Urine toxicology testing to support pain management and treatment for substance use disorder

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Learning Objectives and Presentation Outline

• Describe the general analytical workflow of urine drug testing
• Understand the testing approaches for medication compliance in pain management and treatment for substance use disorder (SUD) settings
• Recognize the utilities and limitations of qualitative and quantitative test results
• Discuss case-based unexpected urine drug testing results and considerations for results interpretation
Urine toxicology testing to support controlled substance prescription and monitoring

• Pain management and SUD treatment
  • Long-term prescription of controlled substances
  • Various opiates: hydrocodone, oxycodone, etc. at various doses
  • Buprenorphine, with naloxone (Suboxone)
  • Co-medication with benzodiazepines, heroin, and other opiates can increase risk for over-dose

• Urine toxicology testing is recommended:
  • Baseline testing prior to prescription
  • Annual monitoring (minimal), interval up to clinician discretion
  • Detect undisclosed medication use
  • Confirm expected medication use

Urine toxicology testing is used to confirm the presence of prescribed medications

- Drug presence prevalence:
  - High positivity rate
  - Patients are mostly taking medications

- Appropriate positive cutoffs are needed for effective detection
  - Sensitivity requirement is high
  - Metabolites of parent drugs are often used to confirm compliance

- Assays should be able to differentiate and identify specific medication (specificity):
  - Hydrocodone (Norco) vs. oxycodone (Oxycotin)
  - Amphetamine vs. Methamphetamine
Urine toxicology test is used to detect non-disclosed substance use

• Critical to examine undisclosed exposure to other co-medications
  • Co-medication can increase overdose risk
    • Benzodiazepines and opiates
    • Multiple classes of opiates drugs
    • Alcohol use and opiates medication
  • Appropriate positive cutoffs are required for efficient detection and to minimize false positive

• Use of certain illicit substances use predict treatment failure for SUD
  • Heroin, cocaine, methamphetamine

Blum K et al. Subst Use Misuse, 2018
Traditional urine drug of abuse testing: Screening assay reflexed to confirmation testing

- Immunoassays screens to detect different classes of drugs
  - Urine Opiates, Benzodiazepines, etc.
  - Assays normally adopt a high cutoff to optimize specificity
  - Immunoassays are traditionally designed for low prevalence, low positivity setting (work place drug testing)

- Confirmation assay is performed following a specific class produces a positive results
  - Urine opiates immunoassay screen: positive (detected)
  - Urine opiates confirmation assay is performed accordingly
  - Confirmation assay detects urine morphine at 4345 ng/mL
Common questions based on traditional reflex testing mechanism

- Low sensitivity (false negative)
  - Common question: My patient is taking lorazepam, why the urine benzodiazepine immunoassay is negative?

- Poor specificity (false positive)
  - Common question: My patient has a positive result for urine amphetamine/methamphetamine immunoassay, but he/she denies use. Is this a false positive?
Common questions based on traditional reflex testing mechanism

• Low sensitivity (false negative)
  • Common question: My patient is taking lorazepam, why the urine benzo immunoassay is negative?
  • Immunoassay has different sensitivities to drugs belonging to the same class

• Poor specificity (false positive)
  • Common question: My patient has a positive result for urine amphetamine/methamphetamine immunoassay, but he/she denies use. Is this a false positive?
  • Multiple drugs/metabolites have shown to cause false positive for urine amphetamine immunoassays
    • Ranitidine based on case report

Moeller, K et al Mayo Clin Proc. 2017

Table 7 — Concentrations (ng/mL) of Benzodiazepine Compounds That Produce a Result Approximately Equivalent to the 200 ng/mL and 300 ng/mL Lorazepam Cutoffs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration (ng/mL) at 200 ng/mL Cutoff</th>
<th>Concentration (ng/mL) at 300 ng/mL Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>65</td>
<td>79</td>
</tr>
<tr>
<td>7-Aminobenzodiazepine</td>
<td>5300</td>
<td>8000</td>
</tr>
<tr>
<td>7-Aminofluorobenzepan</td>
<td>930</td>
<td>1400</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>600</td>
<td>890</td>
</tr>
<tr>
<td>Lorazepam glucuronide</td>
<td>&gt;20000</td>
<td>&gt;20000</td>
</tr>
</tbody>
</table>

Siemens Syva urine benzodiazepine assay package insert
Confirmation assay uses definitive techniques to improve sensitivity and specificity

• Definitive Techniques:
  • Gas Chromatography (GC) or Liquid Chromatography (LC) as separation technique
  • Tandem Mass Spectrometry (MS/MS) or High Resolution Mass Spectrometry (HRMS) as detection and identification

• Highly Specific and sensitive based on multiple identification criteria
  • Molecular mass over charge (m/z)
  • Retention time (RT)
  • Internal standards
  • Ion ratios
Diversified urine drug testing approaches are designed to meet different clinical needs

• Screen only testing:
  • Drug of abuse screening panel
  • Presumptive positive requires confirmation testing based on different methodology

• Screen with reflex confirmation testing:
  • Drug of abuse screening panel with reflex to confirmation

• Point of Care Drug of Abuse Screen:
  • “Urine cups”
  • Presumptive positive requires confirmation testing based on different methodology

• Direct order of confirmation panels:
  • Quantitative, class based
  • High sensitivity and quantified results reported
Other considerations for test selections

• Results turn-around-time need:
  • Screen results are fast
  • Additional confirmation requires additional testing time (1-4 days)

• Cost of testing:
  • Screen test is low and confirmation can be expensive
  • Presumptive positive results need to be reflex to confirmation testing

• Drugs of interest:
  • Tramadol, methadone and fentanyl are not included in regular opiates immunoassays
  • Certain benzodiazepines and metabolites have poor reactivity to immunoassays
Direct and definitive testing is better suited for pain management and SUD treatment population

• A hybrid approach: LC-MS/MS (definitive techniques) and immunoassays are both adopted

• A hybrid approach can be adopted based on drug classes monitored:

• Qualitative test results reported:
  • “Present”, “Not detected”, or “interference”

• Maximize quality of results and minimize costs of testing
Analytes determined by LC-MS/MS definitive technique

- **Opioids**
  - Heroin metabolite (6-AM)
  - Codeine, Morphine
  - Hydrocodone, Hydromorphone & metabolites
  - Oxycodone, Oxymorphone & metabolites
  - Buprenorphine & metabolite
  - Fentanyl & metabolite
  - Tapentadol & metabolite
  - Meperidine metabolite

- **Zolpidem**

- **Benzodiazepines**
  - Clonazepam & metabolite
  - Alrpaol & metabolite
  - Midazolam & metabolite
  - Lorazepam
  - Diazepam, Nordiazepam, Temazepam, Oxazepam

- **Stimulants**
  - Methamphetamine
  - Amphetamine
  - Methylphenidate
  - MDMA & metabolites
  - Phentermine
Immunoassays are adopted to detect defined drug/metabolites

- Poor physical and chemical fit in the LC-MS/MS assay
  - Marijuana (THC) metabolite
  - Barbiturates
  - Tramadol
  - Ethyl glucuronide

- Good performing immunoassays with high specificity and comparable sensitivity
  - Methadone
  - Cocaine metabolite (Benzoylcegonine): illicit drug
  - Carisoprodol/Meprobamate

- Drugs rarely observed (false positive rate reflects low positivity rate in patient population)
  - Phencyclidine (PCP)
  - Propoxyphene
The “Hybrid” approach benefits from advantages from both testing modalities

- Qualitative and definitive LC-MS/MS approach:
  - Highly sensitive cutoffs for direct detection
  - High specific approach to differentiate drugs in the same class
- Qualitative results are sufficient for most clinical needs
  - Quantitative results can be over-interpreted to make correlations with dose or drug use patterns
  - Exceptions (discuss later)
The “Hybrid” approach benefits from advantages from both testing modalities

• Results reporting turn-around-time (TAT)
  • One LC-MS/MS method + additional immunoassays (random access)
  • Shortened TAT compared to presumptive positive samples needing confirmation

• Costs of testing
  • Quantitative tests are more costly than qualitative tests
  • Multiple quantitative confirmation tests are costly
Analytical differences of qualitative and quantitative methods

• Qualitative Testing Principles
  • One calibrator at the cutoff concentration for each drug/metabolite detected
  • Quality control checked at 50% and 150% cutoff concentrations
  • Results are reported as present or not detected
  • *Certain relative concentrations information can be extracted from qualitative assay (needs toxicologist interpretation)*

• Quantitative Testing Principles
  • Multiple calibrator curve is adopted
  • Defined analytical measuring range
  • Multiple levels of quality control check
  • Results are reported as a quantified number, below or above quantification range
    • Below Lower limit of quantification:
      • <LLOQ

*Note: LLOQ is the abbreviation for Lower Limit of Quantification.*
Urine drug concentrations can be misleading for clinical interpretation

- **Drug Absorption**
- **Circulating blood (First compartment)**
- **Tissue distribution (second compartment)**
- **Urine Elimination (Urine Detection)**

**Drug Metabolism**

- Drug dose, administration frequency
- Blood concentration of drug and its metabolites
- ? Urine concentration of drug and its metabolites in random urine samples
Quantitation of certain drug and its metabolites may provide useful information

- Distinguish pharmaceutical impurities from poly drug use
  - Oxycodone present with low hydrocodone

- Document drug elimination and abstinence
  - Concentration can be further normalized by urine creatinine

- Characterize unusual drug metabolism patterns in individual patients

- Identify addition of drug directly to urine to mimic adherence with therapy
  - Large amount of parent drug present without metabolite present
Case 1: missing zolpidem (unexpected negative)

- Drug prescribed: Ambien (zolpidem), 5 mg, PRN at night
- Drug found: none above cutoff (20 ng/mL)
- Question: Is my patient taking Ambien?
Case 1: missing zolpidem

- Drug prescribed: Ambien (zolpidem), 5 mg, PRN at night
- Drug found: none above cutoff (20 ng/mL)
- Question: Is my patient taking Ambien?

Interpretation consideration:

- Zolpidem is usually used only at night
- Half-life in serum/plasma ~2-3 hrs, urine detection window varies
- Frequently missed:
  - most laboratory tests are either not designed to detect zolpidem, or because methods don’t detect metabolites,
  - most urine samples are not first morning collections, missed detection window
Case 2: unexpected hydrocodone (unexpected positive)

- Drug prescribed: oxycodone, 10 mg, QID
- Drug analytes found in the assay:
  - Oxycodone
  - Noroxycodone
  - Oxymorphone
  - Noroxymorphone
  - Hydrocodone
- Questions: is the patient taking non-disclosed hydrocodone containing medication?
Case 2: unexpected hydrocodone

- Drug prescribed: oxycodone, 10 mg, PRN
- Drug analytes found in the assay:
  - Oxycodone, Noroxycodone, Oxymorphone, Noroxymorphone
  - Hydrocodone
- Interpretation Consideration:
  - Oxycodone and its metabolites are present
  - Could hydrocodone presence be due to impurity?
Case 2: unexpected hydrocodone

- Assay cutoff 20 ng/mL
  - Oxycodone: 1546 ng/mL
  - Noroxycodone: 1423 ng/mL
  - Oxymorphone: 456 ng/mL
  - Noroxymorphone: 2140 ng/mL
- Hydrocodone: 23 ng/mL
- Concentration ratio is consistent with hydrocodone being impurities from oxycodone
Case 3: unexpected noroxymorphone (unexpected positive)

- Drug prescribed: Suboxone (buprenorphine 12 mg + naloxone 3 mg)
- Drug analytes found:
  - Buprenorphine
  - Norbuprenorphine
  - Noroxymorphone
- Question: is noroxymorphone detected due to undisclosed medication?
Case 3: unexpected noroxymorphone

Interpretation consideration:

• Noroxymorphone is chemically identical to nornaloxone (naming convention)
• Naloxone can be taken up through Suboxone sublingual film and further metabolized to nornaloxone

Drug analytes found:
- Buprenorphine
- Norbuprenorphine
- Noroxymorphone
Case 4: no metabolite for morphine

- Drug Prescribed: MS Contin (morphine sulfate) extended release
  - 40 mg, BID
- Drug analytes detected:
  - Morphine
- Question: Is the patient compliant with the medication?
  - No supporting metabolite detected
  - Is the sample adulterated?
Case 4: no metabolite for morphine

- Interpretation Consideration:
  - Hydromorphone is only minor metabolite of morphine
  - Majority of morphine is eliminated by glucuronide conjugation
  - Hydrolysis reaction adopted in assay extraction can convert all conjugated morphine to free morphine
- No hydromorphone could not support sample adulteration
Interpretation to resolve unexpected results

• Unexpected positive(s) result
  • Unexpected drug was taken recently
  • Unusual patient pharmacokinetics
  • Drug detected is a metabolite
  • Drug detected is a pharmaceutical impurity

• Drug was added to urine
• Test limitations/errors
• Specimen mixup

• Unexpected negative(s)
  • Expected drug was not taken recently
  • Unusual patient pharmacokinetics
  • Specimen quality prevented detection
  • Drug metabolites not detected

• Test was not designed to detect the drug of interest
• Test limitations/errors
• Specimen mix-up

Summary and discussion

• Toxicology testing is widely adopted in pain management and treatment of SUD
  • Patient population differs from traditional drug of abuse screening
  • Appropriate urine toxicology tests should be used

• Analytical workflows and techniques are diversified to meet different clinical needs

• Urine drug and metabolites concentrations have limited utility to correlate medication dose and frequency