Controlled Substance Monitoring
and the Opioid Epidemic
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Disclosure
• Relevant Financial Relationships:
  - None
• Off Label Usage:
  - None

Objectives
• Summarize the clinical utility and limitations of urine screening assays and definitive tests for controlled substances.
• Identify the challenges of correctly interpreting urine drug testing results.
• Assess the role of adulterant/specimen validity testing and the use of alternative specimen types.

Why Do Physicians Use UDTs to Monitor Controlled Substances/Pain Management Patients?
1. 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)
   - Identify undisclosed drugs
   - Discourage drug misuse, abuse, diversion

   - CDC Recommendations (2016)
     - 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.

Participants with Poll Everywhere
This is intended to be an interactive session:
• You will be able to answer using either web voting or you can text answers to the questions/case studies using your smartphone or laptop.

Laboratory Medicine Practice Guideline
26 Evidence-based Recommendations

<table>
<thead>
<tr>
<th>#</th>
<th>Recommendation</th>
<th>Quality/evidence</th>
<th>Target Group</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Testing biological specimens for drug metabolites is recommended and effective for detecting the use of relevant over-the-counter, prescription, and non-prescription drugs, and illicit substances in pain management patients. This should be done in conjunction with other evidence-based pain management protocols.</td>
<td>A, I</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

7 Consensus-based Recommendations

<table>
<thead>
<tr>
<th>#</th>
<th>Expert Opinion</th>
<th>Evidence Level</th>
<th>Target Group</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Why Do Physicians Use UDTs to Monitor Controlled Substances/Pain Management Patients?

1. Clinical Practice Guidelines:
2. Financial Reasons:
   - Non-adherence to opioid therapy leads to increased healthcare utilization and costs
   - Early monitoring of opioid adherence using UDTs may provide substantial cost savings associated with healthcare issues incurred in non-adherent chronic pain patients
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 non-therapeutic 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

Issues With Laboratory Testing for Controlled Substances/Pain Management

- Where are tests done?
  - Office vs. lab
- What specimen should be used?
- Qualitative vs. Quantitative Tests?
- Interpretation of test results
  - Screen vs. definitive assays
  - Complicated metabolic pathways/metabolite ratios
  - Compliance vs. more information (dose)
- Follow-up testing
  - To confirm or not to confirm screening assays
- Regulatory/reimbursement issues

Urine Drug Test Volumes (2000-2010)

- Opiates: VR, 532; P<0.001
- Methadone: VR, 461; P<0.001
- Barbiturates: VR, 450; P<0.001
- Benzodiazepines: VR, 450; P<0.001
- Phencyclidine: VR, 50; P<0.001
- Barbiturates: VR, 599; P<0.001
- Cocaine: VR, 132; P<0.001
- Ethanol: VR, 100; P<0.001
- Meprobamate: VR, 1,510; P<0.001

Medicare Part B Reimbursement Volumes for Lab Tests 2000-2010

- Opiates: VR, 332; P<0.001
- Methadone: VR, 461; P<0.001
- Barbiturates: VR, 450; P<0.001
- Benzodiazepines: VR, 450; P<0.001
- Phencyclidine: VR, 50; P<0.001
- Barbiturates: VR, 599; P<0.001
- Cocaine: VR, 132; P<0.001
- Ethanol: VR, 100; P<0.001
- Meprobamate: VR, 1,510; P<0.001
What Specimen is Best?

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>Ease of collection</td>
<td>Good detection window</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testing widely available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Easy to adulterate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doesn’t identify frequency of dosing:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doesn’t reliably estimate dose taken:</td>
</tr>
<tr>
<td>Blood (serum/plasma)</td>
<td>Recent usage</td>
<td>Insensitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Correlates better to physiological symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short detection window</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited availability</td>
</tr>
<tr>
<td>Oral fluid (saliva)</td>
<td>Recent usage</td>
<td>Low concentrations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mainly parent drug</td>
</tr>
<tr>
<td>Hair</td>
<td>Long detection time</td>
<td>Limited availability</td>
</tr>
</tbody>
</table>

Approximate Detection Times By Specimen Type

- Blood (serum): Minutes
- Oral fluid: Hours
- Urine: Days
- Saliva: Weeks
- Hair and nails: Months

Approximate Detection Times By Specimen Type


Specimen Types

- Based on numerous guidelines, urine is preferred matrix for the detection of relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances.
- Serum or plasma is an acceptable alternative matrix in patients with end-stage renal failure (anuria).
- For dialysis patients, the serum/plasma should be collected prior to dialysis.
- Oral fluid can be used for selected drugs (e.g. amphetamine, benzdiazepines, buprenorphine, tetrahydrocannabinol, cocaine, codeine, hydromorphone, methadone, morphine, oxycodone and oxymorphine) but it also has limitations.

Types of UDTs

- Screening assays
  - Identify drugs and/or drug metabolites with variable specificity often by drug class
  - Typically immunoassay-based
  - POCT or laboratory-based
  - Economic
  - 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

Cross-Reactivity Issues With Immunoassays

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>300 ng/mL, cutoff; % Cross reactivity</th>
<th>2,000 ng/mL, cutoff; % Cross reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-acetylmorphine</td>
<td>386 ng/mL, 73%</td>
<td>2,096 ng/mL, 77%</td>
</tr>
<tr>
<td>Codeine</td>
<td>224 ng/mL, 41%</td>
<td>1,741 ng/mL, 75%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1,425 ng/mL, 13%</td>
<td>10,016 ng/mL, 15%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1,425 ng/mL, 13%</td>
<td>10,016 ng/mL, 15%</td>
</tr>
<tr>
<td>Oxydoline</td>
<td>&gt;75,000 ng/mL, &gt;0.5%</td>
<td>&gt;670,000 ng/mL, &gt;0.2%</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, Pseudoephedrine, Adderall, Selegiline, Benzphetamine, Vicks Inhaler</td>
</tr>
<tr>
<td>Benzo diazepine</td>
<td>Oxaprozin, Sertraline</td>
</tr>
<tr>
<td>Opiates</td>
<td>Poppy seeds, Naloxone</td>
</tr>
<tr>
<td>PCP</td>
<td>Chlorpromazine, Dextromethorphan</td>
</tr>
</tbody>
</table>

**False Negatives and Detection Limits**

- Important variables that need to be considered:
  - Assay cutoff
  - Assay vendor
  - Drug formulation/dosage
  - Patient pharmacokinetics
  - Sample type
  - Collection time from last dose
  - Specimen integrity/quality

- Presumptive positive
- Negative
- Cutoff

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

- Patient is NOT compliant/adherent
- Patient took the drug incorrectly (i.e., 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 (i.e., opiate assay and Methadone; wrong test for the drug of interest)
- Collection or laboratory error/mix-up
- Drug present, but below the cutoff/detection limit (false-negative result)

**When is Quantitative (Confirmatory) Testing Indicated?**

- Unexpected qualitative (screening) results
- Drug prescribed doesn’t cross-react with qualitative screen
- Legal/Forensic implications
- Evaluate patient pharmacokinetics and dose (blood/serum preferred)
- Concentrations may be required to interpret the results or make management decisions
  - Helps determine what drug(s) was taken
  - May identify drug-drug interactions or changes in pharmacokinetics
  - May help interpret serial monitoring for an individual patient
  - May identify adulteration
  - May identify pharmaceutical impurities

**Case Study #1: Where’s Waldo?**

- **Case History:**
  - 45 year old male
- **Medical History:**
  - ADHD
  - Anxiety
  - Low back pain
- **Medications:**
  - Clonazepam (Klonopin)
  - Methylphenidate (Ritalin)
  - Oxycodone/Acetaminophen (Percocet; 5:325 mg qid)
- **Clinical Evaluation:**
  - VAS: Originally 6/10, Now 3/10

**Case#1 Continued**

- **Routine UDT results (Immunoassay):**
  - July 2018

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Opiates</th>
<th>Opiates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine/Methamph</td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Barbiturates</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Cocaine Metabolite</td>
<td>100 mg/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>Methadone</td>
<td>100 mg/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>Opiates</td>
<td>100 mg/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>50 mg/mL</td>
<td>Positive</td>
</tr>
<tr>
<td>PCP</td>
<td>50 mg/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>THC</td>
<td>20 mg/mL</td>
<td>Negative</td>
</tr>
</tbody>
</table>

- **Oxycodone LC-MS/MS Confirmation (Definitive Test):**

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Opiates</th>
<th>Opiates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine/Methamph</td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Barbiturates</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Cocaine Metabolite</td>
<td>50 mg/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>Methadone</td>
<td>50 mg/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>Opiates</td>
<td>50 mg/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>50 mg/mL</td>
<td>Positive</td>
</tr>
<tr>
<td>PCP</td>
<td>10 mg/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>THC</td>
<td>20 mg/mL</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Are these lab results consistent with therapy? How would you interpret these results?

**Medications:**
Clonazepam (Klonopin), Methylphenidate (Ritalin), Oxycodone (Percocet)

1. Patient is NOT compliant
   - No clonazepam, methylphenidate
   - Oxymorphone (Opana) present
2. Patient is Partially compliant
   - Taking Oxycodone (Percocet)
   - Not taking clonazepam, methylphenidate
3. Call the laboratory: unsure of results

**Remember Cross-Reactivity Issues with Immunoassays**
- Patient prescribed Clonazepam (Klonopin)
- Common Benzodiazepine immunoassay targets:
  - Oxazepam
  - Nordiazepam
  - Lormetazepam

- Drug 200 ng/mL cutoff
  - 7-aminoclonazepam 5,700 ng/mL
  - α-hydroxyalprazolam 100 ng/mL
  - Clorazepate >44 ng/mL
  - Lorazepam glucuronide >10,000 ng/mL
  - Meclonazepam 150 ng/mL
  - Meclobemine 130 ng/mL
  - Temazepam 140 ng/mL

**Simplified Benzodiazepine Metabolism**

- where is the methylphenidate (Ritalin)?
  - Amphetamine/Methamphetamine Screening Assay:
    - Designed to detect:
      - Amphetamine
      - Methamphetamine
      - Methylenedioxyamphetamine (MDMA)
      - Methylenedioxymethamphetamine (MDMA)

- Order methylphenidate & metabolite urine confirmation test:
  - Patient is taking methylphenidate

- Where did the oxymorphone (Opana™, Numorphan™) come from?
  - Oxycodone metabolism:
    - In Urine:
      - 13-19% Free oxycodone
      - 7-29% Conjugated oxycodone
      - 8% Free oxymorphone
      - 13-14% Conjugated oxymorphone
Case #1: Conclusion

Waldo is compliant with all medications

Case Study#2
Waldo’s Brother

• Prescribed Medications:
  - Hydrocodone (Vicodin) 10.325 qid

Screening Test Urine Cutoff Result
- Amphetamine/Methamphetamine 500 ng/mL Negative
- Barbiturates 200 ng/mL Negative
- Benzo diazepine 200 ng/mL Negative
- Cocaine Metabolite 300 ng/mL Negative
- Methadone 300 ng/mL Negative
- Opiates 300 ng/mL Presumptive Positive
- Oxycodone 100 ng/mL Negative
- PCP 25 ng/mL Negative
- THC (Marijuana) 20 ng/mL Negative

Definitive Test (LC-MS/MS) Urine Detection Limit Result
- Codeine 100 ng/mL
- Hydrocodone 100 ng/mL
- Hydromorphone 100 ng/mL
- Morphine 100 ng/mL
- Oxycodone 100 ng/mL

Where did the Hydromorphone/Codeine Come From?

Are these lab results consistent with therapy?
How would you interpret these results?

Medications:
- Hydrocodone (Vicodin)

1. Patient is NOT compliant
   - Codeine was confirmed
2. Patient is Partially compliant
   - Taking Hydrocodone
   - Also taking codeine
3. Patient is complaint
4. Unsure of results; Call the laboratory

Other Considerations When Interpreting UDTs Include Pharmaceutical Impurities

<table>
<thead>
<tr>
<th>Drug (generic name)</th>
<th>Allowable Pharmaceutical Impurities Found in-Opside</th>
<th>Allowable pharmaceutical impurity level (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>Codeine</td>
<td>0.15 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td>0.15 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>0.50 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td>0.15 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>0.50 mg/mL</td>
</tr>
</tbody>
</table>

Patient #2 Results:
- Hydrocodone: 68,153 ng/mL
- Hydromorphone: 42,780 ng/mL
- Codeine: 112 ng/mL
Case #2: Conclusion

Waldo’s Brother is compliant with all medications

Ways to Adulterate Urine

1. Substitution
2. In vivo adulterants
3. In vitro adulterants

Substitution

- Certified drug-free urine available through the internet
- Urine can be introduced by external plumbing whereby a small pouch can be hidden in anus, vagina, or under penis
- Donors catheterize themselves to insert drug-free urine directly into bladder

Price $99.95
Popularity: 140,514

In Vivo Adulterants

- Dilutional adulterants
  - Water
  - Diuretics (Lasix)
- Natural products Xanthine compounds (caffeine, theophylline, theobromine) found in coffee, tea, cocoa to increase GFR
- Goldenseal

In Vitro Adulterants (Doping)

- Originally found in bathrooms, purses, pockets, etc., as last minute adulterants
- Lemon juice, vinegar, detergents, soaps, can alter pH to affect conditions for optimum immunoassay screening
- Bleach, Drano, etc. oxidize drugs to other compounds
- Visine interfere with THC by forming micelle bodies

Commercial Adulterants

- Whizzes/Klear:
  - Contains nitrite (850 mg) for use in 30–50 mL water
  - Oxidizes THC and THC internal standard at acid pH conditions
  - No interference for immunassay screening. Low recovery of IS following GC/MS procedures
- Urine Luck, Sweet Pee’s Spoiler, Klear II:
  - Pyridinium chlorochromate (PCC; 200 mmol/L)
  - Slowly oxidizes THC and morphine under neutral or slightly acid conditions
  - Low recovery of internal standards
Effect of PCC on GC/MS Analysis

Countermeasures

NIDA Regulations

- Household solvents/cleaners removed from urinals
- Sources of water removed. Bluing agent in toilet.
- Temperature checks performed within minutes of collection
- Color and unusual odor noted

Basic Lab Counter Measures

- Color
- Temperature
- Creatinine (Cr)
- pH
- Specific gravity (SG)
- Oxidants
- Witnessed collections

Adulterant Survey, Urine

Case Study #3: Raging UTI

- 40 yo Female
- Hx: Chronic back pain
- Medications:
  - Hydromorphone (Dilaudid; 2 mg q8)

Case#3 Continued

- Routine UDT results (Immunoassay):
  - June 2018

<table>
<thead>
<tr>
<th>Adulterant Test</th>
<th>Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>mg/dL</td>
<td>20‐370 mg/dL</td>
</tr>
<tr>
<td>Specific gravity</td>
<td></td>
<td>1.003‐1.035</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td>3.0‐11.0</td>
</tr>
<tr>
<td>Oxidants</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Nitrites</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Testing stopped: Suspect specimen adulteration.

However, physician called and wanted to have opiate confirmation testing performed.
Case 3: Conclusion

- Physician confronts patient with results:
  - Patient doesn’t have UTI; nitrite concentration (>500 mcg/mL) not physiological
  - Patient admits adding “Whizzies/Klear” to urine to try and hide her marijuana usage
  - Nitrite is interfering with confirmatory test for marijuana

- Bad news:
  - Patient is using marijuana

- Good news:
  - Patient doesn’t have UTI
  - Patient is taking hydromorphone

Summary

- Objective measures like laboratory tests are needed to:
  - Identify and evaluate recent drug use/abuse
  - Set and monitor clinical goals/expectations

- UDT results need to be interpreted in the context of the test, drug(s) prescribed, specimen type, specimen validity test results, and the patient

- Unexpected/unexplained results should be discussed with the patient/laboratory, and additional testing performed if needed

Opiate LC-MS/MS Confirmatory Test:

<table>
<thead>
<tr>
<th>Test</th>
<th>Detection Limit</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>25 ng/mL</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>Morphine</td>
<td>25 ng/mL</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>25 ng/mL</td>
<td>3,245 ng/mL</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>25 ng/mL</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>25 ng/mL</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>Noroxycodone</td>
<td>25 ng/mL</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>25 ng/mL</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>Noroxymorphone</td>
<td>25 ng/mL</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>Naloxone</td>
<td>25 ng/mL</td>
<td>&lt;25 ng/mL</td>
</tr>
</tbody>
</table>