

Struggles with Urine Drug Screens

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Disclosures

- Dr. Karen Moeller has no conflicts of interest to declare
- No off-label indications of medications will be discussed

Learning Objectives

1. Compare and contrast the different drug screening modalities.
2. State substances that can be tested for in a urine drug screen (UDS) and other testing modalities.
3. Identify issues with false positive and negative results in drug screens.
4. Interpret drug screen results and determine the possible limitations including the possibility of adulterations of the sample and inability to test for all illicit substances.
5. Redesign treatment plan based on drug screen results.

Patient Case - JR

- JR, a 48 year-old woman, with a history of chronic back pain (work related injury 3 years prior) presents for a routine follow-up visit and for changes in her pain medications. You first met the patient 9 months ago, at which time you reviewed past medication trials, spine films and ruled out any surgical interventions. Hydrocodone/acetaminophen was started at that time.
- PMH: hypothyroidism, anxiety, chronic pain
- Current Medication:
 - Escitalopram 20 mg PO daily
 - Levothyroxine 125 mcg PO daily
 - Clonazepam 0.5 mg PO HS PRN sleep/anxiety
 - Hydrocodone/acetaminophen 5/325 mg- 1 tablet every 6 hours PRN pain
- Behavior: Restless and anxious more than usual

Patient Case - JR

1. Should we order a drug test on this visit?
2. If so, what type of specimen do you want to test (e.g. blood, hair, urine, etc.)?

Prescription Monitoring Program Results		
	Jayhawk Pharmacy	
7/8/18	Hydrocodone/acetaminophen 5/325 mg - #120 Clonazepam 0.5 mg - #90	Insurance
6/10/18	Hydrocodone/acetaminophen 5/325 mg - #120	Insurance
5/12/18	Hydrocodone/acetaminophen 5/325 mg - #120	Insurance
4/15/18	Hydrocodone/acetaminophen 5/325 mg - #120 Clonazepam 0.5 mg - #90	Insurance
3/18/18	Hydrocodone/acetaminophen 5/325 mg - #120	Insurance
2/16/18	Hydrocodone/acetaminophen 5/325 mg - #120	Insurance
	Hospital Pharmacy	
6/5/18	Hydrocodone/acetaminophen 5/325 mg - #10	Cash

Reasons to Order Drug Testing

Pain Patients (non-cancer)

- Pain guidelines recommend periodic UDS
- New patients
- Medications or dosage changes
- Behavioral or appearance changes
- Request specific medications

Hospital/Clinic Settings

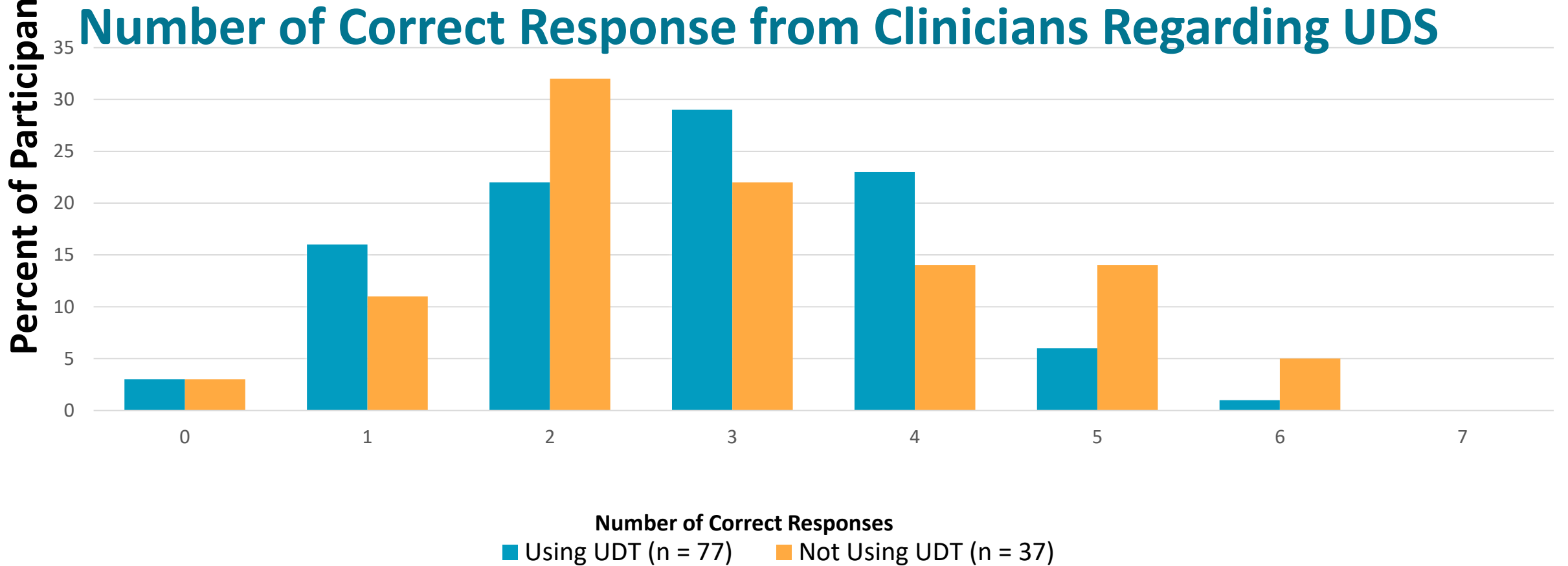
- Assist in diagnosis
- Suspected overdose
- Recent mental status changes
- Bizarre behavior
- Patient presents with trauma
- Compliance with medications or diversion

Before you order, you need

- Detailed medication history
 - Prescription
 - Over-the-counter/ Herbal preparation
- Documentation of last use
- Knowledge of urine drug test
 - Medications you can test for
 - Metabolites of medications
 - Medications that can cross-react
 - Laboratory's cutoff levels

Clinicians Knowledge

• Research has shown lack of knowledge in clinicians' ordering UDS

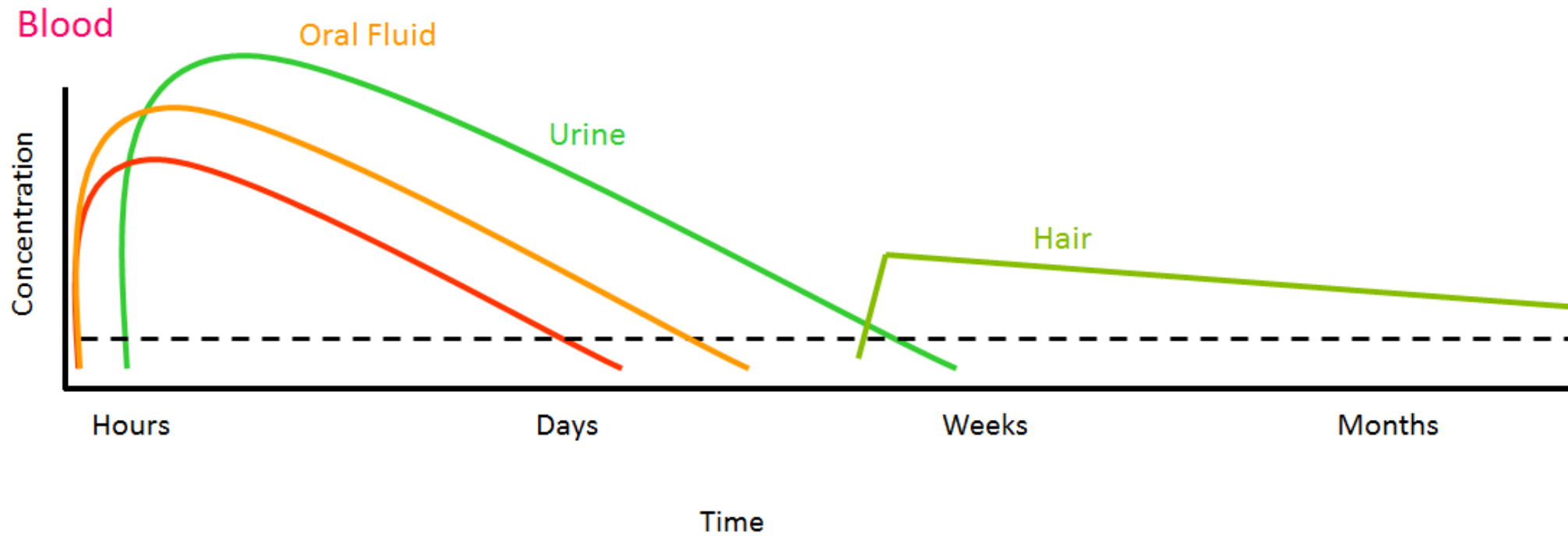
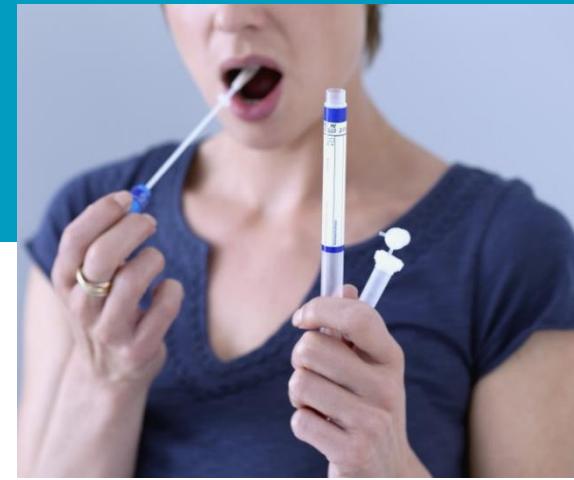


Common Drugs Tested in the Urine

- Federal Workplace Guidelines
 - Amphetamine
 - Cocaine
 - Marijuana
 - Opiates
 - Phencyclidine (PCP)
- Additional Drugs
 - Benzodiazepines
 - Barbiturates
 - Oxycodone
 - Methadone
 - Fentanyl
 - Buprenorphine
 - TCA
 - Designer Drugs
 - Muscle relaxers

Specimens for Drug Testing

- Blood
- Hair
- Oral fluid
- Sweat
- Urine
- Others



Patient Case - JR

- A point of care drug test was preformed in the clinic with the following results

Drug	Result
Amphetamine	NEG
Benzodiazepine	NEG
Cocaine	NEG
Opiates	NEG
Oxycodone	NEG
PCP	NEG
THC	POS



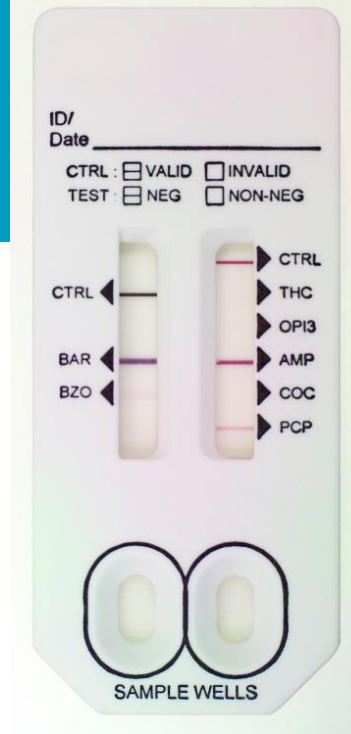
- What do you make of these negative results for her prescribed medications?
- How do you want to proceed with this patient?

Urine Drug Testing Methods – Immunoassay

- Laboratory based or point-of-care
- Mass screening, inexpensive, rapid
- **Screening purposes only (present or not)**
 - Most look for drug metabolites
 - Qualitative not Quantitative
- **“Presumptive results” until confirmed**
- Many types of Immunoassays
 - Enzyme-multiplied immunoassay technique
 - Enzyme-linked immunosorbent assay (ELISA)
 - Fluorescence polarization immunoassay

Point of Care Testing (POCT)

- Immediate results
- Inexpensive
- Visual interpretation allows for subjective interpretation
- Same limitation with laboratory immunoassays
- Still need support for
 - Quality assessment
 - Personnel training
 - Documentation

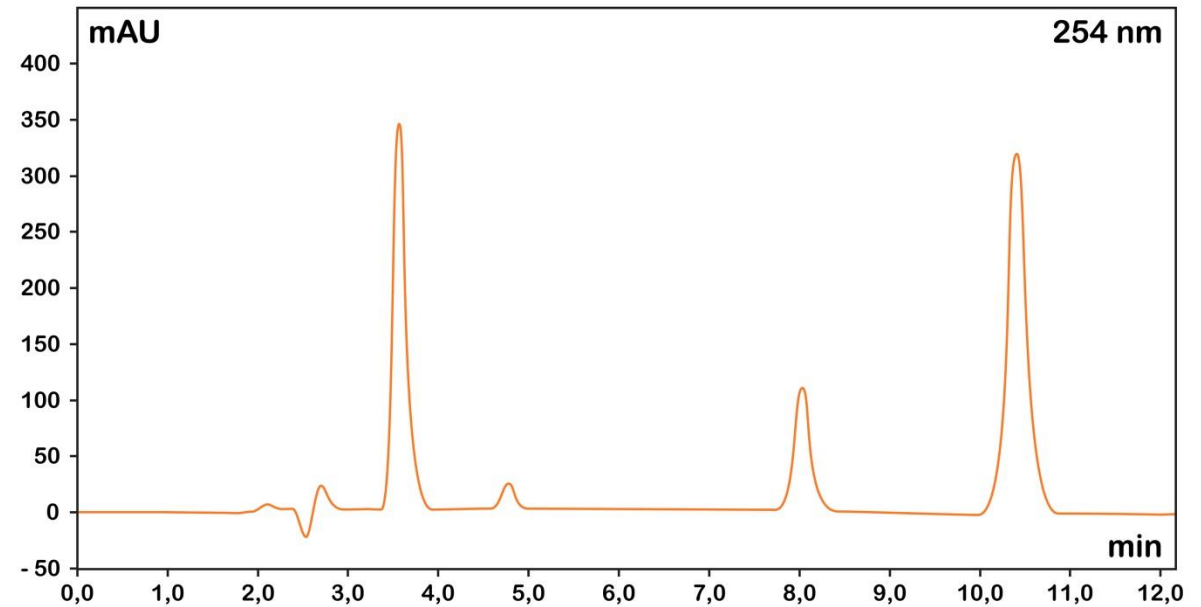


Percentage of False Positives and Negatives on POCT

	False Positive	False Negatives
Benzodiazepines	61%	35%
Opioids	22%	29%
Amphetamines	21%	43%
Marijuana	21%	20%
Cocaine	12%	40%

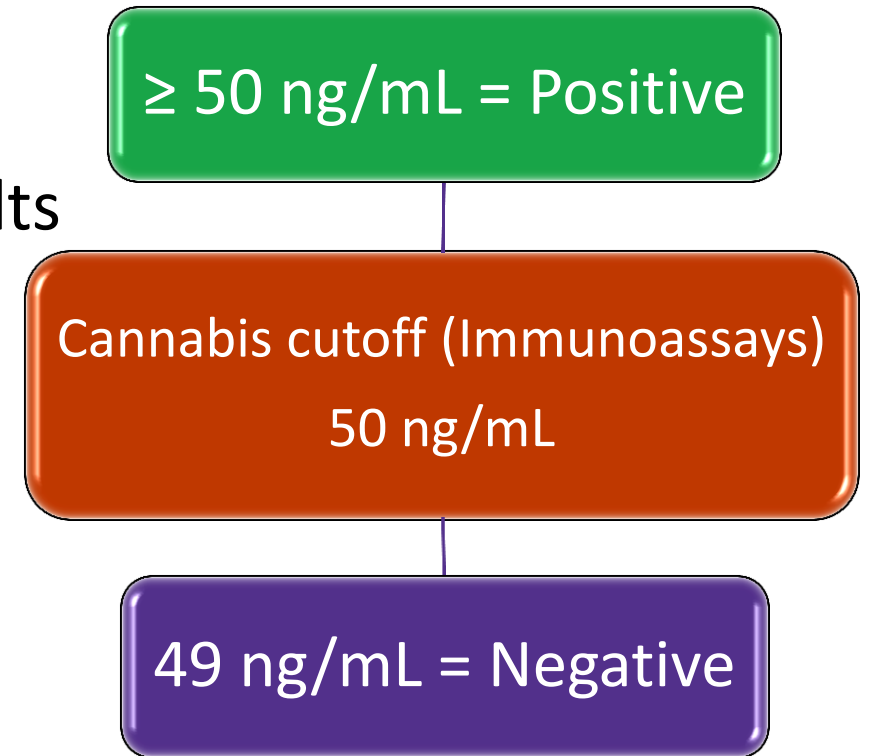
Laboratory-based specific drug identification

- Confirmation test – most accurate
- Gas chromatography/mass spectromet
- Liquid chromatography/mass spectrom
- Liquid chromatography –tandem mass



Cutoff Values

- Federal cutoff limits are designed for workplace
- Suppose to help eliminate false-positive results
- High cutoff values may cause false negatives results
- Different labs can use different cutoff values
- Many pain panels use much lower cutoff values



Always know your lab's cutoff values before interpreting UDS

Federal Workplace Cutoff Values

Initial test analyte	Initial Drug Test Level (Immunoassay) (ng/mL)	Confirmatory test analyte	Confirmatory Drug Test Level (GC-MS) (ng/mL)
Marijuana metabolites	50	*Delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH)	15
Cocaine metabolites	150	Benzoyllecgonine	100
Opiate metabolites			
Codeine/Morphine	2000	Codeine/Morphine	2000
6-Acetylmorphine	10	6-Acetylmorphine	10
Phencyclidine	25	Phencyclidine	25
Amphetamine/Methamphetamine	500	Amphetamine	250
		Methamphetamine	250
MDMA	500	MDMA	250
		MDA	250
		MDEA	250

Detection Time in the Urine

Substance	Length of time
Amphetamine	48 h
Benzodiazepines Short-acting (eg, lorazepam) Long-acting (eg, diazepam)	3 days 30 days
Cocaine metabolites	2 – 4 days
Marijuana Single use Moderate use (4 times/week) Chronic heavy smoker	3 days 5-7 days 30 + days

Detection Time in the Urine

Substance	Length of time
Opiates Screen	
Codeine	48 hours
Heroin (detected as Morphine)	48 hours
Hydromorphone	2-4 days
Morphine	2-3 days
Oxycodone	2-4 days
Methadone	3 days
Phencyclidine	8 days

Patient Case Continued - JR

- After further interview with the patient and review of the POCT package insert you decide to send JR's urine off to the lab requesting a lower cutoff value for the opiate. A positive result is obtained on immunoassay for opiates and you request confirmation testing. You obtain the following results with GC-MS for opioids.

- What do you make of these results?

Drug	Result ng/ml
Buprenorphine	<2
Norbuprenorphine	<2
Hydrocodone	100
Hydromorphone	25
Morphine	<25
Oxycodone	<20
Oxymorphone	<20
Urine Creatine mg/dl	35

Opiates Urine Drug Screens

- The Struggles

- Many opioids will not test positive on routine
- High cutoff levels often result in false negativ
- Many clinicians do not understand common r opioids
- Few medications that cross-react with opiate



Opiate vs Opioids

Opiate

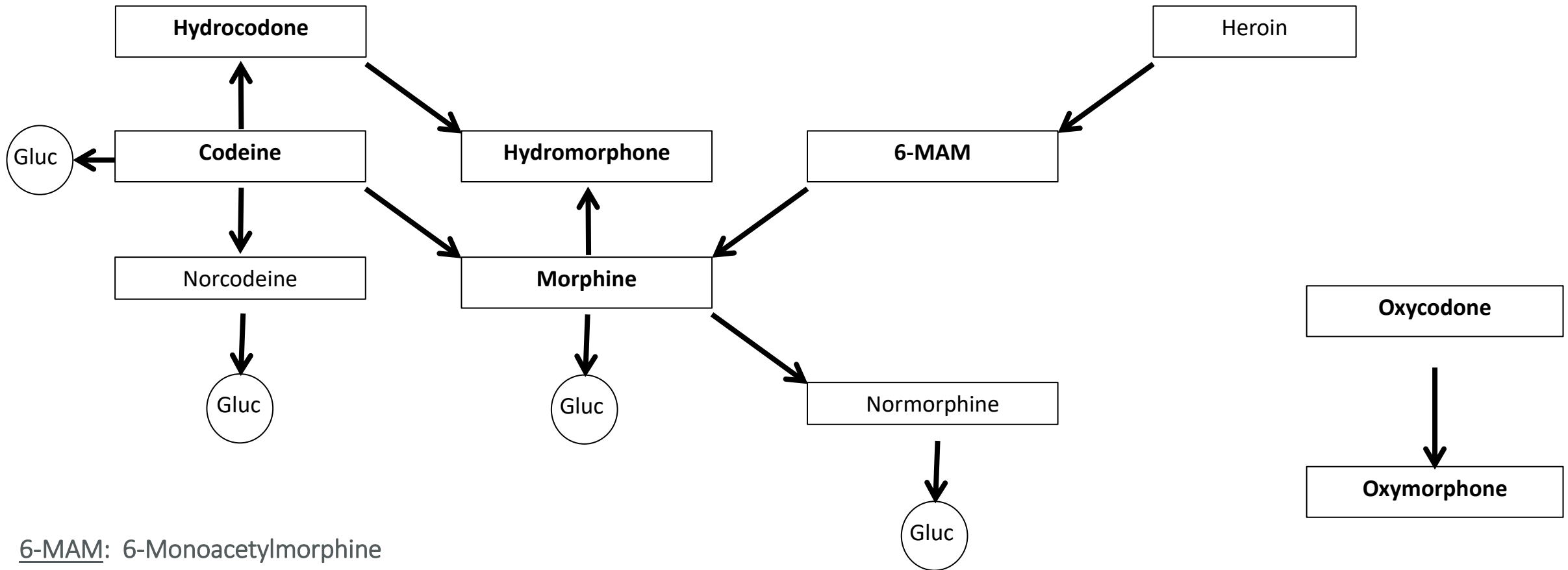
- Often used as a synonym for opioid
- Limited to the natural alkaloids from the resin of the opium poppy (e.g. codeine, morphine)
- Opiate UDS are designed to detect – morphine and codeine metabolites



Opioid

- Chemicals that bind to the opioid receptor
- Include naturally occurring (opiates), semi-synthetics (e.g. hydrocodone, oxycodone) and synthetic drugs (e.g. Methadone, fentanyl)
- Synthetic drugs and several semi-synthetic drugs (e.g. oxycodone) will test **NEGATIVE** on UDS

Opiate Metabolism



6-MAM: 6-Monoacetylmorphine
Gluc: glucuronidation

Expected Urinary Analytes

Substance	Possible Urinary Analytes
Morphine	Morphine Hydromorphone (minor metabolite)
Codeine	Codeine Morphine Hydrocodone (minor metabolite)
Hydrocodone	Hydrocodone Hydromorphone
Heroin	6- Monoacetylmorphine (6-MAM) Morphine
Oxycodone	Oxycodone Oxymorphone

Reasons for False Negative on Opiate Drug Tests

- Drug is not detected
 - Buprenorphine
 - Fentanyl
 - Meperidine
 - Methadone
 - Oxycodone
 - Oxymorphone
 - Tramadol
- Using a high cutoff value
 - Federal cutoff - 2000 ng/ml
 - Consider lowering to - 300 ng/ml
- Uses PRN, infrequently
- Rapid metabolizer

Poppy Seeds

FACT: Poppy seeds can result in positive opiate UDS

- Poppy seed bagel ~ 1 mg morphine
 - Poppy seed muffin ~ 2 mg morphine
 - Poppy seed danish ~ 6 mg morphine
 - Poppy seed streusel ~ 6 mg morphine
-
- If using a lower cutoff (300 ng/ml), high likelihood of positive results
 - Make a contract with your patients not to eat poppy seeds



Potential False Positives on Opiates and Methadone UDS

Opiates

- Fluoroquinolones
- Dextromethorphan
- Quinine
- Rifampin

Methadone

- Diphenhydramine
- Verapamil
- Doxylamine

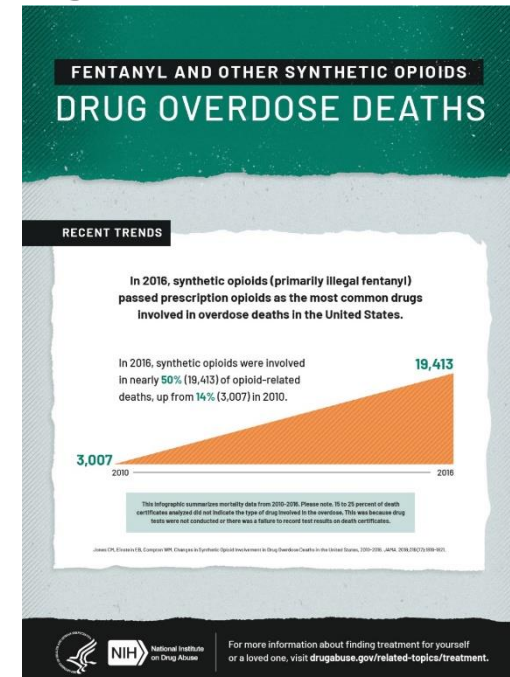
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- Baden LR, Horowitz G, Jacoby H, Eliopoulos GM. Quinolones and false-positive urine screening for opiates by immunoassay technology. *JAMA*. 2001;286(24):3115-3119.
- Rogers SC, Pruitt CW, Crouch DJ, Caravati EM. Rapid urine drug screens: diphenhydramine and methadone cross-reactivity. *Pediatr Emerg Care*. 2010;26:665-666.
- Syed H, Som S, Khan N, Faltas W. Doxylamine toxicity: seizure, rhabdomyolysis and false positive urine drug screen for methadone. *BMJ Case Rep*. 2009;2009.
- Lichtenwalner MR, Mencken T, Tully R, Petosa M. False-positive immunochemical screen for methadone attributable to metabolites of verapamil. *Clin Chem*. 1998;44:1039-1041.

Methadone Immunoassay

- Methadone excretion in the urine
 - Methadone (1/3 of the parent compound)
 - 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP)
- Most Methadone immunoassays only detect the parent compound
 - Patients can spike their urine with their methadone prescription
 - Determine if your methadone immunoassay tests for both EDDP and methadone
 - Consider GC-MS testing if suspected adulteration

Synthetic Opioids

- Illicit, non-pharmaceutical forms of opioids
 - Fentanyl or fentanyl analogues like acetyl, butyl, or furanyl fentanyl
 - 50 – 100 times more potent than morphine
- Often combined or cut with heroin, cocaine and other street drugs
- Complicates urine drug testing
 - In general synthetic opioids will not test positive for opiates screen
 - However, if cut with heroin, then a positive result will occur



Patient Case - JR

- JR's confirmatory testing is positive for marijuana (THC-COOH). She doesn't understand why you are concerned with this positive result since it is legal in your state. However, she states she does not use marijuana but was at a rock concert 3 days ago and everyone was smoking marijuana around her. Is this a reasonable explanation for her positive result?



Marijuana

- The Struggles
 - High lipid solubility and detection time
 - Passive inhalation debate
 - Cross reactivity
 - Testing for prescription THC
 - Accidental ingestion
 - Legal status



Marijuana

- Although legal in some states, still inquire about recreational and medical use
- Although state approved use- many situations still require negative results
 - Federal systems
 - Workplaces
 - Criminal justice systems
 - Schools

59%

- US population lives where THC is legal

29

- States + D.C. Medical THC

8

- States + D.C. Recreational THC

Marijuana

- Immunoassays detect many THC metabolites
 - Cutoff – 50 ng/mL
- Confirmation testing detects
 - Delta-9-tetrahydrocannabinol-9-carboxylic acid
 - Cutoff – 15 ng/mL
- High lipid solubility results in slow excretion of the drug into urine
- Unable to distinguish between acute and chronic use

- Factors that influence detection time
 - Potency
 - Frequency
 - Body mass
 - Metabolism

Marijuana	Detection Time
Single use	3 days
Moderate use (4 times/week)	5-7 days
Chronic heavy smoker	30 + days

FDA Approved Formulations of Marijuana

Dronabinol (Marinol[®])

- Synthetic form of THC
- **Positive result on UDS**
- Challenge is inability to distinguish dronabinol from plant THC

Nabilone (Cesamet[®])

- Synthetic cannabinoid (chemically similar to THC)
- **Negative result on UDS**
 - Distinct metabolites

Fraser AD, Meatherall R. Lack of interference by nabilone in the EMIT d.a.u. cannabinoid assay, Abbott TDx cannabinoid assay, and a sensitive TLC assay for delta 9-THC-carboxylic acid. *J Anal Toxicol.* 1989;13:240.

Marinol [Package insert]. Chicago, IL. AbbVie Inc, June 2016.

Levin FR, Mariani JJ, Brooks DJ, Xie S, Murray KA. Delta9-tetrahydrocannabivarin testing may not have the sensitivity to detect marijuana use among individuals ingesting dronabinol. *Drug Alcohol Depend.* 2010;106:65-68.

False Positives for Cannabis on Immunoassays

- Efavirenz

- Non-nucleoside reverse transcriptase inhibitor
- Extensively reported in the literature
- Glucuronide metabolite (EFV-8-ether glucuronide) has been attributed to causing the false-positive

- NSAIDS

- Commonly reported as a potential to cause false positives on cannabis UDS
- Rollins et al looked at 510 urine samples of patients who received NSAIDS
 - 2 false positive results
 - 1 patient who took a single dose of 1200 mg of ibuprofen
 - 1 chronic naproxen user

Oosthuizen NM, Laurens JB. Efavirenz interference in urine screening immunoassays for tetrahydrocannabinol. *Ann Clin Biochem.* 2012;49:194-196.

Rossi S, Yaksh T, Bentley H, van den Brande G, Grant I, Ellis R. Characterization of interference with 6 commercial delta9-tetrahydrocannabinol immunoassays by efavirenz (glucuronide) in urine. *Clin Chem.* 2006;52:896-897

Rollins DE, Jennison TA, Jones G. Investigation of interference by nonsteroidal anti-inflammatory drugs in urine tests for abused drugs. *Clin Chem.* 1990;36:602-606.

False Positives for Marijuana on Immunoassays

- Proton Pump Inhibitors

- 1 case report or pantoprazole
- Mechanism for interference is unknown
- Unknown if it is a class effect

- Surface contaminants

- Baby wash products used in newborns prior to urine collection caused interference
- Dose dependent effect
- Resulted in positive results at 20 ng/mL cutoff (none reach 50 ng/mL)

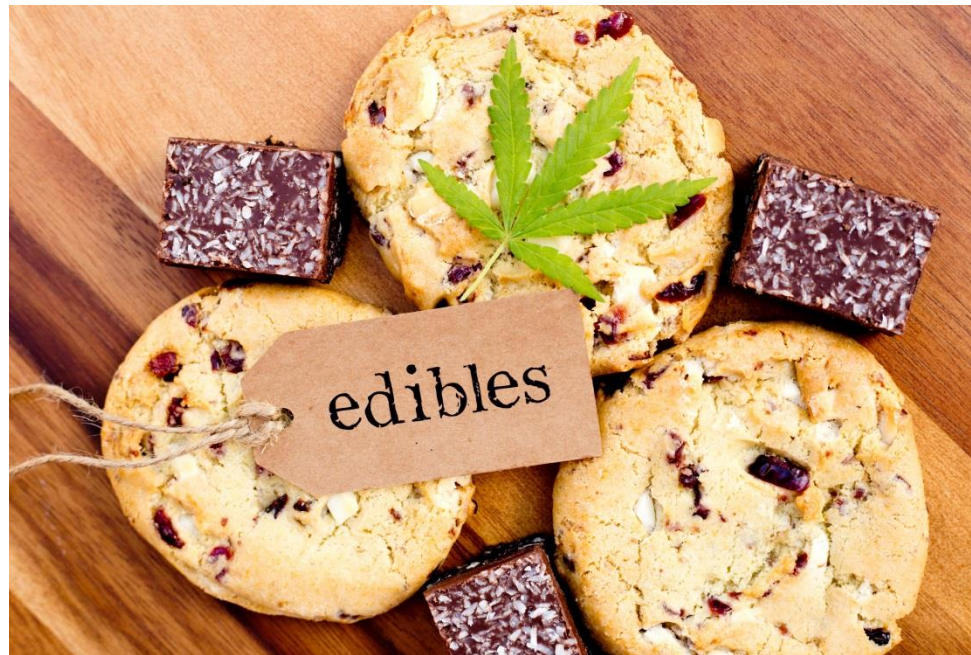
THC and Passive Inhalation

- 6 non-smokers were placed in a small room for 1 hour under 3 room conditions
 1. No air ventilation with people smoking 5.3% THC cigarettes
 2. No air ventilation with people smoking 11.3% THC cigarettes
 3. Active air ventilation with people smoking 11.3% THC cigarettes
- Only positive results were in rooms without air ventilation
 - 1 tested positive at 50 ng/mL
 - Four tested positive with a lower cutoff of 20 ng/mL
 - Detection times ranged from 2 – 22 hours post expose



Don't Forget to Rule out Accidental Ingestion

- Increasing reports of accidental ingestion since state legalization
- Consider ordering a UDS in presence of food-borne illness and unexplainable neurologic conditions
- Children and adults who have never used illicit substance may have more pronounced side effects



Patient Case Continued - JR

- Benzodiazepine confirmatory testing was also conducted. You obtain the following results:

Drug	Result ng/ml
Diazepam	<20
Nordiazepam	<20
Temazepam	<20
Oxazepam	<20
Clonazepam	30
7-Aminoclonazepam	600
Urine Creatine mg/dl	35

- What do you make of these results?

Benzodiazepines (BZD)

- The Struggles

- Metabolic pathways -inability to differentiate parent medication
- Half-lives
- Potencies
- High rates to false negatives
- No standard cutoffs

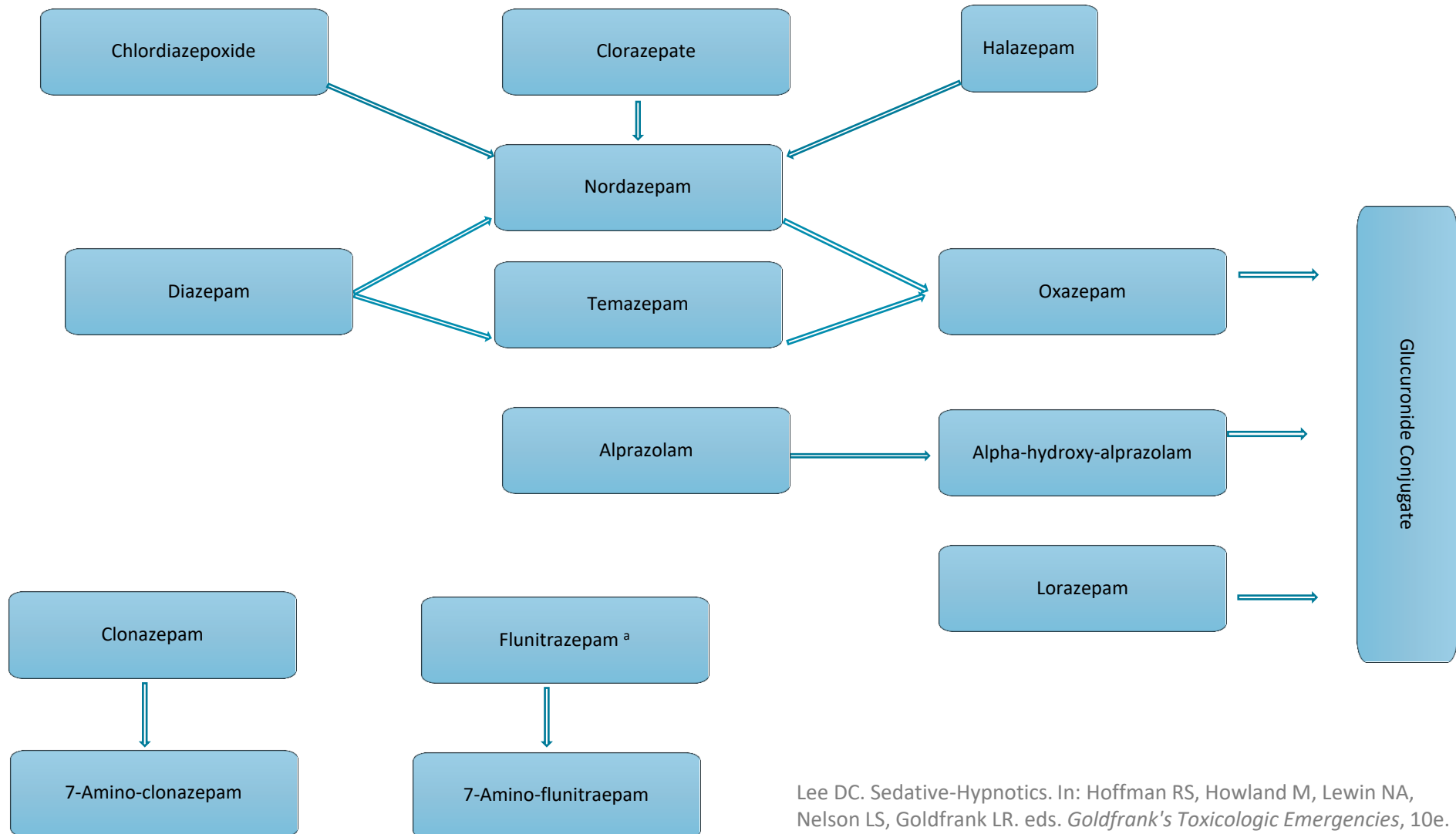


Benzodiazepines (BZD)

- Most immunoassays designed to detect unconjugated forms of oxazepam or nordiazepam
- Many BZD are excreted in glucuronide (e.g. lorazepam, alprazolam) conjugates and may not be detected
- Cutoff value of 200 or 300 ng/mL may be too high for potent BZD (e.g. lorazepam, alprazolam, triazolam)
- Clonazepam's metabolite often not detected on immunoassays

Benzodiazepines	Detection Time
Short-acting (eg, lorazepam)	3 days
Long-acting (eg, diazepam)	30 days

Basic Metabolism of Benzodiazepines



Lee DC. Sedative-Hypnotics. In: Hoffman RS, Howland M, Lewin NA, Nelson LS, Goldfrank LR. eds. *Goldfrank's Toxicologic Emergencies*, 10e. New York, NY: McGraw-Hill; 2015.

Benzodiazepines

Potential False Positives

- Minimal False Positives
 - Sertraline
 - False positive rates 27 – 32 % from 2 retrospective studies
 - Efavirenz
 - Only Triage 8 urine drug test and Drug Screen Multi 5 test.
 - Oxaprozin

Potential Negative Results

- Alprazolam
- Clonazepam
- Lorazepam

- Does not detect eszopiclone, zaleplon and zolpidem



Daypro [package insert]. New York, NY: G. D. Searle LLC, Division of Pfizer Inc; May 2016.

Zoloft [package insert]. New York, NY: Roerig a division of Pfizer Inc; August 2014.

Blank A, Hellstern V, Schuster D, et al. Efavirenz treatment and false-positive results in benzodiazepine screening tests. *Clin Infect Dis*. 2009;48(12):1787-1789.

Fraser AD, Meatherall R. Comparative evaluation of five immunoassays for the analysis of alprazolam and triazolam metabolites in urine: effect of lowering the screening and GC-MS cut-off values. *J Anal Toxicol*. 1996;20(4):217-223.

Amphetamines

- The Struggles
 - Lots of false positives (low specificity)
 - Does not distinguish between the *d* & *l* isomers (both immunoassays and chromatography)
- Immunoassay designed to detect
 - Methamphetamine  Amphetamine (*d* & *l* isomers)
 - MDMA (e.g. ecstasy)  MDA
- Confirmation tests will also test for
 - MDA and MDEA

MDA = methylenedioxyamphetamine;
MDEA = methylenedioxyethylamphetamine;
MDMA = methylenedioxymethylamphetamine;

True Positive Medications for Amphetamines

- Selegiline (Eldepryl[®])
 - Metabolized to *l*-methamphetamine
- ADHD and narcolepsy medication
 - Amphetamine (Adderall[®])
 - Methamphetamine (Desoxyn[®])
 - Dextroamphetamine (Dexedrine[®])
 - Lisdexamfetamine (Vyvanse[®])
- Vick's[®] nasal spray
 - *l*-methamphetamine
 - Negative results with twice the recommended dose

Potential False Positive Results for Amphetamines

- Amantadine
- Aripiprazole
- Bupropion
- Chlorpromazine
- Desipramine
- Ephedrine
- Isometheptene
- Labetalol
- Methylphenidate
- Phentermine
- Phenylephrine
- Phenylpropanolamine
- Promethazine
- Pseudoephedrine
- Ranitidine
- Thioridazine

Dimethylamylamine (DMAA) – dietary supplement – 92% false positive rate on Immunoassays

Cocaine

- The struggles?
 - None, highly Specificity
 - Cross-reactivity is nearly nonexistent
- UDS are designed to detect
 - Benzoylcegonine (main metabolite)
- Reasons for positive results
 - Patient used cocaine or
 - Coca leaf product
 - Use in otolaryngology/ophthalmic procedures
- False positive with Amoxicillin?
 - Reisfield et al - found no cross reactivity on 4 immunoassays
 - No literature to support this claim
- False positive with anesthetic agents (eg. benzocaine, lidocaine, procaine, tetracaine)
 - **NO**
 - These drugs are structurally distinct from cocaine and its metabolites

Phencyclidine (PCP)

- The struggles - potential false positives
- Ketamine
 - Mix data on it's cross reactivity with PCP immunoassay
- Lamotrigine
 - Based on 1 case series. Clinical history ruled out PCP use.
- Venlafaxine
 - Combined concentrations of venlafaxine and O-desmethylvenlafaxine are thought to cause cross reactivity
- Cross reactivity rates
 - Dextromethorphan 24%
 - Tramadol 22%
 - Diphenhydramine 15%

False Positive for PCP

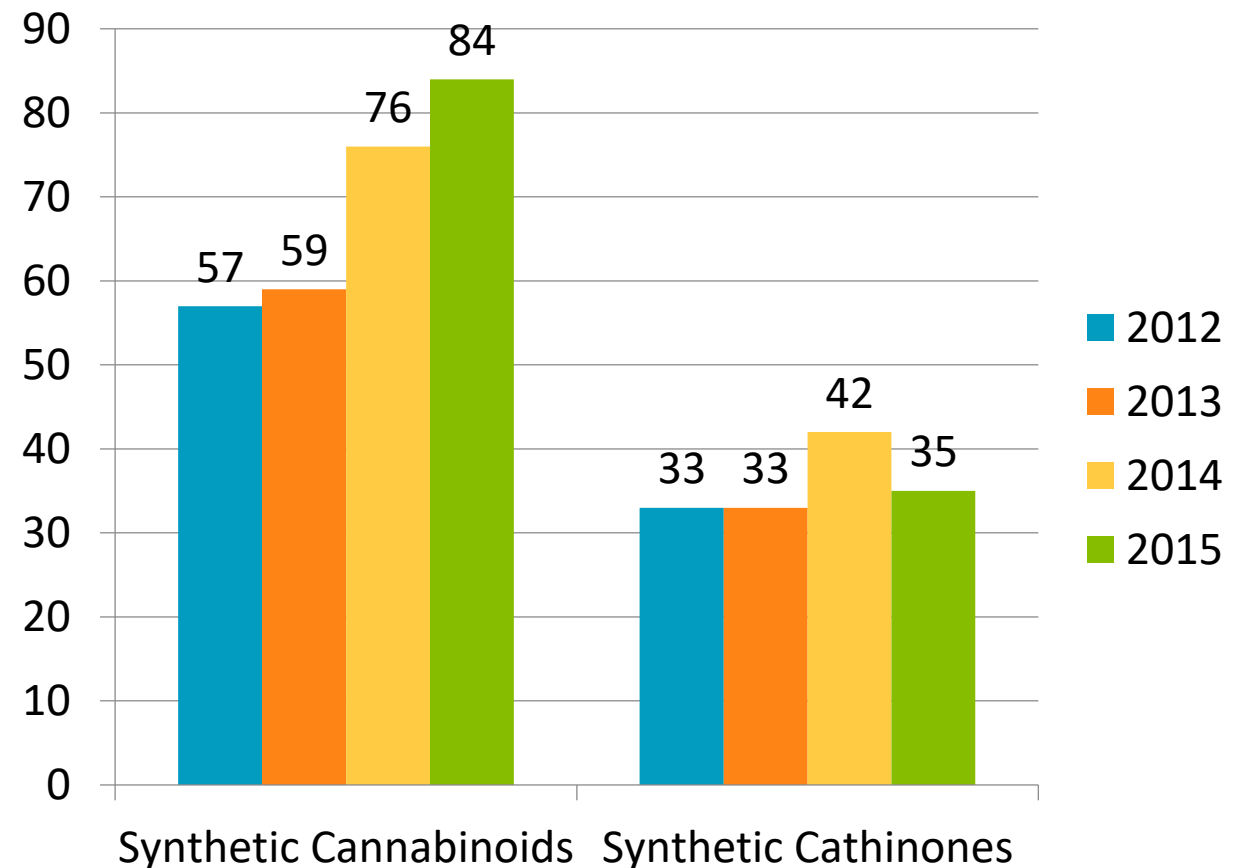
- Dextromethorphan
- Diphenhydramine
- Doxylamine
- Ketamine
- Lamotrigine
- Meperidine
- MDPV
- Thioridazine
- Tramadol
- Venlafaxine

MDPV = methylenedioxyprovalerone

Synthetic Cannabinoids and Cathinones

- Once thought of “Legal Highs”
- Difficult to detect in UDS
- Continual changes to substances
- No acceptable cutoff values

Number of Synthetic Drugs Identified by the National Forensic Laboratory Information System



Synthetic Cannabinoids

- Immunoassays and POCT testing designed to detect JWH-018 and JWH-073
 - Potential Cross-reactivity with
 - JWH-200, JWH-073 N-(3-hydroxybutyl), JWH-073 N-(4-hydroxybutyl) , JWH-019 N-(6-hydroxyhexyl) and AM-2201 N-(hydroxypentyl)
 - Hard to detect newer substances
 - PB-22, RCS-4, RCS-8, XRL-11 and AKB48
- Cutoff values range: 5 – 25 ng/mL
- Detection time: 48 – 72 hours
- Marijuana will not cross-react
- Express Diagnostic lab POCT test
 - Lamotrigine causes false positive results

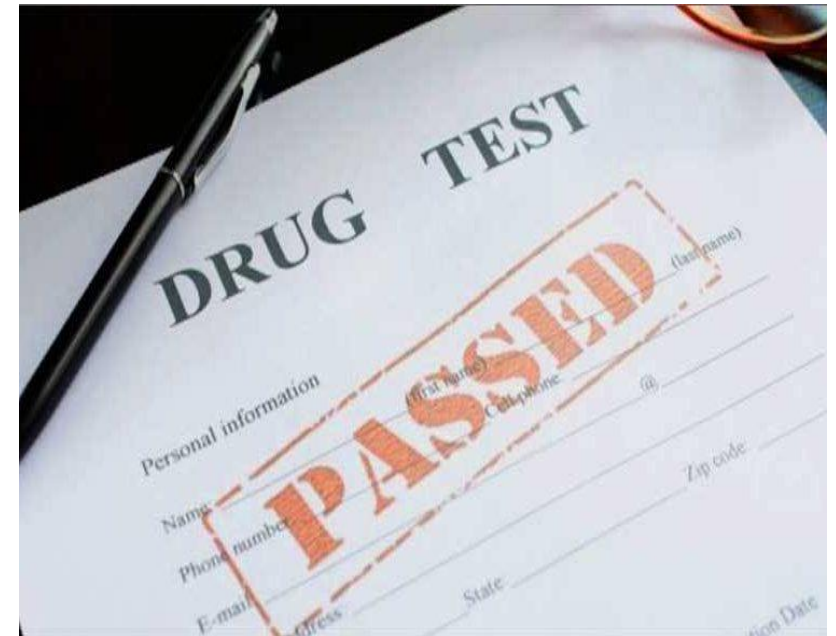
Synthetic Cathinone's

- Dopaminergic agents that increase dopamine levels higher than stimulants
- Most common compounds
 - Mephedrone
 - Methyone
 - MDPV (3,4-methylenedioxypropylone)
- Few UDS tests for synthetic cathinones
- MDPV – will cause a false positive for PCP



Unexpected Negative Results

- Patient has not recently used medication or uses PRN
- Test does not detect specific drug (e.g. synthetic opiates)
- High cutoff value
- Patient fast metabolizer
- Clerical / technical errors
- Tampering



Adulterations / Substitution

- Additives

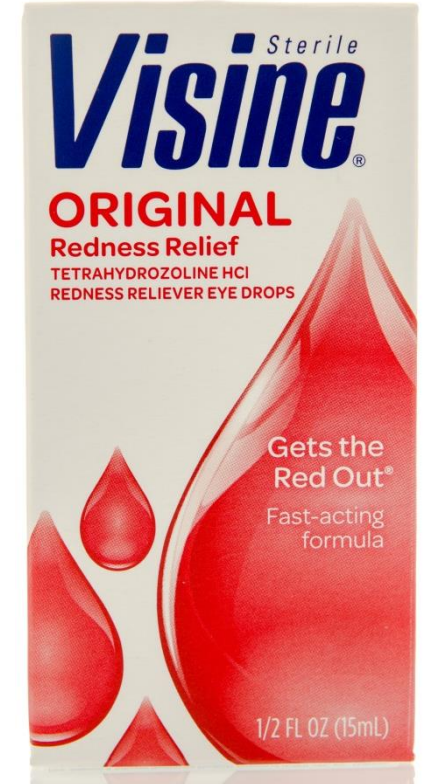
- Aspirin, Goldenseal, Niacin, Drano, bleach, vinegar, etc.
- Visine eye drops (false negative for marijuana)
- Most of these are ineffective
- Marijuana assays are the most easiest to manipulate

- Substitution

- Numerous online sites selling “clean urine”
- Check temperature



(b)



Evaluation of the Urine

- Look at urine creatine
 - Urine creatine should be > 20 mg/dl
- Look at specific gravity
 - Specific gravity should be > 1.002
- Look at color, bubbles, check smell
- Look at pH
 - Normal urine should be 4.5 – 8.0
 - Urine <3 or >10 is likely adulterated
- Look at temperature
 - Range (32 - 38 °C), (89.6 – 100.4 °F)



Consequence of Misinterpretation of UDS

- False sense of confidence of no abuse
- False accusations of abuse
- Loss of opioid / controlled substances privileges
- Potential withdrawal
- Inability to receive appropriate treatment from other physician
- Legal consequences



Patient Case Review - JR

- Don't jump to conclusions!
- Always consult with the patient regarding results
- Identify causes of negative results
 - Frequency of use? When was their last dose?
 - Did they run out early?
 - Is cost an issue?
 - Are symptoms uncontrolled resulting in increase use?
 - Are they diverting?
- Are changes in treatment plan needed based on discussion?
- Make sure your patient understands consequences when nonprescribed/illicit drug presents (even marijuana)
- Have a pain contract
- Consider pill counts at appointments

Take home points

- Address testing results with your patient
- Use clinical information along with interpreting UDS results
- Call lab for package inserts of UDS
- Know cutoff values for your lab
- If needed order confirmation test



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