Medication Monitoring; Drug Testing in Clinical Practice (urine, blood, saliva, hair)

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Objectives

• Learn the principles of urinary, blood, saliva and hair drug testing
• Understand clinical interpretation of the tests
• Grow insight into period of detection of various substances
• Build awareness of samples alteration to combat deception
Most established use of UDTs “Federal Five”
- marijuana (THC)
- cocaine
- 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

Scope of abuse

- Unexpected toxicology results demonstrated in about 50% of patients in treatment with controlled substances*
- Recent study of 200,000 urine specimens showed that 60% of results were inconsistent with prescribed regiments**
  - Different drugs found 15%
  - Additional drugs found 20%
  - No drugs found 25%
  - Illicit drugs found 11-24%

*Quest Diagnostics Health Trends: Prescription Drug Monitoring Report 2013
Drug Screening is a Standard of Care

- Recommended by Institute of Medicine, DEA, American Pain Society, American Academy of Pain Management, American Society of Interventional Pain Physicians, American Society of Addiction Medicine, Federation of State Medical Boards and Indiana Medical Licensing Board
- Only 8% of patients in primary care opioid treatment complete Urine Drug Screening (UDS)

*Indiana Pain Management Prescribing Final Rule (updated October, 2016)
Who Should Be Tested?

- Katz study: 27% of patients with NO behavioral signs suggestive of opioid abuse present with positive urine results*
- No relationship could be established with any variables including sex, pain site, type of opioid, opioid dose, number of opioids prescribed, prescribing physician and type of abnormal toxicology result.**

Drug Monitoring Tests (Effective Jan. 1, 2015)
At any time the physician determines that it is medically necessary, whether at the outset of the treatment plan, or any time thereafter, a prescribing physician shall perform or order a drug monitoring test that must include a confirmatory test using a method selective enough to differentiate individual drugs within a drug class.

The rule applies to:

<table>
<thead>
<tr>
<th>Drug Dose Duration</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal opioid patch</td>
<td>Any</td>
<td>&gt;3 consecutive months</td>
</tr>
<tr>
<td>Any opiate ER medication not in abuse deterrent form if an FDA-abuse deterrent form is available</td>
<td>Any</td>
<td>Day 1</td>
</tr>
<tr>
<td>Tramadol</td>
<td>&gt;60 mg MED/day</td>
<td>&gt;3 consecutive months</td>
</tr>
<tr>
<td>Any other opioid-containing controlled substance</td>
<td>&gt;60 pills/month OR &gt;15 mg MED/day</td>
<td>&gt;3 consecutive months</td>
</tr>
</tbody>
</table>
Exclusions

1. Patients with a terminal medical condition (Refer to definitions section.)
2. Residents of an Indiana-licensed health facility (as defined by state law)
3. Patients enrolled in an Indiana-licensed hospice program (as defined by state law)
4. Patients enrolled in an inpatient or outpatient palliative care program of an Indiana-licensed hospital or hospice (as defined by state law)

When to test?

- At initial appointment
- At least once every 3-6 months for low risk patients
- More frequently in high risk patients
- At least once a year confirmatory testing
- At any time the physician determines that it is medically necessary


When to test?

Patient

- Is on a controlled substance
- Medication regimen is changing
- Resistant to evaluation
- Requests a specific drug
- Displays aberrant behavior
- In a recovery program
- Declines in function
- 18 factors as per Indiana Pain Management Prescribing Rule

Randomization
Summary: Interpretation of UDS Results

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

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

## Specimen Validity

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>&gt;2 mg/dl</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>&gt;1.0020</td>
</tr>
<tr>
<td>pH</td>
<td>3.5-9.0</td>
</tr>
<tr>
<td>Nitrites</td>
<td>&lt;200 mcg/ml</td>
</tr>
<tr>
<td>Chromates</td>
<td>&lt;50 mcg/ml</td>
</tr>
</tbody>
</table>
## Creatinine Interpretation

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Specimen</th>
<th>Possible reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/dl</td>
<td>Average</td>
<td></td>
</tr>
<tr>
<td>&lt;20 mg/dl</td>
<td>Dilute</td>
<td>Adulteration; increase water intake</td>
</tr>
<tr>
<td>&lt;2 mg/dl</td>
<td>Substituted</td>
<td>Not urine</td>
</tr>
</tbody>
</table>
### Specific Gravity Interpretation

<table>
<thead>
<tr>
<th>Value</th>
<th>Specimen</th>
<th>Possible reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.04</td>
<td>Concentrated</td>
<td>Disease state; adulteration with salt or other compound</td>
</tr>
<tr>
<td>1.0200</td>
<td>Average urine</td>
<td></td>
</tr>
<tr>
<td>&lt;1.0020</td>
<td>Dilute</td>
<td>Adulteration; increased water intake</td>
</tr>
<tr>
<td>&lt;1.0010</td>
<td>Substituted</td>
<td>Not urine</td>
</tr>
</tbody>
</table>
Urine Drug Screening 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)

GC/MS = gas chromatography/mass spectrometry; DHHS = Department of Health & Human Services; CAP = College of American Pathologists

*Shults TF. *Medical Review Officer Handbook. 8th ed. 2002.*
Immunoassay

- Based on competitive binding to antibody to a target substance
- If a drug has a similar structure to a target analyte, it may trigger false positive result
- Sometimes a drug without structural similarity may bind to antibody (false positive)
- Lack of cross reactivity across a class may result in false negatives
- Qualitative result only (or semi-qualitative)
- Rapid result

*Jagerdeo E, Schaff JE. UPLC-Orbitrap® Screening for over 35 Drugs of Abuse and Metabolites in Biological Fluids in Under 10 min. Methods Mol Biol. 2018;1810:75-87
## False Positives on Immunoassay

<table>
<thead>
<tr>
<th>Immunoassay</th>
<th>Manchicanti et al. (2011) %</th>
<th>Passik at al. (2013) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>52.9</td>
<td>21.4</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>------</td>
<td>21.5</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>------</td>
<td>11.4</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.0</td>
<td>12.3</td>
</tr>
<tr>
<td>Marijuana</td>
<td>38.7</td>
<td>21.3</td>
</tr>
<tr>
<td>Methadone</td>
<td>18.3</td>
<td>45.3</td>
</tr>
<tr>
<td>Opiates</td>
<td>3.6</td>
<td>22.4</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>38.8</td>
<td>41.3</td>
</tr>
<tr>
<td>MDMA/Meth</td>
<td>85.7</td>
<td>99.5</td>
</tr>
<tr>
<td>PCP</td>
<td>------</td>
<td>100</td>
</tr>
<tr>
<td>TCA</td>
<td>------</td>
<td>76.2</td>
</tr>
</tbody>
</table>
Gas Chromatography/Mass Spectrometry (GC/MS)

- Specialized personnel.
- Quantitative
- Drug is identified based on the molecular mass and ion ratios

False Positives on Gas Chromatography/Mass Spectrometry (GC/MS)

- Technical errors
- Clerical errors
- Poor laboratory methods
- Contaminants
### 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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# Emerging Technologies for Drug Testing

<table>
<thead>
<tr>
<th>Sweat</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantage</strong></td>
<td><strong>Advantage</strong></td>
</tr>
<tr>
<td>• Noninvasive, cumulative measure over days to weeks</td>
<td>• Reduced chance of patients influencing test results</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>• Varying sweat production</td>
<td>• Not amenable to rapid screening</td>
</tr>
<tr>
<td>• Risk of accidentally removing/contaminating collection device</td>
<td>• Low concentration</td>
</tr>
<tr>
<td></td>
<td>• Invasive collection</td>
</tr>
</tbody>
</table>


Relative Drug Detection Times in Biologic Specimens

- Hair & nails
- Blood
- Saliva
- Urine up to x 5 of plasma
- Sweat

## 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>Cannabinoids, 1 cigarette – Chronic smoker</td>
<td>50</td>
<td>2-4</td>
</tr>
<tr>
<td>Benzoylcegonine 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 – Chronic user</td>
<td>25</td>
<td>8</td>
</tr>
</tbody>
</table>

*Shults TF. Medical Review Officer Handbook. 8th ed. 2002.*  
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Workplace screening (ng/ml)</th>
<th>Pain management (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>500-1000</td>
<td>100-250</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>300</td>
<td>100-200</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>300</td>
<td>50</td>
</tr>
<tr>
<td>Cocaine</td>
<td>150-300</td>
<td>50</td>
</tr>
<tr>
<td>Marijuana</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Opiates</td>
<td>300-2000</td>
<td>50-100</td>
</tr>
</tbody>
</table>
## 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><strong>Positive result</strong></td>
<td>True positive</td>
<td>False positive</td>
</tr>
<tr>
<td><strong>Negative result</strong></td>
<td>False negative</td>
<td>True negative</td>
</tr>
</tbody>
</table>

Metabolism of Opioids

- **hydrocodone** → **morphine** ← **6-MAM†** ← **heroin**
- **codeine** → **morphine**
- **hydrocodone** → **hydromorphone**
- **oxycodone** → **oxymorphone**

Not comprehensive pathways, but may explain the presence of apparently unprescribed drugs.

†6-MAM=6-monoacetylmorphine, an intermediate metabolite

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

* Brahmc NC, Yeager LL, Fox MD. Commonly prescribed medications and potential false-positive urine drug screens. Am J Health Syst Pharm. 2010 Aug 15;67(16):1344-50
False-Positive Results

- In OxyContin - 1% of hydrocodone is allowed
- Hydromorphone – hydrocodone and morphine allowed
- Contaminated herbal supplements – about 25% contain diuretics, benzodiazepines, steroids and amphetamines
- In pharmacies pill counters are rarely cleaned other than after dispensing sulfa or penicillin drugs

* Haddox JD, Kupper RJ, Cone EJ Clinical considerations for interpretation of unexpected results from UDS. Pain Med. 2010
UDS 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
  - UDS 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

False-Negative Results

- Technical or clerical error
- Tampering with urine sample
  - Dilution
  - Substitution
  - Adulteration


Dilution

- Most common method – many “cleansing” teas and products available on line, including Vit B to restore color to avoid diluted appearance
- 40oz of water intake under 3h
- 8oz of water under 30min
- Measure Cr
- Measure specific gravity

Substitution

- Another person’s urine
- Synthetic urine
- Animal urine
Adding chemicals to a urine sample after voiding to mask the presence of illicit or prescription drugs

- Household products: bleach, vinegar, lemon juice, dish soap, drain cleaners, ammonia, hydrogen peroxide, Visine, table salt, pectin
- Commercial products: glutaraldehyde, sodium and potassium nitrate, peroxide and peroxidase, pyridinium chlorochromate (PCC)
- Marijuana is the most masked ingredient

Adulteration Products Are Many

- Klear, Whizzies, Urine Luck – not detected by traditional specimen integrity tests
- Mary Jane SuperClean 13, Instant Clean ADD-IT-ive
- UrinAid, Amber 13, THC-Free, Randy’s Clear
- LL418, Sweet Pee’s Spoiler, Stealth
False-Positive Results on Screening

- **Marijuana** - PPIs (especially pantoprazole -Protonix), ASA, baby wash/soaps, ibuprofen, naproxen
- **Opioids** - quinolone antibiotics (levofloxacin, ofloxacin), verapamil, procaine, rifampin and tonic water (quinine), dextromethorphan, diphenhydramine
- **Tramadol** - venlafaxine (Effexor)
- **PCP** – lamotrigine, tramadol, venlafaxine

**References**

False-Positive Results on Screening

- **Amphetamines** – amantadine, bupropion, desipramine, ephedrine, Vicks inhaler, metronidazole, selegiline, ranitidine, promethazine, trazodone
- **Benzodiazepines** – chlorpromazine, fenoprofen, flurbiprofen, indomethacin, sertraline, efavirenz
- **Barbiturates** – ibuprofen, naproxen, phenytoin
- **Fentanyl** – trazodone

**False-Positive Results on Screening**

- **Methadone** – clomipramine, chlorpromazine, diphenhydramine, olanzapine, quetiapine, tapentadol, verapamil, thioridazine
- **Phencyclidine (PCP)** – dextromethorphan, diphenhydramine, ibuprofen, imipramine, ketamine, lamotrigine, meperidine, thioridazine, tramadol, venlafaxine
- **Tricyclic Antidepressants** – carbamazepine, cyclobenzaprine, cyproheptadine, diphenhydramine, hydroxyzine, promethazine, quetiapine
False-Positive Results on Screening

References

• Allen KR. Interference by venlafaxine ingestion in the detection of tramadol by liquid chromatography linked to tandem mass spectrometry for the screening of illicit drugs in human urine Clin Toxicol (Phila) 2006;44(2)
• Christo PJ, Manchikanti L, Ruan Xet al. Urine drug testing in chronic pain. Pain Physician 2011;14:175-87
Studies repeatedly demonstrated that urine drug concentrations MAY NOT be interpreted to determine the amount of drug taken, when the last dose was administered or the source of the drug.

UDS cannot reliably determine whether a pt. is abusing the prescribed medication, has reached a toxic level, has hoarded or binged, taken more than prescribed, or diverted the prescription while taking a few doses before the test.

***Cone EJ, Caplan YH. Urine toxicology testing in chronic pain management Postgrad Med. 2009;121(4):91-102
Pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body) are too complex.

Blood level does not correlate with therapeutic response.
Serum blood levels do not correlate with CNS levels.
Genetic variations in receptor subtypes and P-450 system.
P- Glycoprotein transporter activity.
Drug tolerance.

Therapeutic blood levels are not established for BZs and opiates.

Morphine blood levels are very low due to its hydrophilicity.

Morphine drug testing in urine is, as a rule below 100mg/ml cut off.

Morphine in oral fluid is even lower.

Parental drug frequently is not detectable in the urine due to metabolism, so frequently it is impossible to say which BZ was ingested.

<table>
<thead>
<tr>
<th>Parent Drug</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>alpha-hydroxy-alprazolam</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>7-amino-clonazepam</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>2-hydrohethyl-flurazepam</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>Lorazepam glucuronige</td>
</tr>
</tbody>
</table>

*Substance Abuse and Mental Health Service Administration, Drug Testing Advisory Board meeting, October 2012. National Forensic Laboratory Information System (NFLIS) reports*
Benzodiazepines’ Metabolism

Chlordiazepoxide
Chlorazepate
Nordiazepam
Diazepam
Temazepam
Oxazepam
Testing for Alcohol

- Majority of ethanol testing is done in blood
- Ethanol in urine 7-8h
- Maybe positive due to post collection fermentation (diabetes, Candida) – up to 1/3 of positives caused
- UDS is not admissible as legal evidence of intoxication due to lack of correlation between amount ingested and urine concentration
- Ethyl Glucuronide (EtG) and Ethyl Sulfate (EtS) are metabolites – in urine in 1h and up to 1-5 days

- Foley KF. A Positive Urine Alcohol with Negative Urine Ethyl-Glucuronide. Lab Med. 2018 Jul 5;49(3):276-279
Hand sanitizer does not contribute to EtS levels above 100ng/ml.

Ingestion of an active baker’s yeast combined with sugar may result in high EtS and EtG concentration.

2l apple juice, 1,320g sauerkraut, 690g bananas – produce levels below 500ng/ml of EtS and EtG.

Mouthwash – produce level below 500ng/ml of EtS and EtG.

Grape juice contains EtS and ethanol.

Nonalcoholic beverages contain alcohol (up to 0.5 vol %).

Before passive exposure could result in positive urine tests, the atmosphere has to become so saturated with marijuana smoke that subjects have to wear goggles to protect their eyes; the smoke is also strongly irritating the nose and throat.

Ventilation of any sort prevents positive tests for passive subjects.

Such an exposure is not “passive” as individuals must actively force themselves to remain in the smoke saturated atmosphere to test positive.

The same works for oral fluid

*Lee D1, Huestis MA. Current knowledge on cannabinoids in oral fluid. Drug Test Anal. 2014 Jan-Feb;6(1-2):88-111
*Cone EJ. Marijuana effects and urinalysis after passive inhalation and oral injection. NIDA Res Monogr. 1990;99:88-96
• A myriad of synthetic compounds which are active at cannabinoid receptors

• Introduced in 2004, first reported in the US in 2008, not scheduled before 2011, smoked or ingested, frequently contaminated

• Structurally unrelated to marijuana

• High number of compounds and ever-changing nature of these substances results in detection of some, but not all spice products


Testing for Synthetic Cathinones

Gundersen POM, Spigset O, Josefsson M. Screening, quantification, and confirmation of synthetic cannabinoid metabolites in urine by UHPLC-QTOF-MS.
Drug Test Anal. 2018 Jul 11
Testing for Synthetic Cathinones (Bath Salts)

- Inhalation, oral ingestion, or injections
- Sold under the guise of plant food, jewelry cleaner, etc.
- Derivatives of khat, East African plant
- Abused in Europe since 2009 and the US since 2010
- Stimulants similar to cocaine, methamphetamine and ecstasy
- False positive for meth on immunoassays
- Period of detection in urine 5 days


*German CL, Fleckenstein AE Hanson GR. Bath salts and synthetic cathinones: an emerging designer drug phenomenon. Life Sci 2013
Testing for Cotinine (Nicotine Metabolite)

- In blood 1-3 days depending on usage
- T1/2 18-20h (vs. 2-4h of nicotine)
- In urine 2-4 days and longer
- Not quantitative
- Passive exposure gives concentration below 500ng/ml

Thank You
Additional References

* Park-Lee E, Lipari RN, Hedden SL, Kroutil LA, Porter JD. Receipt of Services for Substance Use and Mental Health Issues Among Adults: Results from the 2016 National Survey on Drug Use and Health. CBHSQ Data Review. Rockville (MD): Substance Abuse and Mental Health Services Administration (US)


* Karjalainen K, Lintonen T. DUI offenders may have multiple health and social problems - doctors play a central role in monitoring the use of medications affecting the central nervous system. Duodecim. 2017;133(10):927-34. Review
* Madry MM, Kraemer T, Baumgartner MR. Systematic assessment of different solvents for the extraction of drugs of abuse and pharmaceuticals from an authentic hair pool. Forensic Sci Int. 2018 Jan;282:137-143