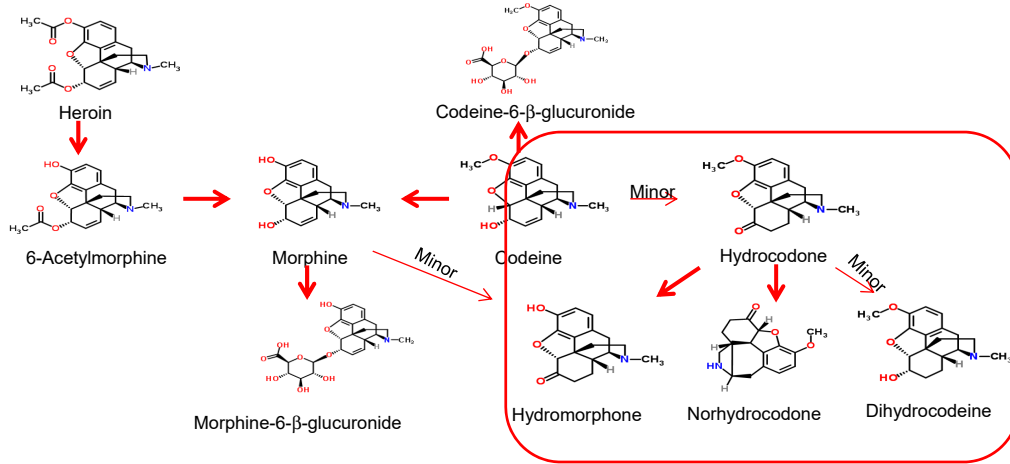
- How do you interpret these results?

Definitive Test	Urine Detection Limit	Result
Codeine	100 ng/mL	<100
Hydrocodone	100 ng/mL	2,153 ng/mL
Hydromorphone	100 ng/mL	1,780 ng/mL
Morphine	100 ng/mL	<100
Oxycodone	100 ng/mL	<100
Oxymorphone	100 ng/mL	<100

- Patient prescribed:
 - Hydrocodone (10-mg bid)
 - Tramadol (50-mg prn)
- Where did the hydromorphone come from?

Where did the Hydromorphone Come From?

Simplified Opioid Metabolism



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Clinical Case Study Continued

Using Conventional Approach with Immunoassays and Reflex to Confirmation Tests

- How do you interpret these results?

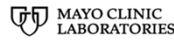
Definitive Test	Urine Detection Limit	Result
Codeine	100 ng/mL	<100
Hydrocodone	100 ng/mL	2,153 ng/mL
Hydromorphone	100 ng/mL	1,780 ng/mL
Morphine	100 ng/mL	<100
Oxycodone	100 ng/mL	<100
Oxymorphone	100 ng/mL	<100

- Interpretation:
 - Patient is taking hydrocodone
- Where is the tramadol?
 - Need to order FFTQU / Tramadol and Metabolite, Urine, Quantitative

Definitive Test	Urine Detection Limit	Result
Tramadol	50 ng/mL	5,675 ng/mL
O-desmethyltramadol	50 ng/mL	3,423 ng/mL

Using High Resolution Targeted Opioid Screen

- Goal: Verify adherence to hydrocodone and tramadol



1-800-533-1710

TOSU

Targeted Opioid Screen, Random, Urine

Patient ID SA00124792	Patient Name VALIDATION, TESTING	Birth Date 1990-08-08	Gender F	Age 29
Order Number SA00124792	Client Order Number SA00124792	Ordering Physician CLIENT,CLIENT	Report Notes	
Account Information C7028846 DLMP Rochester		Collected 24 Dec 2019 08:06		

List prescribed opioids

Hydrocodone, Tramadol

ADDITIONAL INFORMATION

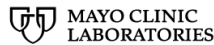
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Opioid Interpretation

Test detected the presence of hydrocodone and several of its metabolites (hydromorphone, dihydrocodeine, norhydrocodone). Suspect use of hydrocodone within the past three days.

Test detected the presence of tramadol and its metabolite (O-desmethyltramadol). Suspect use of tramadol within the past three days.

Drug	Result	Cutoff	Drug	Result	Cutoff
Hydrocodone Lortab, Norco, Vicodin; Also a very minor metabolite of oxycodone and impurity (<1%) of oxycodone.	Present	25 ng/mL	Codeine Tylenol 3	Not Detected	25 ng/mL
Norhydrocodone Metabolite of hydrocodone	Present	25 ng/mL	Codeine-6-beta-glucuronide Metabolite of codeine	Not Detected	100 ng/mL
Dihydrocodeine Metabolite of hydrocodone	Present	25 ng/mL	Morphine Avinza, Kadian, MS Contin; Also a minor metabolite (10% of codeine and can be seen in low concentrations (<2,000 ng/mL) with poppy seed ingestion)	Not Detected	25 ng/mL
Hydromorphone Dilaudid, Exalgo; Also a metabolite of hydrocodone and a minor (<5%) metabolite of morphine.	Present	25 ng/mL	Morphine-6-beta-glucuronide Metabolite of morphine	Not Detected	100 ng/mL
Tramadol Tramal, Ultram, Ultracet	Present	25 ng/mL	6-nonoacetylmorphine Metabolite of heroin	Not Detected	25 ng/mL
O-desmethyltramadol Metabolite of tramadol	Present	25 ng/mL	Hydromorphone-3-beta-glucuronide Metabolite of hydromorphone	Not Detected	100 ng/mL
			Oxycodone Endocet, Percocet, Oxycodone	Not Detected	25 ng/mL
			Noroxycodone Metabolite of oxycodone	Not Detected	25 ng/mL
			Oxymorphone Numorphan, Opans; Also a metabolite of oxycodone.	Not Detected	25 ng/mL
			Oxymorphone-3-beta-glucuronide Metabolite of oxymorphone and/or naloxone (nonnaloxone)	Not Detected	100 ng/mL



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			Oxymorphone-3-beta-glucuronide Metabolite of oxymorphone and/or naloxone (nonnaloxone)	Not Detected	100 ng/mL

Summary

- Objective measures like laboratory tests are needed to:
 - Identify and evaluate recent drug use/abuse
 - Set and monitor clinical goals/expectations
- The new high-resolution targeted opioid assay TOSU / Targeted Opioid Screen, Urine:
 - Identifies 33 different opioids and/or metabolites where immunoassays are not adequate (improved specificity).
 - Has lower detection limits (improved sensitivity)
 - Reduces need for confirmatory testing required with traditional immunoassay screens
 - Improves test utilization
 - Available with enhanced reports and interpretative comments
- UDT results need to be interpreted in the context of the test, drugs prescribed, specimen type, time since last dose, and specimen collection, specimen validity test results, and the patient. Unexpected or unexplained results should be discussed with the patient/laboratory, and additional testing performed if needed.

References

1. Institute of Medicine Report 2011; Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. MMWR 2011;60(43):1487-1492
2. Manchikanti L, Abdi S, Atluri S, et al: American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2-guidance. Pain Physician 2012;15:S67-1164
3. Manchikanti L, Manchukonda R, Damron KS, et al: Does adherence monitoring reduce controlled substance abuse in chronic pain patients? Pain Physician 2006;9(1):57-60
4. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016
5. Stieg RL, Lippe P, Shepard TA: Roadblocks to effective pain treatment. Med Clin North Am 1999;83(3):809-821
6. Mikel C, Almazan P, West R, et al: LC/MS/MS extends the range of drug analysis in pain patients. Ther Drug Monit 2009;31(6):746-748
7. Leider HL, Dhaliwal J, Davis EJ, et al: Healthcare costs and nonadherence among chronic opioid users. Am J Manag Care 2011;17(1):32-40
8. McCarberg BH: Chronic pain: reducing costs through early implementation of adherence testing and recognition of opioid misuse. Postgrad Med 2011;123(6):132-139



Thank you!