Interpretation of qualitative and quantitative urine opiate tests for pain management patients

Presenter:

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**Why Do Physicians Use Urine Drug Tests to Monitor Pain Management Patients?**

- Clinical Practice Guidelines:
  - American Society of Interventional Pain Physicians (ASIPP) Guidelines
  - 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/compliance to prescribed medications
    - Identify undisclosed drugs
    - Discourage drug misuse, abuse, diversion

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**The Abuse Potential for Opioids is High**

- 13.3% (~34 million) Americans >12 years used a pain reliever non-medically at least once in their lifetime
- 4.3% (~11 million) Americans >12 years used a pain reliever non-medically at least once in the past year

• Clinical Practice Guidelines:
• Financial Reasons:
  • Nonadherence to opioid therapy leads to increased healthcare utilization and costs
  • Early monitoring of opioid adherence using urine drug tests may provide substantial cost savings associated with healthcare issues incurred in nonadherent chronic pain patients


1. Clinical Practice Guidelines:
2. Financial Reasons:
3. Regulatory Scrutiny (State and Federal Regulations):
   • State Level:
     • Physicians can prescribe controlled substances with 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
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Types of Urine Opiate Tests

• Qualitative (Screening) Assays:
  • May identify drugs and/or drug metabolites with variable specificity, often only by drug class

• Quantitative (Confirmatory) Assays:
  • Identify and quantitate the individual drug and/or drug metabolites with high specificity

Screening Assays

• Traditional screening assays
  • Point-of-collection tests (POCT)
  • Laboratory-based (commercial immunoassays)

• Targeted screening assays
  • Laboratory-developed-tests (LDT) using time-of-flight mass spectrometry (TOF-MS) or other tandem mass spectrometry (MS/MS) analyzers

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>POCT</td>
<td>Fastest TAT</td>
<td>Limited sensitivity</td>
</tr>
<tr>
<td></td>
<td>CLIA-waived versions available</td>
<td>Higher cutoffs</td>
</tr>
<tr>
<td></td>
<td>Instant result to review/discuss with patient</td>
<td>Limited specificity</td>
</tr>
<tr>
<td></td>
<td>Great if patient resides far from care</td>
<td>Maintain inventory/regulatory compliance</td>
</tr>
<tr>
<td></td>
<td>Good for high-risk patient</td>
<td>Higher cost</td>
</tr>
<tr>
<td>Immunoassay-lab based</td>
<td>Automated</td>
<td>Limited sensitivity</td>
</tr>
<tr>
<td></td>
<td>CLIA environment</td>
<td>Limited specificity</td>
</tr>
<tr>
<td></td>
<td>Most economical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Larger test menu</td>
<td></td>
</tr>
<tr>
<td>Targeted screen</td>
<td>Better sensitivity</td>
<td>Limited availability</td>
</tr>
<tr>
<td></td>
<td>Better specificity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Broadest test menu</td>
<td></td>
</tr>
</tbody>
</table>
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Cross-Reactivity Issues with Immunoassays

- Urine opiate immunoassay antibody target: Morphine
- Concentration required to trigger a “Positive” urine opiate result:

<table>
<thead>
<tr>
<th>Drug</th>
<th>300 ng/mL Cutoff</th>
<th>2,000 ng/mL Cutoff</th>
</tr>
</thead>
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<tr>
<td>6-Acetylmorphine</td>
<td>435 ng/mL</td>
<td>4,182 ng/mL</td>
</tr>
<tr>
<td>Codeine</td>
<td>102-306 ng/mL</td>
<td>660-1,980 ng/mL</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>247 ng/mL</td>
<td>1,545 ng/mL</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>498 ng/mL</td>
<td>5,349 ng/mL</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1,500 ng/mL</td>
<td>48,000 ng/mL</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>9,300 ng/mL</td>
<td>&gt;100,000 ng/mL</td>
</tr>
</tbody>
</table>

What Does a Positive Urine Drug Screen (Immunoassay) Result Really Mean?

- Patient is compliant/adherent (took the prescribed drug as directed)
- Patient added drug to the urine after collection
- Patient took one dose prior to collection (partial compliance)
- Patient took another drug which also cross-reacts with the test
- Collection or laboratory error/mix-up
- False-positive result
### Limitations of Immunoassays

- **False Positives:**

<table>
<thead>
<tr>
<th>Screening test (drug class)</th>
<th>Agents that can give a positive result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine/methamphetamine</td>
<td>Phentermine</td>
</tr>
<tr>
<td></td>
<td>Pseudoephedrine</td>
</tr>
<tr>
<td></td>
<td>Adderall</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
</tr>
<tr>
<td></td>
<td>Benzphetamine</td>
</tr>
<tr>
<td></td>
<td>Vicks inhaler</td>
</tr>
<tr>
<td>Benzo diazepine</td>
<td>Oxaprozin</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
</tr>
<tr>
<td>Opiates</td>
<td>Poppy seeds</td>
</tr>
<tr>
<td></td>
<td>Naloxone</td>
</tr>
<tr>
<td>PCP</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
</tr>
</tbody>
</table>

### What Does a Negative Urine Drug Screen (Immunoassay) Result Really Mean?

- Patient is NOT compliant/adherent
- Patient took the drug incorrectly (ie, less frequently/ lower dosage)
- Altered pharmacokinetic variables
  - Drug wasn’t absorbed
  - Altered metabolism or elimination
- Dilute or adulterated urine
- Test doesn’t cross-react with drug of interest (ie, opiate assay and methadone; wrong test for the drug of interest)
- Collection or laboratory error/mixup
- Drug present, but below the cutoff/detection limit (false-negative result)
**Limitations of Immunoassays**

- False Negatives and Detection Limits
- Important variables
  - Assay cutoff
  - Assay vendor
  - Drug formulation/dose
  - Patient pharmacokinetics
  - Sample type
  - Collection time from last dose
  - Specimen integrity/quality

**Limitations of Immunoassays**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Immunoassay</th>
<th>Immunoassay cutoff</th>
<th>LC-MS/MS cutoff</th>
<th>Samples missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Opiates</td>
<td>300 ng/mL</td>
<td>50 ng/mL</td>
<td>~30%</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td></td>
<td></td>
<td>~23%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
<td></td>
<td>~69%</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
<td></td>
<td>~12%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxycodone</td>
<td>100 ng/mL</td>
<td>50 ng/mL</td>
<td>~5%</td>
</tr>
<tr>
<td>Oxymorphine</td>
<td></td>
<td></td>
<td></td>
<td>~10%</td>
</tr>
<tr>
<td>Alprazolam (alpha-hydroxyalprazolam)</td>
<td>Benzodiazepine</td>
<td>200 ng/mL</td>
<td>20 ng/mL</td>
<td>~53%</td>
</tr>
<tr>
<td>Lorazepam</td>
<td></td>
<td></td>
<td>40 ng/mL</td>
<td>~18%</td>
</tr>
</tbody>
</table>
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**Clinical Case Studies**

- **Patient #1**: Oxycodone 20 mg/day, Urine Opiate Screen, Cutoff: 300 ng/mL, Negative
- **Patient #2**: Oxycodone 20 mg/day, Urine Opiate Screen, Cutoff: 300 ng/mL, Positive

**Questions**: Is Patient 1 noncompliant? Is it a false-negative result?

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**Urine Opiate Confirmation**
- Codeine: Not Detected
- Morphine: Not Detected
- Hydrocodone: Not Detected
- Hydromorphone: Not Detected
- Oxycodone: 1.235 ng/mL
- Oxymorphone: 746 ng/mL
**Where Did the Oxymorphone (Opana, Numorphan) Come From?**

**Oxycodone metabolism**

Oxymorphone can be derived from Oxycodone through a process of conjugation.

```
   HO
  NCH3
 /   \
 HO O O
  HO    CH3O
   O O
Oxymorphone

Conjugation

   HO
  NCH3
  HO O O
  CH3O O O
Oxycodone

   HO
  NCH3
   HO O O
   CH3O O O
Noroxycodone
```

**Why was the Urine Opiate Immunoassay Negative?**

**Concentration required to trigger a “Positive” urine opiate result:**

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<td>247 ng/mL</td>
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<tr>
<td>Hydromorphone</td>
<td>496 ng/mL</td>
<td>5,349 ng/mL</td>
</tr>
<tr>
<td><strong>Oxycodone</strong></td>
<td><strong>1,500 ng/mL</strong></td>
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</tr>
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<td><strong>9,300 ng/mL</strong></td>
<td><strong>100,000 ng/mL</strong></td>
</tr>
</tbody>
</table>

**Patient #1 Results:**
- Oxycodone: 1,235 ng/mL
- Oxymorphone: 746 ng/mL

**Final Interpretation:**
- Patient #1 is likely compliant and taking the prescribed oxycodone.
Clinical Case Studies

Patient #1
Oxycodone 20 mg/day
Negative

Patient #2
Urine Opiate Screen
Cutoff: 300 ng/mL
Positive

Urine Opiate Confirmation
Codeine: Not Detected
Morphine: Not Detected
Hydrocodone: Not Detected
Hydromorphone: Not Detected
Oxycodone: 1,235 ng/mL
Oxymorphone: 746 ng/mL

Is Patient #2 compliant?
Is this patient using any other opiates?

Urine Opiate Confirmation
Codeine: Not Detected
Morphine: Not Detected
Hydrocodone: 2,504 ng/mL
Hydromorphone: 2,013 ng/mL
Oxycodone: 2,407 ng/mL
Oxymorphone: 1,836 ng/mL
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Where did the Hydrocodone/Hydromorphone Come From?¹¹

Simplified Opioid Metabolism

Other Considerations Include Pharmaceutical Impurities¹²

• Allowable Pharmaceutical Impurities Found in Opioids

<table>
<thead>
<tr>
<th>Drug (generic name)</th>
<th>Pharmaceutical process impurities (NOTE: These are NOT metabolites)</th>
<th>Allowable pharmaceutical impurity limit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Morphine, Hydrocodone</td>
<td>0.15</td>
</tr>
<tr>
<td>Morphine</td>
<td>Codeine</td>
<td>0.50</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Hydrocodone</td>
<td>1.00</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Hydromorphone, Oxycodone</td>
<td>0.15, 0.50</td>
</tr>
</tbody>
</table>

Patient #2 Results:
• Hydrocodone: 2,504 ng/mL
• Hydromorphone: 2,013 ng/mL
• Oxycodone: 2,407 ng/mL
• Oxymorphone: 1,836 ng/mL

Final Interpretation:
• Patient #2 most likely taking oxycodone (prescribed) and hydrocodone (not prescribed).
Summary

- Interpretation of qualitative and/or quantitative urine tests in pain management patients to determine compliance is challenging.
- Select and interpret qualitative tests based on the limitations of each assay.
- With quantitative tests, remember metabolic pathways and possible pharmaceutical impurities when interpreting test results.
- Unexpected or unexplained results should be discussed with the patient and/or the laboratory and additional testing performed if needed.

Resources

THANK YOU