Virtual Colorado MAT Learning Forum

February 6, 2020

Urine Toxicology Testing

Joshua Blum MD FACP FASAM

Monthly Webinars

- ***Virtual CO MAT Learning Forum***

  1st Thursday 12:30pm-1:30pm

  REGISTER

- ***Induction Basics: Tips from the Trenches****

  2nd Tuesday 7:30am-8:30am

  REGISTER

  * *same topic each month*

- ***Denver Health Learning Collaborative***

  3rd Wednesday 12:15pm-1:15pm

  REGISTER

Denver Health Addiction Journal Club

- 2020 Dates
  - *Every fourth Tuesday January-October*
  - *November 10th*
  - *December 8th*
  - Time; noon to 1 pm
- To join; email ITMATTTRs2@UCDENVER.EDU

Toxicology Testing

Joshua Blum MD FACP FASAM

Disclosures

- No financial relationships to disclose

Objectives

- Underpinnings of urine toxicology testing
- Toxicology interpretation 101
- Toxicology interpretation 201
- New trends in testing

Case 1

- 65 year old female with chronic hip pain, COPD, smoker
- SOAPP = 5 (low risk)
- On high-dose oxycodone SR
- Regular fills, never early
- What tests do you order for toxicology testing?
- How often do you test?

Case 2

- 45 year old male with low back pain
- SOAPP = 11 (Moderate risk)
- On hydrocodone/apap 5/325 BID
- What tests do you order for toxicology testing?
- How often do you test?

Options for testing/reasons for testing

- Detect prescribed drug
- Confirm absence of non-prescribed therapeutic drugs
- Confirm absence of illicit drugs
- Confirm absence of other legal drugs (alcohol, marijuana)

Urine toxicology testing

- Consensual diagnostic test
- Objective documentation of adherence to the mutually agreed upon treatment plan
- Aid in diagnosis and treatment of drug misuse, diversion, and/or addiction
- Done **for** the patient, not **to** the patient
- Should increase communication, not decrease it
- Not for forensic purposes

Heit, Howard. Patient-Centered Urine Drug Testing. PCSS

Urine toxicology testing as part of a controlled substances agreement

Potential benefits:

Decreases in misuse/abuse, illicit drug use, urgent care visits

Potential harms:

Patients may forgo treatment because of burden/stigma

Restrictive agreements may be hard to comply with

Physician barriers:

- UDT cannot diagnose clinical use disorders (abuse, dependence)
- Difficulty discussing testing with patients
- Confusion about how to interpret or use test results

Why do we need toxicology testing?

- Unreliable to use any of the following alone:
  - Physician intuition: may miss 60% of abuse
  - Patient report: underreport by 50% compared to UDT
  - Observation
  - Documented prior history

Many abusers don't show 'red flags'

- 122 patients in two university pain clinics followed for 3 years and monitored for addictive behaviors
- Regular utox performed on all patients
- 17% had prior history of substance abuse

	Behavioral issues present	No behavioral issues present	Totals
Utox +	10 (8%)	26 (21%)	36 (29%)
Utox -	17 (14%)	69 (57%)	86 (71%)
Total	27 (22%)	95 (78%)	122

Katz et al. *Anesth Analg* 2003

Unexpected results common in pain patients

- Retrospective analysis of 470 chronic pain patients enrolled in a pain management program who underwent urine screening
- 45% abnormal, 55% normal
- Of the 45% abnormal:
  - Half tested positive for an illicit drug
    - 66% marijuana
    - 31% cocaine
    - 9% heroin

Michna et al. *Clin J Pain* 2007

Unexpected results common in pain patients

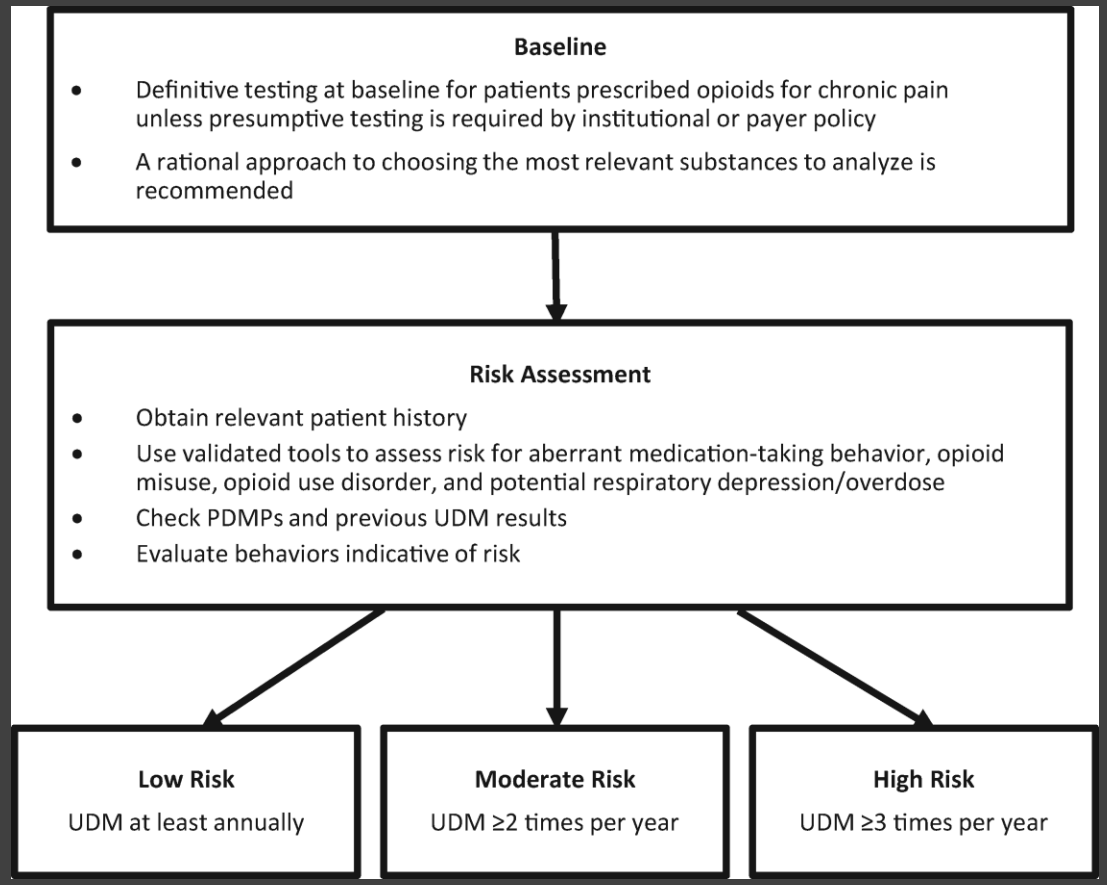
- Among **all** patients:
  - 7% tested positive for cocaine
  - 2% tested positive for heroin
  - ***12% were missing the prescribed opiate***
    - 2/3 said they had run out of their prescription
  - ***2.3% tampered with their urine samples***
- Other studies:
  - Turner et al. *JGIM* 2014: 30.6% abnormal overall; 11.2% absent prescribed opioid, 5% tamper
  - Quest Diagnostics: 54% of 3.1 million samples inconsistent with prescribed regimen

Recommendations for urine toxicology testing

- APS-AAPM Guidelines
  - 5.2: In patients on COT who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the COT plan of care (strong recommendation, low-quality evidence)
  - 5.3: In patients…not at high risk…clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the COT plan of care (weak recommendation, low quality evidence)

Urine toxicology testing

- No high-quality evidence



Argoff CE, et al. *Pain Medicine* 2018;19:97-117

Toxicology testing 101

Case #1

65 yo female with COPD, obesity, bipolar disorder on long-acting oxycodone for sacroiliitis, cervical stenosis reports to the lab for routine toxicology testing. She has recently been to see a new psychiatrist for her chronic anxiety. She denies taking her oxycodone SR except as prescribed.

She appears sedated but arousable. Pulse oximetry is 84%, increasing to 95% with deep respiration.

Immunoassay (opiate, benzo, cocaine, amphetamine, PCP) negative for everything

Case #1

- Opioid quantitative analysis:
- Oxycodone 2310
- Noroxycodone >4000
- Oxymorphone 44
- Noroxymorphone 716

- Is this consistent with her prescribed medication?

- *Patient reports being prescribed clonazepam 1 mg TID by her new psychiatrist.*

Immunoassay basics

Cocaine

Based on benzoylecgonine; sensitive and specific

Amphetamines

Sensitive, **not** specific

Common medications including OTCs can give false + results

Benzodiazepines

Good for many common benzos

Exceptions: clonazepam, alprazolam, +/- lorazepam

Opiates

Based on morphine; reliably detects only morphine, codeine, heroin

Methadone

Sensitive and specific

Presumptive vs Definitive

Presumptive (IA)

- Screen for drug classes rather than specific drugs
- Produce erroneous results due to cross-reactivity with other compounds
- Do not detect all drugs within a drug class, Rx medications or synthetic/analog drugs
- Cut-off may be too high

Definitive (MS)

- Identify all specific drugs, metabolites, and most illicit substances
- Report the results as qualitative or quantitative
- Quantification helps differential assessment of ongoing drug use or cessation of drug use

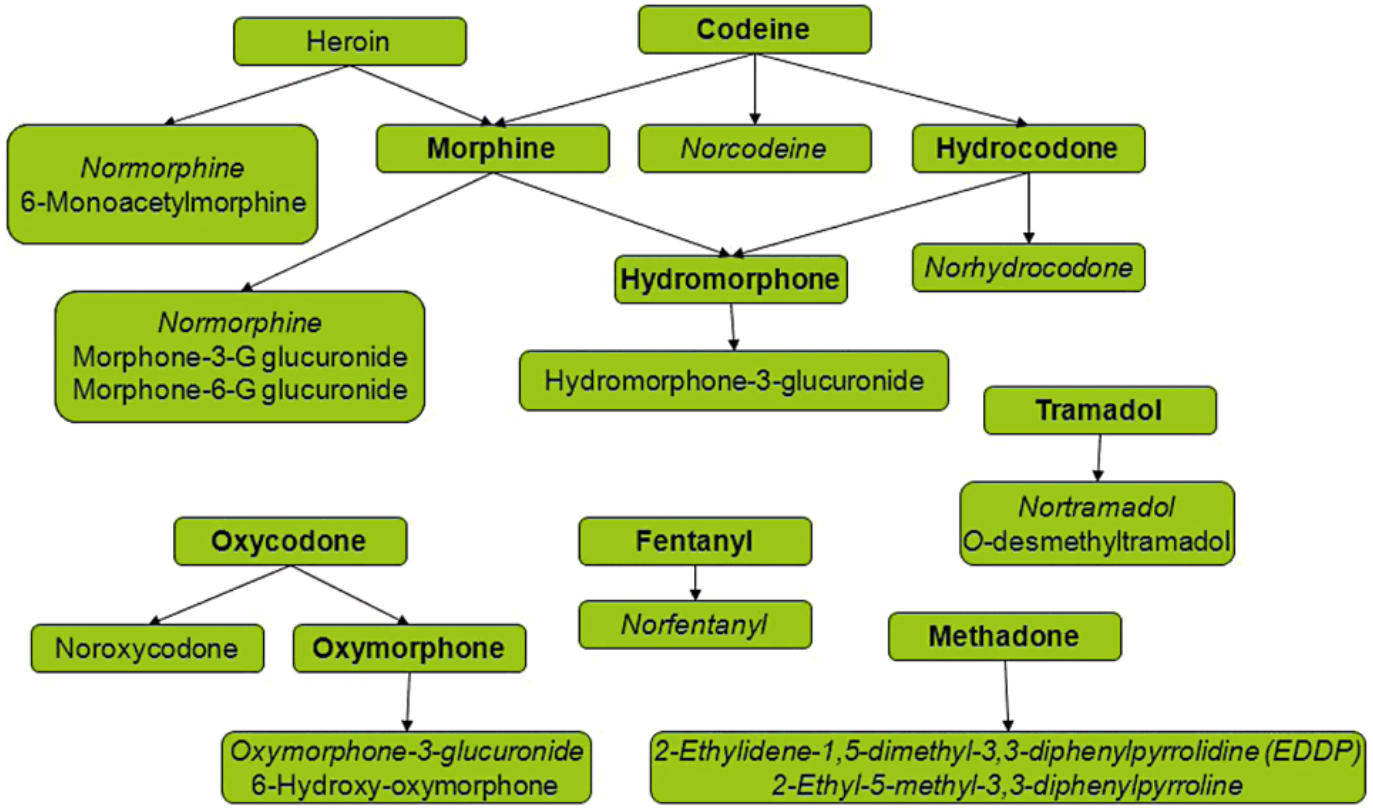
What should we be testing for?

- The “Federal Five”
  - Amphetamine, cocaine, marijuana, opiates, PCP
  - Is this good enough?
- Need to include other opioids, sedatives, and other drugs of abuse:
  - Benzodiazepines
  - Barbiturates
  - Semi-synthetic opioids
  - Methadone
  - Buprenorphine

Providers don’t know what they don’t know

- 99 Internal Medicine residents surveyed
- Mean score 3/7
- 56% felt confident in their ability to interpret UDTs
- 73% of these scored ≤3
- Adolescent medicine-practicing PCPs survey
  - Only 12% aware that oxycodone not detectable on routine opioid screen

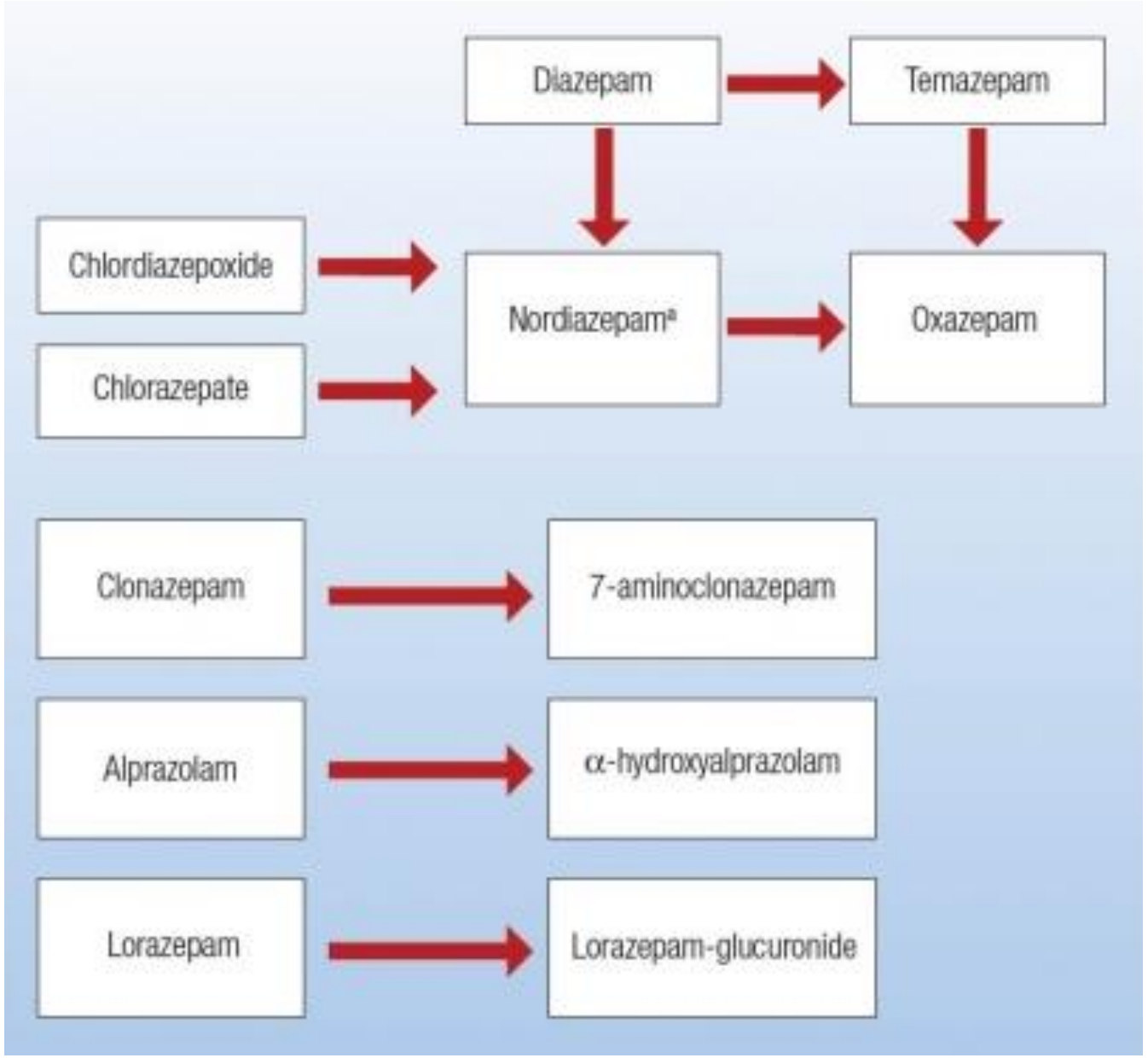
Opioid metabolism



Approximate urine retention times

Drug	Detection Time
Amphetamines	1-3 days
Benzodiazepines	1-3 weeks (long-acting)
Cocaine	1-3 days
Marijuana (infrequent user)	4-5 days
Marijuana (chronic smoker	weeks
Methadone	72
Opioids	48-72

Benzodiazepine metabolism



Craven C, Fileger M, Woster P. Practical Pain Management Volume 14 2014. https://www.practicalpainmanagement.com/treatments/addiction-medicine/drug-monitoring-screening/demystifying-benzodiazepine-urine-drug

This slide should scare you: prevalence of false IA results

False Negatives

Negative POCT but confirmed positive on LC-MS/MS

- Opioid 29%
- Methadone 28%
- Amphetamine 43%
- Benzos 35%
- Cocaine 40%
- Marijuana 20%

False Positives

Positive POCT but confirmed negative on LC-MS/MS

- Opioid 22%
- Methadone 46%
- Amphetamine 21%
- Benzos 61%
- Cocaine 12%
- Marijuana 21%

False positives

Drug	Selected Interferences
Cocaine	Zolpidem (-) Salicylates (-) Fluconazole (-)
THC	Hemp products (+) **Efavirenz** (+) Pantoprazole (+) Ibuprofen (-) Zolpidem (-)
Amphetamines	Phenylpropanolamine (+) **Ephedrine** (+) **Phentermine** (+) **Trazodone** (+) **Bupropion** (+) Selegeline (+) Phenylephrine (+)
Benzodiazepines	**Indomethacin** (+) Ketoprofen, flurbiprofen, fenoprofen (+) Oxaprozin (+) **Sertraline** (+)
Opiates	Poppy seeds (+) **Quinolones** (+)

True negatives

- Drug Absent
  - Lack of recent administration due to symptomatic resolution
  - Unacceptable or intolerable side effects
  - Inability to afford medication
  - Hoarding to be assured of future supply
  - Nonmedical use (abuse, addiction, diversion)
  - Non-adherence (benign or aberrant drug-related behaviors)
- Drug present below cutoff
  - Pharmacologic induction
  - Genetic polymorphism

Quiz Questions

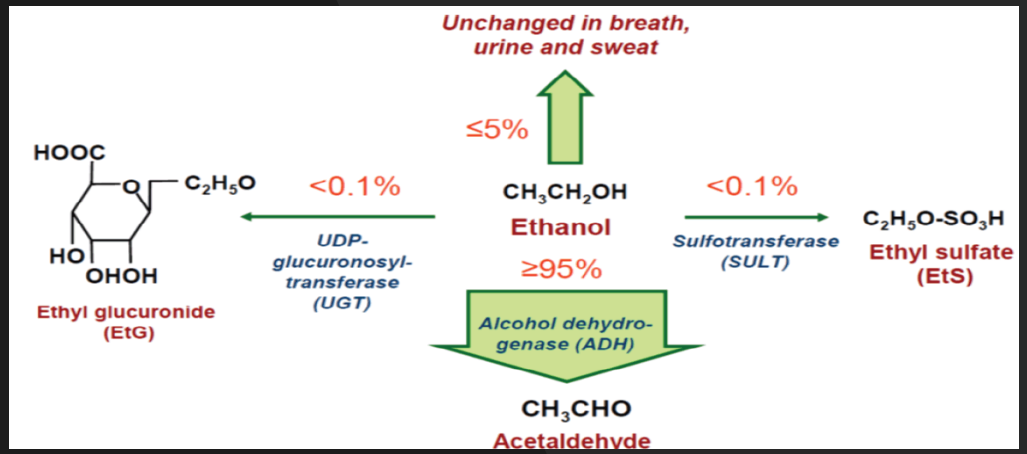
- Can marijuana screening or confirmatory tests differentiate between smoked marijuana and prescribed THC products?
- Can marijuana testing detect synthetic cannabinoids?

Cannabis

- EIA measures main metabolite: 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid
- LC-MS/MS measures 9-THC-9-carboxylic acid
- Impossible to differentiate Marinol, CBD from ingested cannabis
- Synthetic cannabinoids not detected

	EIA (Presumptive)	**MS (Definitive)**
Dronabinol (Marinol®)	+	+
Nabilone (Cesamet®)	-	-
Cannabidiol (Sativex®)	+	+

Monitoring for alcohol



- Urinary alcohol has short detection time (12 hours after last ingestion)
- Instead order alcohol metabolites:
  - Ethyl glucuronide & Ethyl sulfate
    - Minor metabolites of Microsomal Ethanol Oxidizing System (MEOS)
    - Detectable for up to 80 hours
    - Usually present within 1 hour

Case #2

45 year old male prescribed short-acting oxycodone for failed back surgery syndrome. Intermittently irritable in clinic, sometimes runs out early and asks for additional medication

Urine toxicology:

IA positive for opiates, all else negative

Confirmatory testing: **morphine 3804, Codeine 1262**

Patient tells you he has been taking her regular medications, but supplementing with a friend's morphine because you don't prescribe him a high enough dose. Is he telling the truth?

Case #2

2 weeks later patient returns for repeat testing.

IA: positive for opiates

Confirmatory: morphine 4992, codeine 1565, 6-acetylmorphine 488

Does this help explain his previous result?

Urine integrity check

- Temp 90-100 F (at 4 minutes; >30 ml)
- pH 4.5-8.9
- Nitrite <500
- Creatinine >20 mg/dL
- Signs of adulteration:
  - pH <3 or >8
  - Nitrite >500 ug/mL
- Signs of dilution:
  - Creatinine < 20 mg/dL
- Signs of substitution:
  - Creatinine <5 mg/dL

- Quest study: 1.5% adulteration rate
  - 60% dilution
  - 21% oxidant added
  - 12% substitution
  - 7% other adulterant

Urine testing 101 key points

- Screening tests are qualitative
- Need to be confirmed– significant false positive rate
- Semi-synthetic and synthetic opioids not reliably detectable or not detectable at all on opiate screening assays
- Common benzodiazepines often missed on benzo assays
- Urine alcohol has short detection time; EtG/EtS preferable as it is detectable for 72 hours or longer
- Cannabis may be detectable weeks after cessation in chronic heavy users
- Unexpected results are conversation generators, not diagnoses

Techniques to maximize UDT yield

- Screening for adherence:
  - How are you taking your pain medication?
  - When did you take your last dose?
- Screening for other drug use:
  - Are you taking any other prescribed or non-prescribed drugs?

- Further tips:
  - Normalize behavior
  - Encourage honesty to improve care and maintain trust
  - Follow up unexpected results quickly with a conversation

Urine testing 201

Case #3

27 year old male with regular cannabis use and a diagnosis ADHD is requesting amphetamine salts. He has been evaluated by psychiatry, who have confirmed the ADHD diagnosis. As a precondition for being prescribed stimulants, he is required to cease cannabis use.

Urine toxicology became negative for cannabis after 4 weeks and patient was initiated on amphetamine salts. After 1 appropriate urine toxicology result, next is positive for cannabis at 80 ng/ml.

He denies any use but tells you he spent an evening at a friend's house where a lot of his friends were smoking marijuana.

Can secondhand smoke induce a positive UDT for cannabis?

- Early studies demonstrated THC metabolites below limit of detection
  - But marijuana potency in 1980s: 3%

- Recent study evaluated passive inhalation of high-potency THC (11.3%) in small room
  - Compared ventilated and un-ventilated rooms
  - With ventilation: no positive tests
  - Without ventilation: multiple positive tests, but nearly all <50 ng/ml
  - Only 1 test positive >50 ng/ml; detection time very short

Case #4

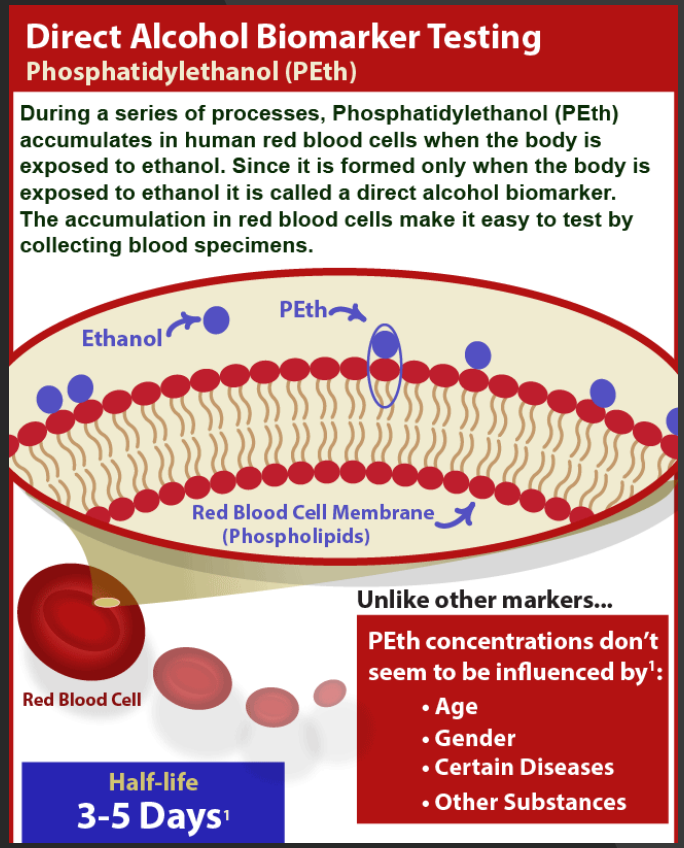
54 year old former oil field worker on disability is prescribed extended-release oxycodone as part of a multi-modal plan to treat spinal stenosis and osteoarthritis. Monthly urine toxicology testing is always consistent. Denies alcohol use “except a drink on New Year’s.” Urine EtG/EtS were positive once 6 months ago. He has NAFLD with persistent transaminitis and chronic depression with mood lability. You suspect he may be drinking more regularly than he admits, despite recent negative EtG/EtS testing.

Is there another way to evaluate for surreptitious drinking?

Monitoring for alcohol: PEth

- Phosphatidylethanol
  - Abnormal cellular membrane phospholipid found in mammals exposed to alcohol
  - Highly sensitive and specific
  - **Serum test**

- **Can detect *single episode* of drinking for up to *12 days***
  - Becomes positive after about 8 hours
  - Median half life variable, typically 3-10 days
  - Useful for detecting surreptitious drinking



PEth for employee or patient monitoring

- Study of 53 consecutive male security employees; 37 claiming alcohol abstinence
  - 12/37 tested positive for PEth >20 ng/ml
  - Of the 16 who self-reported alcohol use, PEth levels suggested drinking at much higher levels than reported

PEth Guidelines

- <20 ng/ml: no or light consumption
  - <2 drinks/day, several days/week
- 20-200 ng/ml: significant consumption
  - 2-4 drinks/day, several days/week
- >200 ng/ml: heavy consumption
  - 4 or more drinks/day, several days/week

Case #5

28 year old female with multiple sclerosis, history of amphetamine and heroin use on long-acting morphine for severe spasticity.

Recent urine toxicology shows:

Morphine 7532 ng/ml

Hydrocodone 3202 ng/ml

Hydromorphone 718 ng/ml

Codeine 220 ng/ml

What's going on?

Case #5

- Morphine: consistent with prescribed medication
- Hydrocodone: consistent with illicit hydrocodone use
- Hydromorphone: consistent of morphine and hydrocodone metabolism
- Codeine: possibly consistent with production impurities
    - Alternate explanation: recent/remote heroin use

Process Impurities

Opiate	Process Impurity	Allowed amt (%)	Usual observed (%)
Hydrocodone	Codeine	0.15	0-0.1
Hydromorphone	Morphine	0.15	0-0.025
	Hydrocodone	0.1	0-0.025
Morphine	Codeine	0.5	0.01-0.05
Oxycodone	Hydrocodone	1	0.02-0.12
Oxymorphone	Hydromorphone	0.15	0.03-0.1
	Oxycodone	0.5	0.05-0.4

Case #6

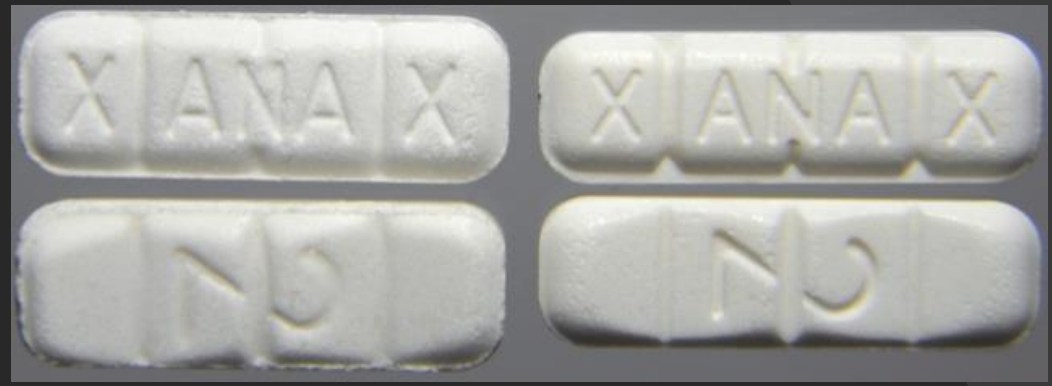
38 yo male on depot-naltrexone for heroin and alcohol use disorders reports buying alprazolam (Xanax®) off the street. Notes that normally these make him feel really relaxed but this time he had to take “four or five” to barely get any effect. Patient later went to outside provider who prescribed alprazolam. Took 1 tablet and felt “an immediate effect.”

Why did the first alprazolam tablets not work?

Case #6: Fentanyl

- 2017 Pfizer & DEA purchased Xanax from dark web
- 7/138 samples authentic

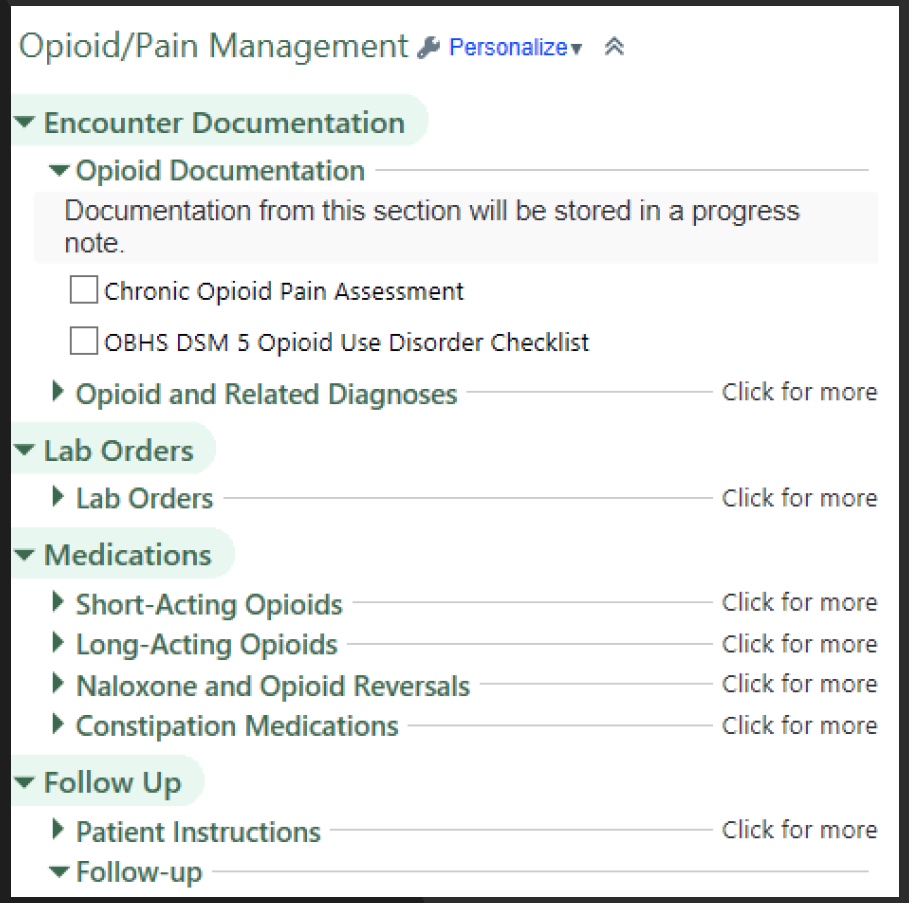
- Case 2: patient urine toxicology positive for fentanyl

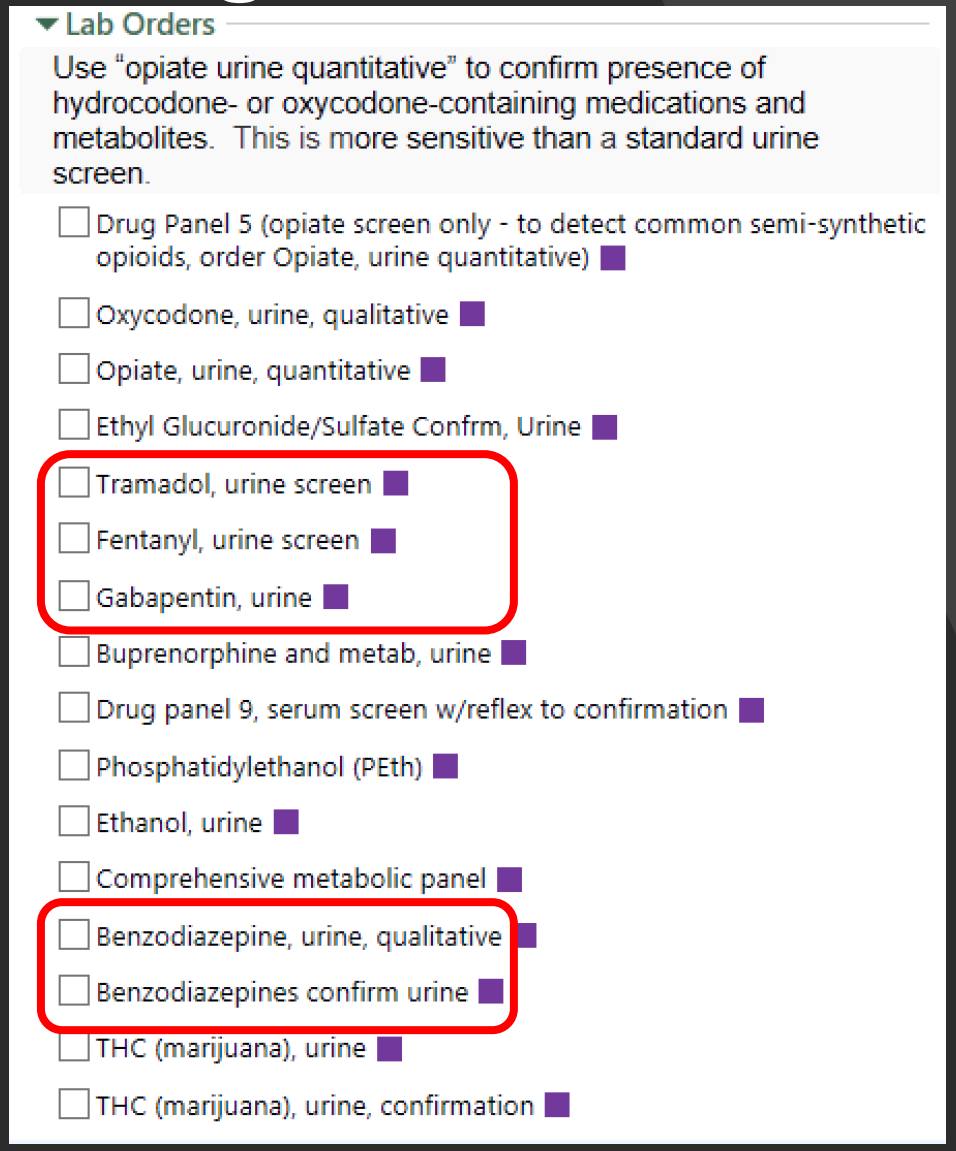


Fentanyl detection

- Most toxicology labs screen for fentanyls
- Designer fentanyls
  - Thermo DRI® Fentanyl Enzyme IA vs ARK™ Fentanyl Assay IA vs. Immunalysis® Fentanyl Urine SEFRIA™ Drug Screening Kit
  - LC/HRMS used as reference
  - **33%-95% cross-reactivity** for blank urine samples spiked with multiple fentanyl analogs
    - (acetylfentanyl, acrylfentanyl, butyrfentanyl, 4-chloroisobutyrfentanyl, 4-fluorobutyrfentanyl, 4-fluorofentanyl, 4-fluoroisobutyrfentnyl, isobutyrfentanyl, methoxyacetylfentanyl, or tetrahydrofuranfentanyl)
  - 4-methoxybutyrfentanyl showed low cross-reactivity
- SEFRIA kit available for use in physician offices
  - FDA 510(k) approval
  - Inexpensive ($1.50-$8/test)

Other drugs of abuse testing





Urine drug testing summary

- Something we do *for* the patient, not *to* the patient
- Know the limits of your testing strategy
  - Abnormal UDT does not diagnose SUDs
  - Send the right tests for the right drugs
    - Synthetic and semi-synthetic opioids
    - Benzodiazepines: clonazepam, alprazolam
    - Ethyl glucuronide/Ethyl sulfate, PEth for alcohol
  - Important IA false positives:
    - Ciprofloxacin for opioids
    - Sertraline for benzodiazepines
- Repeat testing often necessary to get a real sense of what's going on

Selected References

Schrock J, et al. *Int J Legal Med* 2017;131:153-160.

Moeller KE, et al. *Mayo Clin Proc* 2017;92:774-796.

Cone EJ et al. *J Anal Toxicol* 1987;11:89-96.

Starrels JL, et al. *J Gen Int Med* 2012; 27:1521-1527.

Reisfield GM, et al. *J Opioid Manag* 2007.

Chou R et al. *J Pain* 2009;10:113-130.

Turk D et al. *Clin J Pain* 2008;24:497-508.

Helander A et al. *Drug Test Anal* DOI: 10.1002/dta.2382 2018

Guerrieri D et al. *J Anal Toxicol* 2019;43(1):18-24.

Ulwelling W, Smith K. *Crit Review Toxicol* 2018;63:1634-1640.

Mahajan, G. *Anesth Analg* 2017;125:2094-2104.

Kwong, TC et al. *Clin Lab Sciences* 2017;54:443-445.

Darragh A et al. *Pain Physician* 2014;17:359–366.

Reisfield GM, et al. *Ann Clin Lab Sci* 2007;37:301-314

Pesce A, et al. *Pain Med* 2012;13:868-885

Reisfied GM, et al. *Bio Anal* 2009;1(5):937-952.

Drug Testing: A White Paper of the American Society of Addiction Medicine 2013 available at: https://www.asam.org/docs/default-source/public-policy-statements/drug-testing-a-white-paper-by-asam.pdf. Accessed March 7, 2019

Setnik B, et al. *Postgrad Med* 2017;129:5-11.

Kaye AD, et al. *Pain Physician* 2017;20:S93-S109

Turner JA et al. *JGIM* 2014;29:1663-1671

Michna E et al. *Clin J Pain* 2007;23:173-179

Jarvis M et al. *J Addict Med* 2017;11:163-173

Katz NP, et al. *Anesth Analg*. 2003;97:1097–1102.

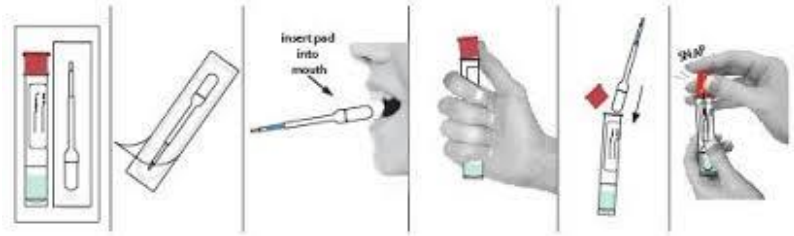
End

Questions?

jblum@dhha.org

Oral specimens

- **Advantages**
  - Earlier detection
  - Correlation to serum levels
  - Easy to collect
  - Hard to adulterate
- **Disadvantages**
  - Shorter detection time
  - Salivary pH affects concentrations
  - Impact of cross-reactivity, adulterants not well-studied



Some content courtesy of Pyxant labs

Urine vs Oral specimens

	URINE	ORAL FLUID
Detection Window	72-120 hours (most drugs)	6-48 hours
Ease of Collection	Required facilities may be logistically difficult. Collection procedures could be viewed as an invasion of privacy if not conducted properly.	Sample can be collected anywhere that has privacy. Collection procedure is less intrusive. Collecting adequate sample volume can be problematic in certain individuals.
Adulteration or Substitution	Detection may be avoided through an adulterated/substituted specimen.	Avoiding detection may be as simple as rinsing mouth prior to collection. Recommendation is no fluids or food 20 minutes before collection.
Ease of detection of target drugs	Primarily testing for drug metabolites since they are available in the urine at much greater concentrations	Parent drugs are tested for in oral fluid due to their availability in the saliva at higher concentrations.

Table courtesy of Pyxant labs

QUESTIONS / DISCUSSION

Webinars

See our website for previous presentations & resources as well as upcoming topics

- https://www.practiceinnovationco.org/opioids/mat-forum/