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4. Slide Contributors

Slide Contributors

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5. **Goal**

The goal of this presentation is to provide healthcare professionals with the requisite information to rationally employ urine drug testing in clinical practice in order to improve patient care, protect one’s practice, & aid compliance with medical board guidelines & regulations.

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6. **Objectives**

- Distinguish between urine drug testing for detecting illicit drug use & for monitoring adherence to treatment
- Describe test methodology, instrumentation, & sensitivity/specificity of results
- Highlight strategies to improve analysis & interpretation of results
- Understand limitations of testing

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7. Background

**Background**

- Term urine drug "screening" is a misnomer
- All UDTs are not equal
  - No "standard" UDT is suitable for all purposes & settings
    - Indicate whether any substance(s) is suspected or expected
    - Communicate with testing laboratory

UDT=urine drug test


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8. Background

**Background**

- Controversies exist regarding clinical value of UDTs
  - Most designed for deterrent-based testing for illicit drug use
- When used with appropriate understanding, UDTs can improve ability to
  - Manage controlled substance therapy
  - Diagnose substance misuse/addiction
  - Advocate for patients


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9. Federally Regulated Urine Drug Testing

**Federally Regulated Urine Drug Testing**

- Most established use of UDTs
- “Federal Five”
  - marijuana (THC)
  - cocaine (benzoylcegonine)
  - opiates
  - phencyclidine (PCP)
  - amphetamine/methamphetamine
- Mandated cutoff concentrations too high to be of value in clinical practice
- Requirements of federally regulated testing not always applicable to clinical practice


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10. Nonregulated Urine Drug Testing

**Nonregulated Urine Drug Testing**

- Inform laboratory personnel of purpose
  - Forensic
    - Preemployment
    - Child custody
    - Driver’s license renewal
    - Criminal justice system
    - Insurance/workers’ compensation
  - Clinical


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11. Urine Drug Testing in Clinical Practice

Urine Drug Testing in Clinical Practice

- Why to test
  - Evaluate patients
  - Support assessment & diagnosis
  - Monitor adherence
  - Identify use of undisclosed substances
  - Patient advocacy
  - Uncover diversion


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12. Urine Drug Testing in Clinical Practice

Urine Drug Testing in Clinical Practice

- *Consideration* of whom to test
  - New patients already taking controlled substances
  - Any patient for whom you are considering prescribing controlled substances
  - Patients who are resistant to full evaluation
  - Patients who request a specific drug(s)


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13. Urine Drug Testing in Clinical Practice

Urine Drug Testing in Clinical Practice

- **Consideration** of whom to test
  - Patients who display aberrant behavior
  - Patients in recovery


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14. Urine Drug Testing in Clinical Practice

Urine Drug Testing in Clinical Practice

- **When to test**
  - Considering controlled substances treatment
  - Making major treatment changes
  - Support decision to refer
  - Treatment agreements
  - Any aberrant drug-related behavior
  - Third-party reports about aberrant drug-related behaviors (family, friends, insurers, law enforcement, etc)


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15. Specimen Collection in Clinical Practice

**Specimen Collection in Clinical Practice**

- Random collection preferred
  - Adulterants, substituted specimens
- Unobserved usually acceptable
- Collection facility
  - No basin
  - Pigment toilet water
- If tampering suspected, check
  - Temperature 90°F-100°F
  - pH 4.5-8.0
  - Creatinine >20 mg/dL
  - Color


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16. Urine Drug Testing Process

**Urine Drug Testing Process**

1. Immunoassay screening
   - Laboratory-based or at point of care
   - Classify substances as present or absent
   - Presumptive positives
2. Confirmatory & quantitative
   - Laboratory-based specific drug identification
   - GC/MS standard
   - No correlation between urine drug concentration & dose
   - Use a reputable laboratory (DHHS or CAP certified)

GAMS=gas chromatography/mass spectrometry, DHHS=Department of Health & Human Services, CAP=College of American Pathologists


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17. Urine Drug Testing Process: Immunoassays

**Urine Drug Testing Process: Immunoassays**

- Proprietary antibody screens
  - Examples: EMIT® II, KIMS®, CEDIA®, DRI®, AxSYM®
- Know which screen is being used
  - Sensitivity & specificity vary
- Continually updated/changed by
  - Manufacturer
  - Laboratory


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18. Urine Drug Testing Process: Confirmatory

**Urine Drug Testing Process: Confirmatory**

- Identifies specific drug &/or metabolite(s)
  - GC/MS is standard
  - Variation still exists
    - Different methods for performing assays
    - Variation in factors affecting assays
    - Potential for carryover from another specimen
    - Cutoffs
- Clinically used to
  - Confirm presence of given drug &/or metabolite(s)
  - Identify drugs not included in immunoassay (oxycodone, hydromorphone, hydrocodone, fentanyl, etc)

GC/MS = gas chromatography/mass spectrometry

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19. GC/MS of Oxycodone

![GC/MS of Oxycodone](image)

20. Drug-Class Specific Windows of Detection in Urine

### Drug-Class–Specific Windows of Detection in Urine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Federal immunoassay cutoff (ng/mL)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine (misuse)</td>
<td>1000</td>
<td>≤5</td>
</tr>
<tr>
<td>Cannabis, 1 cigarette</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzylecgonine after street doses of cocaine</td>
<td>300</td>
<td>≤7</td>
</tr>
<tr>
<td>Opiates (morphine, codeine)</td>
<td>2000</td>
<td>1-2</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic user</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤30</td>
</tr>
</tbody>
</table>


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21. Interpretation of UDT Results

**Interpretation of UDT Results**

- Immunoassays report each sample as positive or negative for particular drug/class
  - Based on predetermined cutoffs
- Positive UDT results
  - Reflect recent drug use
  - Cannot determine exposure time, dose, or frequency of use


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22. Interpretation of UDT Results

**Interpretation of UDT Results**

<table>
<thead>
<tr>
<th></th>
<th>Patient has taken drug</th>
<th>Patient has not taken drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive result</td>
<td>True positive</td>
<td>False positive</td>
</tr>
<tr>
<td>Negative result</td>
<td>False negative</td>
<td>True negative</td>
</tr>
</tbody>
</table>


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23. "Opiate" Immunoassay Screens

"Opiate" Immunoassay Screens

- Designed to detect heroin use, not adherence to therapeutic opioid regimen
- Heroin metabolized $\rightarrow$ 6-MAM $\rightarrow$ morphine
  - Morphine in urine not proof of heroin use
    - Codeine metabolized $\rightarrow$ morphine
    - Morphine use or misuse
    - Morphine from poppy seeds addressed by cutoff change from 300 to 2000 ng/mL
  - 6-MAM by GC/MS is absolute proof of heroin use
- Street heroin often contaminated with codeine

6-MAM=6-monooacetylomorphine

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24. Metabolism* of Opioids

Metabolism* of Opioids

codeine $\rightarrow$ morphine $\leftarrow$ 6-MAM$^*$ $\leftarrow$ heroin

hydrocodone $\rightarrow$ hydromorphone

*Not comprehensive pathways, but may explain the presence of apparently unprescribed drugs
$^*$6-MAM=6-monoacetylmorphine, an intermediate metabolite

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25. **Opiate Screens**

<table>
<thead>
<tr>
<th>Natural (from opium)</th>
<th>Semisynthetic (opium-derived)</th>
<th>Synthetic (man-made)</th>
</tr>
</thead>
<tbody>
<tr>
<td>codeine</td>
<td>hydrocodone</td>
<td>meperidine</td>
</tr>
<tr>
<td>morphine</td>
<td>oxycodone</td>
<td>fentanyl</td>
</tr>
<tr>
<td>thebaine</td>
<td>hydromorphone</td>
<td>sufentanil</td>
</tr>
<tr>
<td></td>
<td>oxymorphone</td>
<td>propoxyphene</td>
</tr>
<tr>
<td></td>
<td>buprenorphine</td>
<td>methadone</td>
</tr>
</tbody>
</table>


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26. **Common Error of Interpretation**

- Patient taking oxycodone
- Urine screen for “opiates” reported as “none detected”
- GC/MS not performed
- Patient accused of not adhering to treatment plan & discharged
- Solution: order GC/MS

GC/MS = gas chromatography/mass spectrometry


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27. Common Error of Interpretation

**Common Error of Interpretation**

- Patient taking hydrocodone
- Urine screen for opiates reported as positive
- GC/MS confirms hydrocodone & hydromorphone
- Patient accused of not adhering to treatment plan & discharged
- Solution: understand metabolism

GC/MS = gas chromatography/mass spectrometry

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28. Medical Explanations for Positive Results: Opiates

**Medical Explanations for Positive Results: Opiates**

- Codeine metabolized to morphine
  - Prescribed codeine may explain both drugs in urine
  - Prescribed codeine does not usually explain only morphine
    - Codeine alone possible in patients who lack CYP450 2D6
  - Prescribed morphine does not account for codeine
  - Prescribed codeine may explain codeine with trace of hydrocodone


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29. Medical Explanations for Positive Results: Cocaine

Medical Explanations for Positive Results: Cocaine

- Used in trauma, dental, ophthalmoscopic, & otolaryngologic procedures
  - Urine may test positive for cocaine metabolite 2-3 days after procedure
  - Licensed healthcare professional must order use
  - No structural similarity with other topical anesthetics that end in “caine”
    - Cross-reaction does not occur

- Herbal teas
  - Illicit, not valid medical explanation


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30. Medical Explanations for Positive Results

Medical Explanations for Positive Results: Amphetamine/Methamphetamine

- Prescription medication

- Cross-reaction with structurally similar prescription drugs for Parkinson’s disease & OTC diet agents & decongestants
  - dopamine, isoxsuprline, ephedrine, phenmetrazine, phentermine, fenfluramine, mephentermine

- Drugs metabolized to amphetamine/methamphetamine
  - selegline, benzphetamine, clobenzorex, dimethylamphetamine, fenproporex, mefenorex


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31. Medical Explanations for Positive Results

**Medical Explanations for Positive Results: Amphetamine/Methamphetamine**

- Methamphetamine & amphetamine exist as 2 isomers
  - \(d\)-form has strong CNS stimulant effect
  - \(l\)-form has peripheral action in therapeutic doses
- Vicks\textsuperscript{®} Inhaler contains desoxyephedrine, the \(l\)-form of methamphetamine
  - Separation reveals \(\sim100\%\) \(l\)-methamphetamine
  - \(>20\%\) \(d\)-methamphetamine suggests source other than Vicks\textsuperscript{®} Inhaler
- Illicitly manufactured methamphetamine/amphetamine is a mixture of \(d\)- & \(l\)-forms


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32. False-Positive Possibilities/Myths: Marijuana

**False-Positive Possibilities/Myths: Marijuana**

- Previously, ibuprofen interfered with EMIT\textsuperscript{®} immunoassay
  - EMIT\textsuperscript{®} II no longer gives ibuprofen-triggered false-positive results
- Proton pump inhibitors
- “Medical” marijuana
- Passive smoke inhalation
- Hemp food products


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33. **False-Positive Results**

**False-Positive Results**

- Technician or clerical error
- Cross-reaction with other compounds in urine
  - May be structurally unrelated; e.g., quinolone antibiotics can cause positive opiate results
  - GC/MS not influenced by cross-reacting compounds

GC/MS = gas chromatography/mass spectrometry


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34. **UDT Results Reported as None Detected**

**UDT Results Reported as “None Detected”**

- May mean any of following
  - Patient
    - Does not use drug
    - Has not recently used drug
    - Excretes drug/metabolite faster than normal
  - UDT used not sufficiently sensitive to detect drug at concentration present
    - Ask for “no threshold” testing
  - Clerical error
- In adherence testing, may raise concerns about misuse/diversion


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35. **False-Negative Results**

**False-Negative Results**

- Technical or clerical error
- Tampering with urine sample
  - Adulteration
  - Substitution
    - Suspect if sample characteristics are inconsistent with normal human urine


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36. **Case Study 1**

**Case Study 1**

- 47-year-old man, new patient, with severe low back pain due to motor vehicle accident 3 years ago
- States physician in town he recently moved from treated him with around-the-clock morphine
- Only enough medication left for 7 days
- No self-reported substance misuse
- Not yet in receipt of previous medical records


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### Case Study 1

- History & physical examination performed
- Recommended immunoassays
  - Opiates (expect positive)
  - Common drugs of misuse (cocaine, marijuana, amphetamines, methadone, benzodiazepines)
- Follow with more specific GC/MS to identify drug(s) present

---

**Case Study 1: Possible Outcomes of Urine Drug Testing**

<table>
<thead>
<tr>
<th>GC/MS results</th>
<th>Immunoassay results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ opiates</td>
</tr>
<tr>
<td>1. Morphine</td>
<td>✔</td>
</tr>
<tr>
<td>2. None detected</td>
<td></td>
</tr>
<tr>
<td>3. Meperidine</td>
<td></td>
</tr>
<tr>
<td>4. Morphine &amp; cocaine</td>
<td>✔</td>
</tr>
</tbody>
</table>

---

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Case Study 1: Second Outcome

- Immunoassay negative for opiates
- GC/MS failed to detect morphine
  - Suggests patient has not recently taken morphine
  - May be consistent with diverting drugs or bingeing pattern of drug use
  - Requires further investigation
  - Verify with laboratory that morphine was not detectable (no threshold)

GC/MS = gas chromatography/mass spectrometry

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Case Study 1: Third Outcome

- Immunoassay negative for opiates
- GC/MS positive for meperidene
  - Suggests patient is doctor-shopping &/or misusing drugs
  - Requires further investigation
  - Initiate or refer for counseling or treatment

GC/MS = gas chromatography/mass spectrometry

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41. Case Study 1: Fourth Outcome

**Case Study 1: Fourth Outcome**

- Immunoassay positive for opiates & cocaine
- GC/MS confirms presence of morphine & cocaine
  - Suggests patient abusing illicit drugs & may be misusing morphine or abusing heroin
  - Investigate whether pain syndrome exists
    - Tighten boundaries
    - Counseling
    - Refer if necessary

[GC/MS=gas chromatography/mass spectrometry](c) 2007, Purdue Pharma L.P., “Restricted use.

42. Case Study 2

**Case Study 2**

- 35-year-old woman with increasing fibromyalgia pain
- Obtained relief with oxycodone 40 mg/day for 7 months, but no longer effective
- Before increasing dose, order UDT to support & document adherence to current regimen

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Case Study 2

- Detection of oxycodone (semisynthetic opioid) by opiate immunoassay (designed to detect morphine, codeine) unreliable
  - Even large quantities may not be detected
  - Positive results may occur because of cross-reactivity
- Order GC/MS (no threshold)
  - Will detect & identify oxycodone, when present

GC/MS=gas chromatography/mass spectrometry


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Case Study 3

- 39-year-old man with increasing low back pain
- Pain score of 8/10 on presentation 18 months ago
- Modified-release morphine 30 mg bid provided some relief (5-6/10)
- Increasing morphine dose caused unacceptable side effects
- Prior to switching opioid, you order a UDT to document adherence to current regimen


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Case Study 3

- UDT positive for morphine & hydromorphone
- Suspect patient obtaining hydromorphone from "street" or another clinician
- Laboratory director reports that hydromorphone may be a metabolite of morphine
  - Concentration at ~15% compared to morphine
- A positive result for parent drug & lower levels of its metabolite supports adherence to the regimen

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Emerging Technologies for Drug Testing

- Saliva
  - Advantages
    - Collection ease
    - Minimal invasiveness
    - Close supervision
    - Limited preanalytical manipulation
  - Disadvantages
    - Shorter retention, lower levels than typically in urine

- Hair
  - Advantage
    - Long-term measure related to hair length
  - Disadvantages
    - Dark hair greater capacity to bind drug
    - Irregular growth
    - Accessibility
    - Labor-intensive sample preparation

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47. **Emerging Technologies for Drug Testing**

**Emerging Technologies for Drug Testing**

- **Sweat**
  - Advantage
    - Noninvasive, cumulative measure over days to weeks
  - Disadvantages
    - Varying sweat production
    - Risk of accidentally removing/contaminating collection device

- **Blood**
  - Advantage
    - Reduced chance of patients influencing test results
  - Disadvantages
    - Not amenable to rapid screening
    - Low concentration
    - Invasive collection


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48. **Relative Drug Detection Times in Biologic Specimens**

**Relative Drug Detection Times in Biologic Specimens**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Minutes</th>
<th>Hours</th>
<th>Days</th>
<th>Weeks</th>
<th>Months</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saliva</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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Summary: Before You Order a UDT

• Ask patient
  – Are you taking any prescribed, OTC, or herbal drugs?
    • When was last dose? Quantity?
  – Drug misuse/addiction history
• Let laboratory know what you are looking for
  – Illicit substance
  – Prescription drug misuse
  – Presence of prescribed medication

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Summary: Interpretation of UDT Results

Requires that you know
• How specimen is collected
• What is prescribed
• Retention times
• Alternative medical explanations
• Metabolism of drugs
• Scams
• Laws, regulations, & guidelines

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Conclusion

- UDT can be valuable tool in clinical practice
- Interpretation requires information
  - Get to know your laboratory director or certifying scientist
  - Consider medical review officer consult

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