

Urine Drug Testing and its Impact on the Opioid Crisis

Clinical Pearls of Drug Testing Case Studies



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Disclosures

Affiliation	Role
AcelRx Pharmaceuticals	Advisory Board
Acutis Diagnostics, Inc	Speaker
Astra Zeneca	Speakers Bureau
BioDelivery Sciences International	Consultant
Daiichi Sankyo	Advisory Board, Speakers Bureau
Firstox Laboratories	Consultant
GlaxoSmithKline (GSK)	Advisory Board
Quest Diagnostics	Advisory Board
Scilex Pharmaceuticals	Advisory Board
Salix Pharmaceuticals	Advisory Board

Learning Objectives

- Differentiate between In-Office Qualitative Testing & Laboratory Quantitative Testing
- Explain how to interpret unexpected UDT results
- Explain how to incorporate UDT results into ongoing clinical assessment and decision making
- Describe how to communicate with patients about unexpected results in a positive, therapeutic manner

PRETEST POLL: At a morphine equivalent daily dose of 20mg, which of the following will test positive by immunoassay drug screen?

- A. Methadone
- B. Codeine
- C. Fentanyl
- D. None of the above

PRETEST POLL : Which of the following can cause a false positive methadone by IA urine testing?

- A. Quetiapine
- B. Diphenhydramine
- C. Chlorpromazine
- D. All of the above

The Whizzinator Kit



<http://www.thewhizzinator.com/lifestyle-products/lilwhizz>

Urine Drug Testing (UDT) Rationale

- Guidelines recommend UDT as standard of care when prescribing chronic opioid therapy, especially for CNCP
- Helps to ensure compliance and mitigate risk
 - Detects presence of illicit substances
 - Detects absence of prescribed medication
- Helps to justify continual prescriptions
- Supports clinician decision to discontinue controlled substance medication

1. Argoff CE, Alford DP, Fudin J, et al. Rational Urine Drug Monitoring in Patients Receiving Opioids for Chronic Pain: Consensus Recommendations. *Pain Medicine*. 2017;19(1):97-117.
2. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The Journal of Pain*. 2009 Feb 1;10(2):113-30.
3. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *Jama*. 2016 Apr 19;315(15):1624-45.
4. Raouf M, Bettinger JJ, Fudin J. A Practical Guide to Urine Drug Monitoring. *Federal Practitioner*. 2018 Apr;35(4):38.

Urine Drug Testing (UDT) Rationale

- Supports justification for closer monitoring (more frequent visits / lab monitoring)
- Supports behavior modification and referral to psychologist

Potential Pitfalls

- Patient reliability to report compliance, use and misuse is dubious and often poor
- Behavior alone is unreliable for identifying patients at risk non-compliance, abuse, misuse, and diversion

Urine Drug Monitoring Guidelines

- Federal Agencies
 - CDC¹, HHS², SAMHSA³
- Consensus Guidelines
 - APS/AAPM⁴, AAPM Consensus 2018⁵, AACC⁶, ASAM⁷, others

1. CDC Guideline for Prescribing Opioids for Chronic Pain: <https://www.cdc.gov/drugoverdose/prescribing/guideline.html>
2. HHS: Pain Management Best Practices Inter-agency Task Force Report: <https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf>
3. Federal Guidelines for Opioid Treatment Programs: <https://store.samhsa.gov/system/files/pep15-fedguideotp.pdf>
4. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, **Fudin J**, Gilson AM. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The Journal of Pain*. 2009 Feb 1;10(2):113-30.
5. Argoff CE, Alford DP, **Fudin J**, Adler JA, Bair MJ, Dart RC, Gandolfi R, McCarberg BH, Stanos SP, Gudim JA, Polomano RC. Rational urine drug monitoring in patients receiving opioids for chronic pain: consensus recommendations. *Pain Medicine*. 2017 Dec 1;19(1):97-117.
6. AACC: <https://www.aacc.org/media/press-release-archive/2018/01-jan/aacc-releases-practice-guidelines-for-using-laboratory-tests-to-combat-opioid-overdoses>
7. ASAM: <https://www.asam.org/resources/publications/magazine/read/article/2017/07/11/asam-releases-consensus-document-outlining-appropriate-use-of-drug-testing>

Implementing Guidelines if Hospitals, ED's, and Clinics

- Why should hospitals test prior to surgery?
- Elective vs. nonelective
- Why should hospitals have ED policies for testing?
- Why should clinics routinely screen patients receiving controlled substances?
 - Opioids, amphetamines/methylphenidate, anabolic steroids, etc.

For purposes of this presentation, Clinical Chemistry (CC) Testing will be synonymous with Immunoassay (IA) Testing, as both terms are commonly used.

MOST COMMON TOXICOLOGY SCREENS

Types of Urine Drug Testing

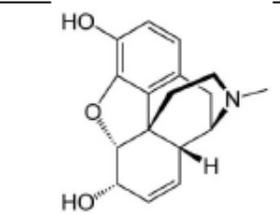
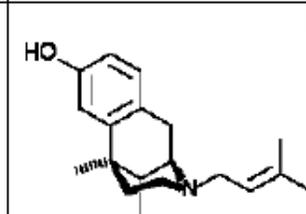
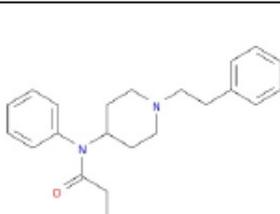
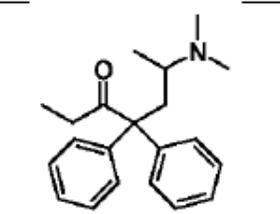
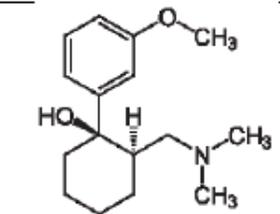
Immunoassay

- In office or send out
- Inexpensive
- Results are quick (minutes)
- Helps for initial detection
- Presumptive Testing
 - False negatives/positives
 - ✓ KNOW YOUR PATIENT!
- Easier for pts to manipulate
low sensitivity, esp w/ synthetics
- Presence/absence of RX class
only, no metabolites
- No option for synthetics, designer
drugs, and unique natural
products

Chromatography

- Usually send-out
- More expensive
- 24 hours to 1 week (per lab)
- Final result
- Definitive testing
- Justifies RX decisions
- 99.999 percent reliability
high sensitivity
- Presence/absence of RX
metabolites
- Custom option for synthetics,
designer drugs, and unique
natural products

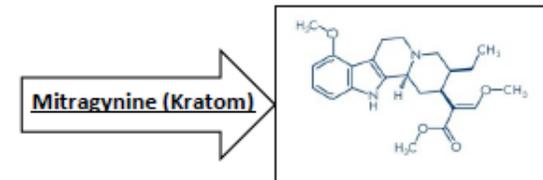
Opioid Chemistry and Cross-sensitivity

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	PENTAZOCINE Pentazocine	FENTANYL Alfentanil Fentanyl Remifentanyl Sufentanil Meperidine Diphenoxylate ^a Loperamide ^a Illicit Fentanyl Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil Others ^b	METHADONE Methadone Propoxyphene	TRAMADOL Tapentadol Tramadol
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK
*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group				
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation				

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<http://paindr.com/resources/quick-references/> (See "Opioid Chemistry")

- Previously incorrectly listed as "Benzomorphans"
- Bettinger JJ, Trotta ND, Fudin J, Wegrzyn EL, Schatman ME. Understanding the differences between pharmaceutical and illicit fentanyl and their analogues could save the opioid crisis. *Practical Pain Management*. 2018. July/August 18(5):59-67.



Opioid and Benzodiazepine Metabolites plus Validity Testing

Lab Value Resources

Table 5. SAMHSA Criteria for Validity Testing of a Urine Specimen^{3,64}

Urine specimen is reported as:	When:
Dilute	Creatinine concentration ≥ 2 mg/dL, but < 20 mg/dL, & specific gravity* > 1.001 , but < 1.003
Substituted	Creatinine concentration < 2 mg/dL & specific gravity* ≤ 1.001 or > 1.020
Adulterated	pH [†] < 3 or ≥ 11 , nitrite concentration ≥ 500 $\mu\text{g/mL}$; chromium (VI) concentration ≥ 50 $\mu\text{g/mL}$; presence of a halogen (eg, from bleach, iodine, fluoride), glutaraldehyde, pyridine, surfactant [‡]

*Using refractometry; [†]using a pH meter

1. Hammett-Stabler CA, Webster LR. A Clinical Guide to Urine Drug Testing. An educational activity designed for primary care physicians, family physicians, and pain physicians.
2. Clinical Drug Testing in Primary Care, Technical Assistance Publication Series TAP 32. SAMHSA

Opioid and Benzodiazepine Metabolites

- Alprazolam ★
 - alpha-hydroxyalprazolam
 - oxalprozolam
- Chlordiazepoxide
 - nordiazepam
 - oxazepam
- Chorazepate
 - nordiazepam
 - oxazepam
- Clonazepam ★
 - 7-aminoclonazepam
- Diazepam
 - nordiazepam
 - oxazepam
 - temazepam
 - hydroxynordiazepam
- Diazepam
 - nordiazepam
 - oxazepam
 - temazepam
 - hydroxynordiazepam
- Flunitrazepam ★
 - 7-amino-flunitrazepam
- Lorazepam ★
 - Lorazepam-glucuronide
- Temazepam
 - Ldesmethyltemazepam
 - oxazepam

Opioids and Benzodiazepine Metabolites

(continued from previous slide)

Buprenorphine

- Norbuprenorphine

Codeine

- Morphine
- Norcodeine
- Normorphine
- Hydrocodone
- Codeine 6-glucuronide

Fentanyl (Transdermal, Transbuccal, Transmucosal, Sublingual)

- Norfentanyl
- 4-N-(N-propionylanilino) piperidine
- 4-N-(Nhydroxypropionylanilino) piperidine
- 1-(2-phenethyl)-4-N-(Nhydroxypropionylanilino) piperidine

Hydrocodone

- Hydromorphone
- Norcodeine
- 6-beta-hydrocodol
- 6-alpha-hydrocodol
- 6-beta-hydromorphol
- 6-alpha-hydromorphol
- norhydrocodone

Heroin

- 6-acetylmorphine
- Morphine
- Morphine-3-glucuronide
- Normorphine
- 6-acetylmorphine 3-glucuronide
- Normorphine glucuronide

Hydromorphone

- Hydromorphone-3-glucuronide
- Hydromorphone-3-glucoside
- Dihydroisomorphine-6-glucuronide
- Dihydroisomorphine-6-glucoside
- Dihydroisomorphine
- Dihydromorphine

Levorphanol

- 3-glucuronide

Meperidine

- Normeperidine
- meperidinic acid
- normeperidinic acid

Methadone

- EDDP (2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium)
- EMDP (2-ethyl-5-methyl-3,3-diphenylpyraline)

Morphine

- Morphine-3-glucuronide
- Morphine-6-glucuronide
- Normorphine
- 7,8-dihydromorphinone
- codeine (minor)
- hydromorphone (minor)

Morphine/Naltrexone (Embeda)

- Morphine-3-glucuronide
- Morphine-6-glucuronide
- Normorphine
- 7,8-dihydromorphinone
- codeine (minor)
- 6-beta-naltrexol
- hydromorphone (minor)

Oxycodone

- Noroxycodone
- Oxymorphone
- Oxycodyl
- Oxymorphol
- Noroxycodyl

Oxymorphone

- Oxymorphone-3-glucuronide
- 6-OH-oxymorphone

Tapentadol

- Tapentadol-O-glucuronide

Addressing Unexpected Results

- False or Unexpected Positive
 - Discuss findings with patient
 - Confirm false positive (as a true negative) to support and document patient's integrity and compliance
 - Confirm unexpected positive to justify
 - ADT products, and or other RX adjustments (partial agonist, partial agonist/antagonist, etc.)
 - substance abuse counseling
 - Alternative and other behavior health intervention
- False Negative
 - Confirm false negative (as a true positive) to support and document patient's integrity and compliance

Select Opioid Analgesic Choices

- **Extended Release Products:**
 - Buprenorphine Transdermal Patch
 - Buprenorphine Buccal Film
 - Fentanyl Transdermal Patch
 - Hydrocodone ER
 - Hydromorphone-ER
 - Morphine-ER (several products available)
 - Oxycodone-ER
 - Oxymorphone-ER
- **Synthetic Atypical:**
 - Long Biological $T_{1/2}$ & intermediate analgesic $T_{1/2}$
 - Levorphanol
 - Methadone

Case Study 1 | Face Pain

- 43 year old Caucasian male
- TMJ and trigeminal neuralgia
- Failed NSAIDs, cartilage implants, nerve blocks, iontophoresis
- Past Medical History (PMH):
+ Hep C, but otherwise inconsequential
- Current pharmacologic regimen includes:
 - Gabapentin 1200mg PO TID
 - Hydrocodone ER 20mg PO QAM
 - Oxycodone tabs 5mg, 1 PO TID PRN

Case Study 1 | Face Pain

What do these results mean?

In-Office Results	
Test	Result
Opiate	Negative

Gabapentin 1200mg PO TID
Hydrocodone ER 20mg PO QAM
Oxycodone tabs 5mg, 1 PO TID PRN

Chromatography [send out] Results	
Test	Result
Oxycodone	Negative
Hydrocodone	Negative
Gabapentin	Positive

Case Study 1 | Unexpected Results

Negative for Prescribed Medications

- Lack of oxycodone PRN use
- pharmacokinetics (when was urine collected?)
- Noncompliance
- Test is not specific for the drug tested (opiate vs. synthetic)
- Drug-drug, drug-disease, drug-food/supplement interactions
- Genetic polymorphism

Case Study 1 | Face Pain

- Speak with patient
- Give patient an opportunity to explain
- Assessment: Document justification for plan
 - Low dose hydrocodone should be negative on IA test as indicated
 - Had IA opiate screen been positive, it may have indicated use of an opiate other than what was prescribed
- Devise actionable medical plan based on lab findings
 - Change in drug therapy (Patch, ADF, no opioid)
 - Justification for f/u lab testing or not ordering chromatography
 - Justification for alternative therapies / behavioral health

Case Study 2 | Chronic Back Pain

- 50 year old Caucasian female
- History of chronic low back pain with justifiable pathology
- Back surgery x 3 (failed back)
- PMH: chronic pain, depression, hypothyroidism
- Current pharmacologic regimen includes:
 - Duloxetine 60mg PO QAM
 - Fentanyl 50mcg/hr changed Q72 hours
 - Hydrocodone + APAP 5/325, 1 PO Q4H PRN

Case Study 2 | Chronic Back Pain

What do these results mean?

IA In-Office Results	
Test	Result
Opiate	Negative
Benzodiazepines	Positive
Benzoyllecgonine (cocaine metabolite)	Positive

Duloxetine 60mg PO QAM
Fentanyl 50mcg/hr changed Q72 hours
Hydrocodone + APAP 5/325, 1 PO Q4H PRN

Chromatography [send out] Results	
Test	Result
Fentanyl	Positive
Hydrocodone	Negative
Diazepam / oxazepam	Positive
Benzoyllecgonine	Positive

Case Study 2 | Is definitive testing needed?

Negative for Prescribed Medications

Positive for RX's not prescribed and illicit

- Lack of hydrocodone PRN use
- Pharmacokinetics (when was urine collected?)
- Noncompliance (illegally obtained drugs?)
- Opiate test should be negative if PRN hydrocodone not used
 - Opiate vs. synthetic, in this case fentanyl
- Drug-drug, drug-disease, drug-food/supplement interactions
- Genetic polymorphism

Case Study 3 | Lower Chest & Abdominal Pain

Negative for Prescribed Medications

False Positive for non-prescribed and Illicits

- 33 year old American Indian male
- Lung cancer, now free of disease
- Chronic upper abdominal & chest pain following his original tumor resection and radiation
- PMH: depression
- Current pharmacologic regimen includes:
 - Morphine 90mg PO QAM
 - Venlafaxine ER 225mg PO QAM

Case Study 3 | Is definitive testing needed?

What do these results mean?

In-Office Test Results	
Test	Result
Opiate	Positive
Phencyclidine (PCP)	Positive

Morphine 90mg PO QAM
Venlafaxine ER 225mg PO QAM

LC-MS/MS Laboratory Test Results	
Test	Result
Morphine	Positive
Hydromorphone	Positive
Phencyclidine (PCP)	Negative
Venlafaxine	Positive

Knowledge of P-Kinetics is Essential

- Morphine Metabolism
 - Phase II Glucuronidation by UGT2B7
 - M3G (morphine-3-glucuronide)
 - M6G (morphine-6-glucuronide)
 - Less than 5% → hydromorphone
- Positive PCP explainable by test results

Case Study 3 | Is definitive testing needed?

- Patient was compliant with
 - Morphine
 - Venlafaxine
- PCP was false positive because of venlafaxine
- Hydromorphone confirmation unexpected?
 - It is a rare metabolite of morphine
- Educate patient and clearly document in the chart

Case Study 4 | Icing on the Cake

Drugs:

- Butrans 15mg TD Patch, changed Qweek
- Quetiapine 50mg PO QHS
- Alprazolam 0.5mg PO TID
- Ibuprofen 600mg PO TID PRN

Case Study 4 | Unexpected Results

What do these results mean?

In-Office Test Results	
Test	Result
Opiate	Negative
Buprenorphine	Negative
Benzodiazepine	Negative
Cannabinoid	Positive
Methadone	Positive

Butrans 15mg TD Patch, changed Q week
Quetiapine 50mg PO QHS
Alprazolam 0.5mg PO TID
Ibuprofen 600mg PO TID PRN

LC-MS/MS Laboratory Test Results	
Test	Result
Buprenorphine, norbuprenorphine, buprenorphine-glucuronide, and norbuprenorphine-glucuronide	Positive
Alpha-hydroxyalprazolam	Positive
Cannabinoid	Negative
Methadone	Negative

Case Study 4 | Is definitive testing needed?

- Buprenorphine is a POTENT synthetic opioid and will not test positive for IA opiate screen at most buprenorphine TD doses
- Positive “opiate” screen would indicate that the patient was using another unprescribed drug
- Alprazolam generally will not test positive on an IA test
- Alprazolam and buprenorphine were confirmed by definitive test results
- Quetiapine may cause false positive methadone
- Ibuprofen may cause false positive cannabinoid

Patient's RX's include...

- Hydrocodone 20mg per day
- Alprazolam 2mg per day
- Venlafaxine 250mg per day
- Naproxen 1000mg per day

Latest Street Trends and Designer Drugs

- Synthetic Cathinones (Bath Salts)
- Synthetic Cannabinoids (K2/Spice)
- Fentanyl and other Synthetic Opioids
- Mitragynine (Kratom)
- Cannabidiol (CBD)

POST TEST POLL: At a morphine equivalent daily dose of 20mg, which of the following will test positive by immunoassay drug screen?

- A. Methadone
- B. Codeine
- C. Fentanyl
- D. None of the above

POST TEST POLL: Which of the following can cause a false positive methadone by IA urine testing?

- A. Quetiapine
- B. Diphenhydramine
- C. Chlorpromazine
- D. All of the above

Conclusions

- Urine Drug Monitoring (UDM) by immunoassay(IA) is the recognized standard of care for routine monitoring
- Every consensus guideline and federal agency that addresses safe opioid prescribing recommends routine UDM
- IA UDM is a cost-effective, efficient, and quick point-of-care test
- Clinicians must know how to interpret urine tests and should not falsely accuse patients of wrongdoing
- UDM could help detect early warning signs so that patients are referred for appropriate counseling