

# Utilization of the urine drug screen: The good, the bad, and the ugly

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## Learning Objectives

- Describe the utility of the urine drug screen in clinical practice
- Describe the utility of the urine drug screen in the evaluation of the drug endangered child
- Discuss the limitations of the urine drug screen and what it cannot provide

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## Drug Testing

- Use has increased in past decade
  - Health care
  - Criminal justice
  - Workplace (pre-employment, random)
  - Military
  - Athletics

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**Misinterpretations**

- Can have serious consequences of test is in accurate or misused
  - Unjust termination from job
  - Risk of prison sentence
  - Inappropriate exclusion from sporting event
  - Inappropriate medical treatment in emergencies

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**Methods of Drug Testing**

- Urine, blood, hair, saliva, sweat and nails
  - Urine is preferred test due to ease of collection
  - Urine allows for higher concentrations of drug and metabolites and longer detection times (exception: hair)
- Each provide different levels of specificity, sensitivity and accuracy

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**Background**

- Diagnosis should be made on a clinical basis
- Laboratory should only be used to aid diagnosis not as tool for diagnosis
- Tests must be:
  - analytically valid
  - clinically reliable
  - applied correctly to monitor, diagnose or screen
  - useful

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**Toxicology Screens**

- Limited utility and should be used only when diagnosis is unknown
- Methods
  - chromatography
  - immunoassay
  - chemical ("spot") tests
  - spectrometry

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**A UDS means different things to different folks**

- Spot tests (ASA, phenothiazines)
- Immunoassays (codeine-morphine, benzo metabolites, amphetamine-meth, methadone, PCP, ethanol, cocaine metabolites, barbs)
- TLC for 30-60 drugs
- GC (or GC/MS) for >100 drugs
- Some drugs not detected by any means

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**Immunoassays**

- Ease of automation, rapid turnaround, and adaptability for use in ER
- Drug-specific antibodies bind to drug in patient's sample or known concentration of "labeled" drug
- Measure about 12 different drugs in serum and >10 classes or specific drugs in urine
- Should be confirmed by GC/MS as false positives are common

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## What are Antibodies and Antigens?

- Antibodies are a type of protein produced in the immune system in response to a foreign substance (antigen)
- Antibodies bind to the antigen responsible for their production

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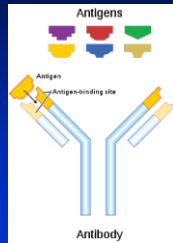
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## Immunoassay Principles I

- **Antibodies:**
  - Usually harvested from sheep or rabbits
  - Developed against classes of drugs
  - Recognize the antigen (drug) by its shape




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## Immunoassay principles II

- Test with antibody on it
- Add urine sample
- Wait
- Drug binds to antibody if structure similar to original antigen
- Colormetric change if above threshold positive




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**Testing with Immunoassays**

- Used to screen donor specimens for the possible presence of a drug or class of drugs
- May be conducted on-site as part of the collection process or in a laboratory or other facility
- On-site testing is called Point of Care Test (POCT)

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**Immunoassay Specificity**

- Specificity is the affinity of an immunoassay for the target drug
- Specificity is measured by cross reactivity
  - The response exhibited when an immunoassay reacts with a compound other than the target drug
- Specificity limits the conclusions that can be drawn from immunoassay results

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**Low Specificity**

- Reaction with many antigens (drugs) with similar structure
- Example: One amphetamine assay with cutoff of 300 ng/mL of D-amphetamine gives positive result with:
  - D,L-Amphetamine (300 ng/mL), Phentermine (400 ng/mL), Methamphetamine (1000 ng/mL, ephedrine (1000 ng/mL or phenylpropanolamine (1000 ng/mL)
  - A positive result from this assay would not prove use of amphetamine

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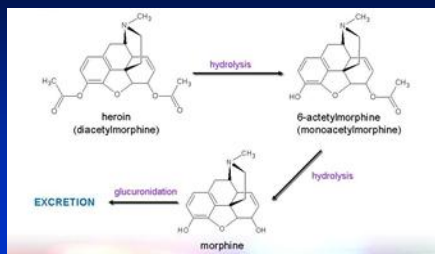
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## Heroin Metabolism




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## High Specificity

- A highly specific immunoassay will not react with similar antigens (drugs) and may not detect their presence in a donor's specimen
- Example: Immunoassay for 6-acetylmorphine (6-AM) with cutoff of 10 ng/mL will provide, in the absence of 6-AM, a positive result only when the urine specimen contains 9000 ng/mL of free morphine (free morphine = ~10 percent of total morphine)
- As a result, morphine may not be detected in urine specimens with less than 90,000 – 100,000 ng/mL of Total morphine

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## Oplate Immunoassay Cross Reactivity with Synthetic Opioids (Cutoff = 300 ng/mL Morphine)

Assay	Reported Cross Reactivity (ng/mL = positive)			
	Hydrocodone	Hydromorphone	Oxycodone	Oxymorphone
EMIT EIA	247	498	1,500	9,300
CEDIA	625	525	9,500	16,000
DRI EIA	1,700	4,000	16,000	40,000
KIMS	1,086	1,425	>75,000	Not Available

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## Benzodiazepines

- Prescription use is high
  - Alprazolam, lorazepam, clonazepam in top 25 of number of generic prescriptions
- Diversion is significant
  - Alprazolam, lorazepam, clonazepam in top 25 of number of crime lab drug seizures

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## Benzodiazepine Immunoassay Cross Reactivity (Cutoff = 200 ng/mL Benzodiazepine)

Assay	Reported Cross Reactivity (ng/mL = positive)			
	Alprazolam	Clonazepam	Diazepam	Lorazepam
EMIT EIA	65	260	44	600
CEDIA	138	188	110	208
DRI EIA	25	3,000	40	4,000
KIMS	240	540	200	674

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## Chromatographic assays

- Sensitivity is adequate for overdoses
- Thin-layer chromatography (TLC)
  - good specificity, but low sensitivity
- High-performance liquid chromatography (HPLC)
  - useful for screening classes of structurally similar drugs
- Gas chromatography (GC)
  - provides great specificity and sensitivity

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### Gas Chromatography – Mass Spectrometry

- Considered standard for confirmatory testing
- Pros
  - Able to detect small quantities of substance and confirm presence of a specific drug
  - Most accurate, sensitive and reliable method of testing
- Cons
  - Time consuming
  - Costly
  - High level of expertise is needed

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### Cutoff Limits

- DHHS established levels that define a positive level for the workplace
  - Designed to eliminate false positives
  - Below cutoff are reported negative (increased false negative)
  - Controversial role in other settings (eg. health care, substance abuse programs)
- Developed for adults (not appropriate for pediatrics)

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TABLE 1. Federal Workplace Cutoff Values<sup>a</sup>

Substance	Initial drug test level (immunoassay) (ng/mL)	Confirmatory drug test level (GC-MS) (ng/mL)
Marijuana metabolites <sup>b</sup>	50	15
Cocaine metabolites <sup>c</sup>	300	150
Opiate metabolites	2000	2000
Phencyclidine	25	25
Amphetamines	1000	500
Methamphetamine <sup>d</sup>	Incomplete data	500

<sup>a</sup> GC-MS = gas chromatography-mass spectrometry.  
<sup>b</sup> Delta-9-tetrahydrocannabinol-9-carboxylic acid.  
<sup>c</sup> Benzoylcegonine.  
<sup>d</sup> Specimen must also contain amphetamine at a concentration greater than or equal to 200 ng/mL.

Mayo Clin Proc. 2008; 83: 66-76

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TABLE 2. Length of Time Drugs of Abuse Can Be Detected in Urine

Drug	Time
Alcohol	7-12 h
Amphetamine	48 h
Methamphetamine	48 h
Barbiturate	
Short-acting (eg, pentobarbital)	24 h
Long-acting (eg, phenobarbital)	3 wk
Benzodiazepine	
Short-acting (eg, lorazepam)	3 d
Long-acting (eg, diazepam)	30 d
Cocaine metabolites	2-4 d
Marijuana	
Single use	3 d
Moderate use (4 times/wk)	5-7 d
Daily use	10-15 d
Long-term heavy smoker	>30 d
Opioids	
Codeine	48 h
Heroin (morphine)	48 h
Hydrocodone	2-4 d
Methadone	3 d
Morphine	48-72 h
Oxycodone	2-4 d
Propoxyphene	6-48 h
Phencyclidine	8 d

Mayo Clin Proc. 2008; 83: 66-76

### Evaluation of Urine Samples

- Adulterating, substituting, and diluting are common practice
- Specific characteristics of urine
  - Appearance and color
  - Temperature (taken within 4 minutes of collection) should be 32-38 degrees C.
  - pH should be between 4.5-8
  - Specific gravity between 1.002 -1.020
  - Urine creatinine greater than 20 mg/dL
  - Urine nitrite levels less than 500 mcg/mL

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TABLE 3. Summary of Agents Contributing to Positive Results by Immunoassay

Substance tested via immunoassay	Potential agents causing false-positive result	Substance tested via immunoassay	Potential agents causing false-positive result
Alcohol <sup>19</sup>	Short-chain alcohols (eg, isopropyl alcohol)	Cannabis <sup>19,20,21</sup>	Dronabinol Elixance
Amphetamines <sup>19,21</sup>	Amantadine	Cocaine <sup>19,21</sup>	Herp-containing foods
	Benzphetamine		NALDs
	Bupropion		Proton pump inhibitors
	Chlorpromazine		Tolazoline
	Clobazam <sup>2</sup>		Coca leaf tea
	-D-Deprenyl <sup>2</sup>		Typical anesthetics containing cocaine
	Desipramine <sup>2</sup>		Dextromethorphan
	Dextroamphetamine		Diphenhydramine <sup>6</sup>
	Ephedrine		Etosia
	Enoxiprone <sup>3</sup>		Opates (codeine, hydrocodone, hydrocodone, morphine)
	Isocarboxipazine	Poppy seeds	
	Isosipazine	Quinine	
	Labetalol	Quinolones	
	MDMA	Sulfamylon	
	Mefenorex <sup>2</sup>	Verapamil and metabolites <sup>6</sup>	
	-1-Methamphetamine (Vick's inhaler) <sup>2</sup>	Dextromethorphan	
	Methylphenidate	Diphenhydramine <sup>6</sup>	
	Phentermine	Doxylamine	
	Phenylephrine	Propofol	
	Phenylpropranolamine	Isoprenaline	
	Proparacaine	Ketamine	
	Propoxyphene	Meprobamate	
	Ranitidine	Mercurazine	
	Ratidone	Thioridazine	
	Selenazine	Tramadol	
Thioridazine	Vedolizine, O-desmethylnaloxone		
Trifluoperazine	Carbamazepine <sup>6</sup>		
Timololol	Cycloheximide		
Tizanidine	Cyproheptadine <sup>7</sup>		
Tizanidine	Diphenhydramine <sup>6</sup>		
Tizanidine	Hibiscus <sup>10</sup>		
Tizanidine	Quinine		
Benzodiazepines <sup>19,21,22</sup>	Sertraline		

Mayo Clin Proc. 2008; 83: 66-76

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## Clinical Utility

- Tox screens have little usefulness
  - diagnosis and management decisions made before results are back
  - diagnostic interventions may aid diagnosis
  - few antidotes available
  - low morbidity
  - toxicity apparent on presentation

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## Case 1

- 1 day old in newborn nursery found to have positive urine cannabinoids with negative meconium.
- Mom denies any exposure during pregnancy (herself and environment)

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TABLE 3. Summary of Agents Contributing to Positive Results by Immunassay\*

Substance tested via immunassay	Potential agents causing false-positive result	Substance tested via immunassay	Potential agents causing false-positive result
Alcohol <sup>10</sup>	Short-chain alcohols (eg, isopropyl alcohol)	Cannabinoids <sup>10,11,16</sup>	Dronabinol Elixacin Hemp-containing foods NADA's Proton pump inhibitors Tobacco
Amphetamines <sup>10,11</sup>	Amantadine Benzphetamine Bupropion Chlorpropamide Clobetasol <sup>17</sup> -Dopexyl <sup>17</sup> Desipramine <sup>18</sup> Dextroamphetamine Ephedrine Fenproporex <sup>19</sup> Isosorbepine Isotretinoin Labetalol MDMA Mefenbutamine -Methamphetamine (Vick's inhaler) <sup>16</sup> Methylphenidate Phentermine Phenylephrine Pseudoephedrine Propylthiouracil Ranitidine Ritalin Sibutramine Thioridazine Tizanidine Tramadol Tramadolacetamide Tropisetron Oxycodone Sertraline	Cocaine <sup>10</sup> Opioids, opiates, and heroin <sup>10,11,12</sup> Phencyclidine <sup>10,11,15</sup> Tricyclic antidepressants <sup>10,11</sup>	Cocaine <sup>10</sup> Cocaine free base Typical anesthetics containing cocaine Dextromethorphan Diphenhydramine <sup>18</sup> Eicos Opiates (codeine, hydrocodone, hydrocodone, morphine) Poppy seeds Quinine Quinolones Etilupin Verapamil and metabolites <sup>16</sup> Dextromethorphan Diphenhydramine <sup>18</sup> Doxylamine Propofol Imipramine Ketamine Meperidine Meperidine Theoracine Tramadol Venlafaxine, O-desmethylvenlafaxine Carbamazepine <sup>17</sup> Cyclobenzaprine Cyclopropylamine <sup>17</sup> Diphenhydramine <sup>18</sup> Hydroxyzine <sup>18</sup> Quartipine
Benzodiazepines <sup>10,11,12</sup>			

Mayo Clin Proc. 2008; 83: 66-76

## Case 1 continued

- Review of mother's and baby's drug history did not reveal any known cross-reacting agents.
- Urine sent for confirmation
- Evaluation of nursery found that more babies in past 6 months had positive urine THC
- Discussion found nursery specific factors in sample collection

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Interference of various commercial soaps with the cannabinoid immunoassay.

Commercial soaps	Apparent cannabinoids (µg/L)	Interference <sup>a</sup>	Fold change
Drug-free urine	<5.0		
J&J Head to Toe	16.2	+ 11.2	3.24
J&J Bedtime Bath	25.2	+ 20.2	5.04
CVS Night-Time Baby	27.3	+ 25.3	5.46
CVS Baby Wash	15.8	+ 10.8	3.16
Aveeno Soothing Relief Creamy Wash	23.6	+ 18.6	4.72
Aveeno Wash Shampoo	23.4	+ 18.4	4.68
Baby Magic	18.2	+ 13.2	3.64
Hospital hand soap (Gel)	12.8	+ 7.8	2.56
Hospital hand soap (Foam)	<5.0		

<sup>a</sup> Calculated as apparent cannabinoids concentration measured-response of drug-free urine.

Cotton SW, et al. Clinical Biochemistry 2012; 45: 605-609

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## Case 2

- 3 year old female is brought to the ED by law enforcement accompanied by CPS.
- Patient was found locked in a crib in "drug home" with drug paraphenalia noted in the home.
- Patient has multiple bruises noted over body that are in different states of healing

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**Case 2 continued**

- Due to “policy”, CPS and law enforcement ask for a urine drug screen to help their case.
- Urine drug of abuse screen is performed and reported negative
- Due to this result, lesser charges are filed against parents

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**Prevalence of the positive UDS**

- Multiple studies show that drug testing in children is beneficial
  - Oral et al. Pediatric Emer Care 2011; 27: 490-495
  - Grant et al. Pediatric Emer Care 2010; 26: 10-14
- Remember the false positives!
- All must be confirmed!
- What about the false negatives or the ones that aren't done?

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**Illicit Drug Exposure in Alleged Child Abuse and Neglect**

- Children presenting to academic medical center with alleged maltreatment
- Retrospective chart review
- 665 charts met inclusion criteria
- 232 tested for illicit drugs
- 15% of population were “positive” for illicit drugs

Oral et al. Pediatric Emer Care 2011; 27: 490-495

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### Closer look....

- Urine samples were screened at by fluorescent immunoassay.
- The **positive** screening samples were sent for confirmation via gas chromatography and mass spectroscopy.
- The drugs that were screened on urine samples included marijuana, opioids, cocaine, amphetamines, barbiturates, and benzodiazepines.

Oral et al. Pediatric Emer Care 2011; 27: 490-495

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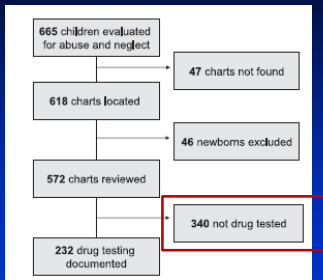
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### Closer look....



Oral et al. Pediatric Emer Care 2011; 27: 490-495

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### Closer look....

Variable	n (%)
Age <5 yr, n (%)	170 (73.3)
Age <2 yr, n (%)	130 (56.0)
Mean (SD)	50.9 (65.5)
Male sex, n (%)	123 (53.0)
Race (non-white), n (%)	32 (13.8)
Insurance status (no/public insurance), n (%)	146 (62.9)
Domestic violence, n (%)	45 (19.4)
Parental incarceration, n (%)	18 (7.8)
Single parent, n (%)	96 (41.4)
Teenage parent, n (%)	13 (5.6)
Unemployed parent, n (%)	33 (14.2)
Parental childhood abuse, n (%)	26 (11.2)
Parental report of drug abuse, n (%)	48 (20.7)
Parental drug rehabilitation, n (%)	7 (3.0)
Previous CPS involvement, n (%)	46 (19.8)
One time	26 (12.5)
Multiple times	17 (7.3)

Variable	n (%)
Long-term abuse findings	120 (55.6)
Retinal examination done	94 (40.5)
Skeletal survey done	149 (64.2)
CT/MRI* done	121 (52.2)
Skeletal survey positive	68 (29.3)
Retinal examination positive	29 (12.5)
CT/MRI positive	75 (32.3)
Drug testing positive	34 (14.7)

Variable	Odds of Positive Drug Test (95% CI)	P
Insurance status (no vs public insurance)	4.49 (1.47-13.66)	0.008
Clinical presentation (physical maltreatment)	6.70 (1.26-35.49)	0.026
Domestic violence	2.81 (1.08-7.39)	0.034
Parental drug abuse history	3.42 (1.38-8.46)	0.008

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### **Environmental Factors**

- Study assessing attention in 5-12 year olds
- Three groups: environmental deprivation alone (low SES), moms/dads with heroin dependency, control group with average SES
- Children born to parents with heroin dependency and those with low SES showed intellectual impairment on verbal and performance skills and reading and arithmetic skills.

Ornoy A, et al. Develop Med and Child Neuro. 2001; 43: 668-675

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### **Environmental Factors, cont.**

- Children born to heroin addicted mothers but adopted out at young age had normal intellectual and learning abilities, except for slight decrease on intelligence scales
- High rate (and similar rates) of ADHD to those born to heroin mothers kept at home, those adopted out, and those in low SES
- Highest rate of ADHD was in children born to heroin mothers and kept at home (twice other groups)

Ornoy A, et al. Develop Med and Child Neuro. 2001; 43: 668-675

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### **Conclusions**

- Relying on immunoassays is fraught with problems due to false positives and false negatives
- All positive immunoassays MUST be confirmed by GC-MS
- Need frank discussions with policy makers about false negatives and that environment plays a bigger role than whether drug screen is positive or not

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