Lab Testing in Assessment of Substance Use Disorders

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Kevin A. Sevarino, MD, PhD, has no financial relationships with an ACCME defined commercial interest relevant to the content of this presentation.

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.
Target Audience

• The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.
Educational Objectives

At the conclusion of this session, participants should be able to:

- Discuss clinical issues in performing urine drug testing (UDT).
- Describe the basic types of UDT and when they should be used.
- Define the metabolism of opioids and benzodiazepines in order to interpret UDT results.
- Describe other laboratory testing used as part of substance use disorder evaluations.
Outline

• Purpose and Use of UDT
• Types of UDT
• Interpretation of UDT
• Forensic Issues in UDT
• Other Lab Testing
In the following we will meet Bill, a patient you maintain on buprenorphine/naloxone. He provides a urine drug screen positive for opiates and buprenorphine. We’ll discuss how to interpret this result, as well as other aspects of the case moving forward.
Urine Drug Testing: 
*Purpose and Use*
Key Resource


An excellent summary of the topic.
Goals of Urine Drug Testing

- **Clinical: Improve Patient Care and Safety**
  - Facilitate doctor-patient communication
  - Provide objective information
  - Confirm use of prescribed medication: Adherence testing
  - Confirm lack of use of non-prescribed medications or illicit drugs

- **Legal:**
  - As a condition of parole/probation
  - Custody/parental issues
  - Workplace testing
Choice of Matrix

Urine by far most widely used:

- Typical window of detection hours to days (except cannabinoids)

- Advantages: ease of collection, cost, mature technology, point of care (POC) testing

- Disadvantages: most prone to tampering (substitution, dilution, \textit{in vivo} and \textit{ex vivo} adulteration), GC/MS confirmation more expensive

- Observed vs. unobserved

- Normalization to creatinine, temp., sp. gravity, pH, IgG, special testing for adulterants
Choice of Matrix

- **Breath**: window of detection – minutes to hours
  - Most widely used POC test for EtOH; now use is expanding; cons: contaminant and volume effects.

- **Blood**: window of detection – minutes to hours
  - Invasive, costly, usually restricted to EDs or forensics
Choice of Matrix

- Oral Fluid: window of detection - minutes to days. Unobtrusive and easily observed, but poor sensitivity due to higher cutoffs than for urine, especially marijuana, prone to contamination.

- Sweat: window of detection - hours to weeks. Resistant to cheating, prospective; patch may fall off.

- Hair/Nails: window of detection - weeks to months. Directly observed but poor for marijuana; hair bias based on color, treatments etc.
Practical Issues

- Sending specimens to offsite or onsite labs versus qualitative test in office
- Random versus scheduled collection (new ASAM guidelines heavily favor random)
- Observed versus non-observed
- Maintaining a Chain of Custody
How to Discuss UDT

• New patient initiating on treatment: (as part of treatment agreement discussion)
  ▪ “This is our routine practice as a patient safety issue.”
  ▪ “We need this to be able to follow whether treatment is working”
  ▪ “This is consistent with standards of care”

• Patient who has been in treatment for a while:
  ▪ “Why now?” → “New clinic policy, guidelines are clear this should be done to determine whether treatment is working and help us adjust our care appropriately.”

How to Discuss UDT (cont.)

• Patient says: “But I’m not a drug addict”:  
  “Routine testing…not singling anyone out.; this is consistent with standard of care. We need to be able to determine that our treatment is working.”

• Patient says: “I refuse”:  
  “We can’t prescribe certain meds if we’re unable to do the routine safety monitoring discussed in the treatment agreement. Also, we are not here to judge, but need to treat addiction as a disease, and test accordingly.”

Validity of Collected Urine Specimens

- Temperature between 90 and 100 degrees Fahrenheit
- pH between 4.5 and 8.0
- Creatinine greater than 20 mg/dL
- Color/Shake Test
Levels of UDT

**First:**
- Screening:
  - Enzyme-Mediated Immunoassay (EIA)
  - Field Dip Stick

**If any unexpected findings, then:**
- Confirmatory:
  - Gas Chromatography/ Mass Spectrometry
Requirements for In-Office UDT

- Must obtain a CLIA* Certificate of Waiver thru the US Dept. of Health and Human Services website (Form SMS-166).

- Use products that are CLIA waived (demonstrated by the manufacturer to be accurate and low risk when used by untrained personnel, approved for home use).

- CMS will allow billing for a single test per patient encounter, NOT number of tests, thus usual code is G0477 x 1 unit.

* = Clinical Laboratory Improvement Amendments
https://www.aapc.com/blog/33209-cms-drug-testing-codes-for-2016/
Revised* CFR 42 Part 2

Remember UDT results have special protection!

1. Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970, the Drug Abuse Prevention, Treatment, and Rehabilitation Act of 1972, Revision 1/13/17.

2. Provides special protections for release of alcohol and drug abuse treatment records.

3. Revision meant to improve dissemination of data for research while better protecting privacy.

*https://www.samhsa.gov/newsroom/press-announcements/201701131200
Summary

• The most widely used matrix is urine
• Decisions include whether to use POC testing, and whether to make collection observed or random; legal validity requires Chain of Custody.
• Remember UDT results are protected by CFR42, Part 2
• Discuss UDT with patient as a “universal precaution”
• UDT has screening and confirmation steps
Urine Drug Testing: Types and Interpretation
Immunoassay UDT

- CODI (cloned-enzyme donor immunoassay)
- EMIT (enzyme-multiplied immunoassay technique)
- FPIA (fluorescence-polarized immunoassay)
- Immuno-turbidity assay
- RIA (radioimmunoassay)
- "Widely available cost-effective and well understood, but prone to cross reactions and false positives"
Common False Positives for EIAs

Amphetamines: bupropion, DMI, pseudoephedrine, ranitidine, trazodone
Benzodiazepines: sertraline
Cannabinoids: efavirenz, NSAIDs, PPIs
Cocaine: -
EtG isopropyl alcohol, *mouthwash, Nyquil
Opioids: dextromethorphan, diphenhydramine, rifampin, poppy seeds, quinine
PCP: dextromethorphan, diphenhydramine, tramadol, venlafaxine, IMI, ketamine

* Some mouthwashes are alcohol-free
Package inserts for POCT also list common cross-reactants
Urine Testing for Ethanol Exposure

- Cutoff of 100 ng/ml ethylglucuronide (EtG) fairly specific for true EtOH exposure
- Ethyl sulfate (EtS) very specific for alcohol exposure
- Positive can come from external exposure: hand sanitizer, mouthwash, hair products, cooking wine
- Window is 3 – 5 days post use; breathalyzer often <6 hours; in blood phosphatidylethanol (PEth) has window of 2-3 weeks.
- Very sensitive – not very quantitative – result very dependent on how much and when EtOH was consumed

When the result of a drug test is: 1) contested, 2) guiding clinical decision-making or 3) done for forensic purposes, the immunoassay must be confirmed with GC/MS or LC/MS.
### Substance Immunoassay vs GC/MS

<table>
<thead>
<tr>
<th>Substance</th>
<th>Immunoassay</th>
<th>GC/MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆9THC</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>Benzoylecgonine</td>
<td>300</td>
<td>150</td>
</tr>
<tr>
<td>Opiates</td>
<td>2000*</td>
<td>2000*</td>
</tr>
<tr>
<td>PCP</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>1000</td>
<td>500</td>
</tr>
</tbody>
</table>

Units = ng/ml

Defined for workplace testing, may be too high for clinical work; “no threshold” testing.

*Most labs have modified these cutoffs to 300/50 ng/ml*
Opioids

- Natural opioids (the opiates) include codeine and morphine that are well detected by standard opioid screens.
- Hydrocodone and hydromorphone (semi-synthetic opiates) are less well detected. These special tests now included in Mandatory Guidelines for Fed. Workplace Drug Testing (UrMG).
- Oxycodone (semisynthetic opioid) and its metabolite oxymorphone not well detected. Special tests are now included in UrMG.
- At high levels semi-synthetic opioids like oxycodone are detected in standard opiate screens.
- Methadone, buprenorphine, fentanyl, meperidine (synthetic opioids) not detected and require separate tests.
Opioid Metabolism

poppy seeds* → codeine → morphine ← 6-monoacetylmorphine

hydrocodone → hydromorphone

dihydrocodeine/norhydrocodone

oxycodone → oxymorphone

noroxycodone → noroxymorphone

*Not common
Sample Two-Stage EIA then GC/MS (Rx is oxycodone CR 20 mg TID)

EMIA:
- Amph (-)
- BZD (-)
- Barb (-)
- Cannab (-)
- Cocaine (-)
- Methadone (-)
- Opiate (+)
- Oxycodone (+)
- PCP (-)

Opiate GC/MS:
- Codeine (-)
- Morphine (-)
- Hydrocodone (-)
- Hydromorphone (-)
- Oxycodone 1000 ng/ml
- Oxymorphone 730 ng/ml
- 6-acetylmorphine (-)
- Meperidine (-)
Benzodiazepines

- Clonazepam and lorazepam often not well detected.

- Modification of test cutoffs cause variability between labs.

- Confirmatory testing often needed to identify specific metabolites for positive screening, or confirm absence of metabolites in negative screenings.
Benzodiazepine Metabolism

chlordiazepoxide → chlorazepate

chlordiazepoxide → nordiazepam → oxazepam

diazepam → temazepam

clonazepam → 7-aminoclonazepam*

alprazolam → α-hydroxyalprazolam

lorazepam* → lorazepam-glucuronide

* Poorly detected by immunoassays
# Typical Detection Times

<table>
<thead>
<tr>
<th>Substance</th>
<th>Typical Days Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ9THC</td>
<td></td>
</tr>
<tr>
<td>1 cigarette</td>
<td>&lt;6</td>
</tr>
<tr>
<td>chronic</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Benzoylecgtonine</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Opiates</td>
<td>6h – 3d (14d+ high-dose, LA)</td>
</tr>
<tr>
<td>PCP</td>
<td>8 (30 for chronic)</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>
# Common Opioids and Benzodiazepines

<table>
<thead>
<tr>
<th>Substance</th>
<th>Days Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxycodone</td>
<td>1 – 3d</td>
</tr>
<tr>
<td>methadone</td>
<td>2 – 11d</td>
</tr>
<tr>
<td>buprenorphine</td>
<td>1 – 7d</td>
</tr>
<tr>
<td>diazepam*</td>
<td>1 – 21d</td>
</tr>
<tr>
<td>lorazepam*</td>
<td>1 – 3d</td>
</tr>
<tr>
<td>alprazolam*</td>
<td>1 – 2d</td>
</tr>
</tbody>
</table>

* sig. variability in acute vs. chronic use

See ASAM 2017
Summary

• UDT begins with immunoassay-based screening, followed by GC/MS confirmation, if needed.
• False positive EIAs most common for amphetamines, least common for cocaine.
• EtG/EtS testing for ethanol use coming into wider use.
• Understand the catabolism of opioids and benzodiazepines to interpret GC/MS results.
Urine Drug Testing: *Forensic Issues*
The Federal Government Regulates UDT for:

1. Federal Employees

2. Public/Private Sector workers in transportation and pipeline industries

3. All other drug testing regulated by the states, about 1/2 have drug testing statutes.
Requirements for Forensic Specimen Collection

• Appropriate collection site, with proper space, equipment and security
• Trained collection personnel
• Inspect sample immediately after collection
• Specimen in view of testee and collector at all times until labeled, and the testee should confirm the label
• Immediately record temperature/pH (no longer than 4 min)
• Logbook completed, signed by collector; testee signs certification statement
Requirements for Specimen Collection (cont.)

- Collector completes a CCF (chain-of-custody-form)
- Securely store
- Use colored toilet water
- Any handling or transfer of the sample must be noted on the CCF
- Seal the container with tape, sign, and package for approved transportation to certified lab; attach to CCF
2001 Regulations:

• Licensed physician
• Clinical experience in substance use disorders
• Training course every 3 years
• Certified by MRO Coordinating Council or American Association of MROs
If a negative:

a. Is specimen within expected parameters (e.g., temperature and creatinine)

b. Custody and Control Form examination
If a positive:

a. Confirmed by GC/MS or LC/MS

b. Cutoffs meant to eliminate results from passive exposure

c. “Invalid” reported as “test cancelled” (immediate reorder)

d. Adulterated or substituted samples reported as “refusal to test”

e. If prescribed, reported as “negative”
Summary

• The Federal Gov’t regulates UDT for certain classes of employees.

• Chain of Custody requirements must be understood and followed.

• The Medical Review Officer (MRO) provides interpretation of results to protect the testee.
Urine Drug Testing: 
*Other Lab Testing*
Lab Testing in Treatments of SUDs

- For Diagnosis
- For Treatment Monitoring
- For Detection of Physical Sequelae
- For Detection of Co-Morbidity
Lab Testing in SUD Treatment

- To complement the H & P for Chronic Alcohol Use:
  - In CBC look for macrocytosis (MCV) +/- anemia, low platelets (not sensitive).
  - Biomarkers include carbohydrate-deficit transferase (CDT), GGT, LFTs (SGOT2X>SGPT).
  - Check B12 and folate, Mg, phosphorus, PT/PTT; stool guaiac
  - Elevated bilirubins with normal SGOT/SGPT seen in cirrhosis; amylase in pancreatitis
Lab Testing in SUD Treatment

- For people who inject drugs:
  - Elevated WBC, Hep B/C/HIV, uncommon infections

- For SUDS in general:
  - Indices of malnutrition, STDs indicative of risk behavior, Hep B/C/HIV/TB
Your patient Bill, maintained on buprenorphine/naloxone, provides a urine drug screen positive for opiates and buprenorphine.

*Is this expected for someone on buprenorphine/naloxone?*
Case Vignette – Question #1

What is the correct answer?

A. Yes, because buprenorphine is a semi-synthetic opioid.
B. No, the UDS should be positive for buprenorphine only.
C. Yes, because naloxone is an opioid derivative.
D. Yes, because buprenorphine will metabolize to opioids.
E. No, buprenorphine should have metabolized completely to opioids.
Case Vignette – Answer #1

And the Answer Is?

A. Yes, because buprenorphine is a semi-synthetic opioid.
B. No, the UDS should be positive for buprenorphine only.
C. Yes, because naloxone is an opioid derivative.
D. Yes, because buprenorphine will metabolize to opioids.
E. No, buprenorphine should have metabolized completely to opioids.
Opioid/Naloxone Metabolism

poppy seeds* → codeine → morphine → 6-monoacetylmorphine → 6-monoacetylmorphine

hydrocodone → hydromorphone → dihydrocodeine/norhydrocodone

buprenorphine → norbuprenorphine

naloxone → naloxone-3-glucuronide

*Not common
Case Vignette – Question #2

What would you do next?

A. Ask the patient what has happened.
B. Discharge the patient.
C. Raise you patient’s bup/nal dose.
D. Begin to taper your patient’s bup/nal dose.
E. Repeat the lab test.
Case Vignette – Answer #2

And the answer is?

A. Ask the patient what has happened.
B. Discharge the patient.
C. Raise your patient’s bup/nal dose.
D. Begin to taper your patient’s bup/nal dose.
E. Repeat the lab test.

*Often patient report tells the story making further testing unnecessary, and guide the next steps.*
• The result supports heroin or codeine use (poppy seeds unlikely). Poppy seeds can be contaminated with opium milk during harvesting; for a few hrs after eating a baked product, you can test positive!

• You obtain more history to help with insight and motivation, assess cravings etc.; as well you check your state’s prescription monitoring program.

• You may need to consider raising the dose of buprenorphine/naloxone if not at your clinic’s max dose, and if adherence, triggers etc. do not explain the lapse.


PCSS-MAT Mentor Program

- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.

- PCSS-MAT mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medication-assisted treatment.

- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

- No cost.

For more information visit: pcssmat.org/mentoring
Have a clinical question?

Ask a Colleague
A simple and direct way to receive an answer related to medication-assisted treatment. Designed to provide a prompt response to simple practice-related questions.

Ask Now
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For more information: www.pcssmat.org

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Funding for this initiative was made possible (in part) by grant nos. 5U79TI026556-02 and 3U79TI026556-02S1 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.