Perils & Pitfalls:
Drug Toxicology Interpretation

October 25, 2014 | Scott A. Clingan, MSHS, PA-C

Disclosures

No conflicts

Objectives

1. Discuss the utility of urine drug monitoring in chronic pain management
2. Review limitations and pitfalls in point of care urine drug screening interpretation
3. Discuss the role and need for confirmatory urine drug testing


Is this cup half full or half empty?
Are you going to give me that urine sample or not?

Why drug monitor?

- Is the patient taking the medication you have prescribed?
- Is the patient abusing the medication you have prescribed?
- Is the patient taking an undisclosed medication or illicit substance that might complicate treatment?

Point of Care (POC) Urine Drug Screen (UDS)

- An enzyme immunoassay
- Results within minutes
- Detects the presence or absence of a drug class, a few medications, and select illicit substances
- Higher cutoff levels resulting in more false negatives
- Cross-reactivity common resulting in more false positives

Benefits of POC UDS Results

- May help reduce risk of unrecognized drug misuse/abuse and can be a catalyst to initiate such conversations
- Provides a rationale to limit pharmacotherapy in patients with unexpected results

Limitations of POC UDS Results

- Test is subjective (results can be read differently between clinicians)
- Poor reactivity may occur for specific drugs within a drug class leading to inaccurate results
  - Benzodiazepines calibrated to oxazepam, therefore clonazepam and lorazepam may require a higher concentration to return a positive result…

Limitations of POC UDS Results

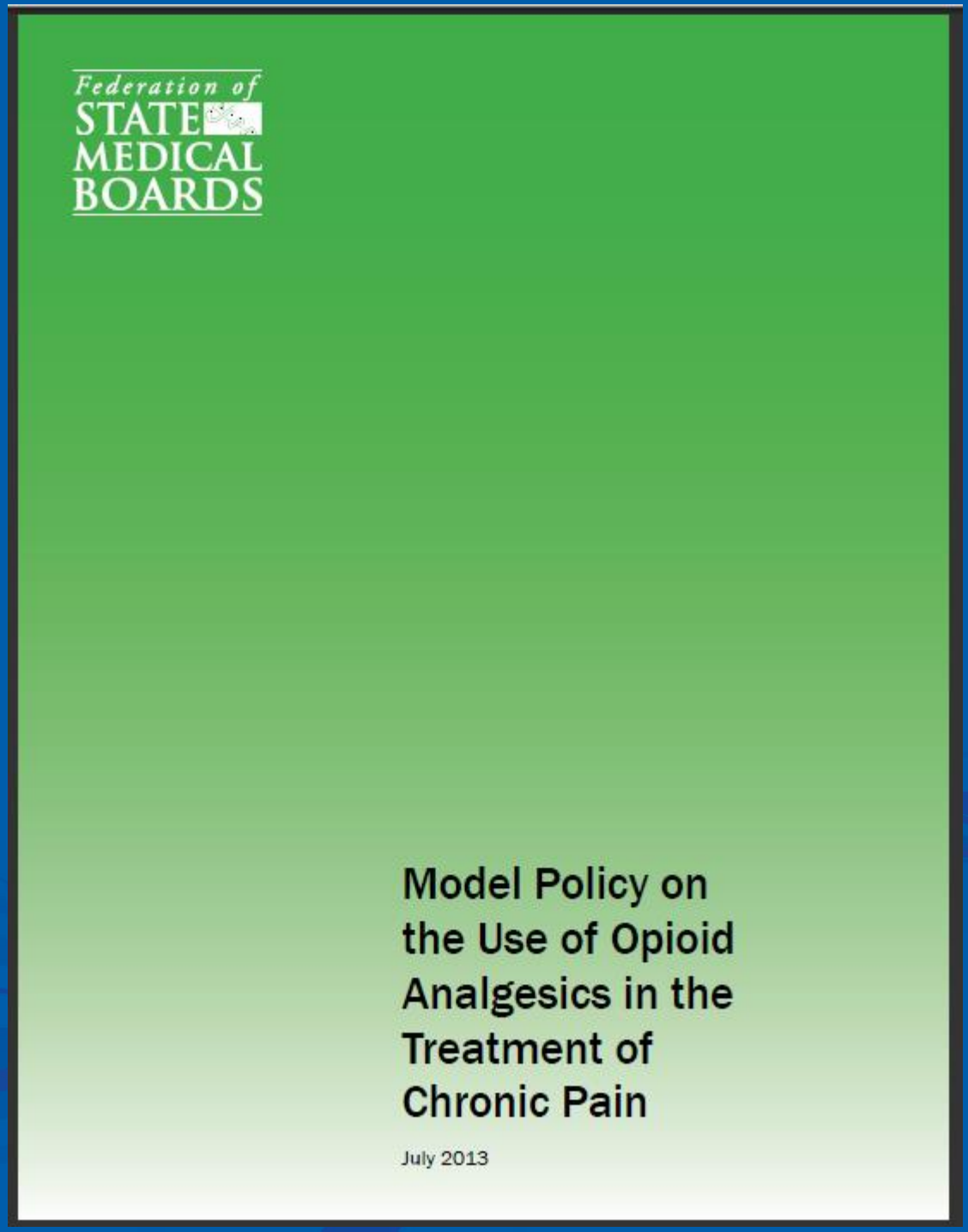
- Commonly encountered substances are not included
  - Fentanyl, tramadol, carisoprodol, meperidine, and ethyl glucuronide (alcohol)
- False negative results due to high cutoff levels
  - Cocaine metabolite cutoff of 300 ng/mL on POC UDS; 50 ng/mL on LC-MS/MS
  - Amphetamine cutoff of 1,000 ng/mL on POC UDS; 100 ng/mL on LC-MS/MS

Confirmatory Urine Drug Test (UDT)

- Liquid chromatography-tandem mass spectrometry (LC-MS/MS) and gas chromatography mass spectrometry (GC-MS)
  - Both highly sensitive and specific
  - Virtually no false (+) or (-) results
  - GC-MS more time intensive and requires more sample amount vs LC-MS/MS…

Confirmatory UDT

- Provides quantification, measuring concentrations of all medications, illicit substances and metabolites
- Definitive identification and analysis
- Lower cutoff levels are more likely to detect the presence of undisclosed prescription and illicit drugs


Federation of
STATE
MEDICAL
BOARDS
Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain
July 2013

Model Policy

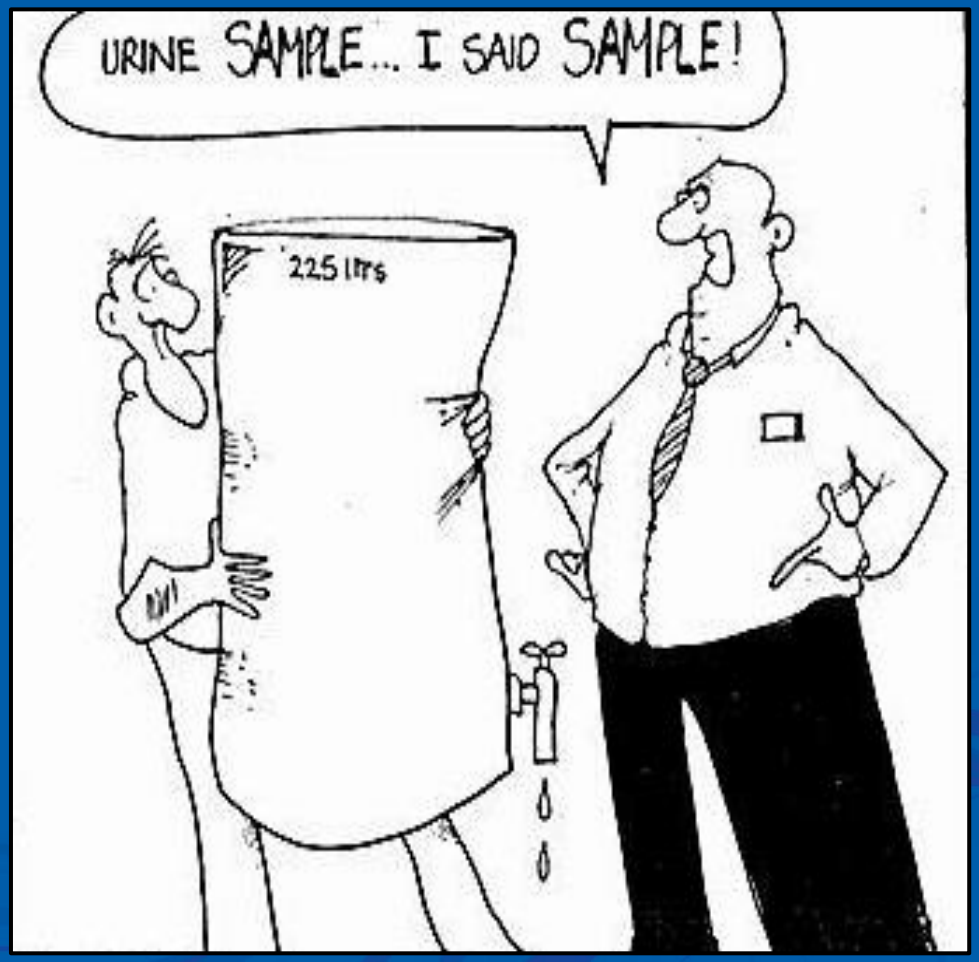
- **Urine** is the preferred biologic specimen for testing
  - Ease of collection and storage
  - Cost-effectiveness
- When testing as part of pain treatment, forensic standards are generally unnecessary and **not** in place
  - Collection is **not** observed (exceptions exist)
  - Chain-of-custody protocols are **not** followed

Model Policy

- POC UDS
  - Utility in the making of temporary and "on the spot" changes in clinical management
  - **Limitations with regard to accuracy** have recently been the subject of study
- A recent study on LC-MS/MS results following immunoassay POC UDS in addiction treatment settings found **very high rates of "false negatives and positives."**

Model Policy

- These limitations are such that the use of POC UDS for the making of more **long-term and permanent changes in management** of people with the disease of addiction and other clinical situations may not be justified until the results of **confirmatory testing with more accurate methods, such as LC-MS/MS,** are obtained.


URINE SAMPLE... I SAID SAMPLE!
225 ltrs

Case Example 1

54 yo banker with HTN, DM, HLD on hydromorphone and pregabalin for severe peripheral neuropathy.

- POC UDS (+) for opiates
- Prescription Monitoring Program (PMP) consistent with prescribed/reported medications

Case Example 1

Confirmatory UDT Results

✓	Hydromorphone	11,804 ng/mL
-	Ethanol (EtOH)	255 ng/mL
?	Ethyl Glucuronide	Negative
?	Ethyl Sulfate	Negative

Why are there NO EtOH metabolites?...

Case Example 1 Teaching Points

- EtOH can be detected within 8-12 hours of consumption
- EtOH metabolites, EtG and EtS appear within one hour of alcohol ingestion and last up to 80 hours…
- In pts with DM, (+) urinary EtOH can be caused by fermentation of urinary glucose and **NOT** EtOH consumption
- Case study pt was poorly controlled diabetic

Case Example 2

48 yo female baker with h/o failed back syndrome takes oxycodone CR and tapentadol. She also utilizes alprazolam via her PCP for anxiety.

- POC UDS (+) for oxycodone and benzodiazepines, in addition to opiates (?)
- PMP consistent with prescribed/reported medications

Case Example 2

Confirmatory UDT Results

✓	Oxycodone	1,032 ng/mL
✓	Noroxycodone	2,893 ng/mL
✓	Oxymorphone	498 ng/mL
✓	Tapentadol	4,554 ng/mL
✓	Alpha-hydroxyalprazolam	79 ng/mL
?	Morphine	295 ng/mL

Where did morphine come from?...

Case Example 2 Teaching Points

- Substances known to test (+) for opiates on POC UDS:
  - Oxycodone (at high concentrations)
  - Certain quinolones
  - Poppy seeds which contain morphine
- ***Will poppy seed ingestion impact confirmatory testing?***
  - YES. Consumption of bakery products containing poppy seeds may result in urinary morphine levels of up to 3,000 ng/mL
- Case study pt reported eating poppy seed cake

Case Example 3

63 yo female with CRPS is being treated with fentanyl TD patch, morphine sulfate IR, and gabapentin. She denies taking other controlled substances.

- POC UDS (+) for opiates and amphetamines (?)
- PMP consistent with her prescribed/reported medications

Case Example 3

Confirmatory UDT Results

✓	Fentanyl	14 ng/mL
✓	Norfentanyl	163 ng/mL
✓	Morphine	3,002 ng/mL
?	Methamphetamine (MAMP)	269 ng/mL
?	Amphetamine (AMP)	3,376 ng/mL
?	% *d*-isomer	4%

Patient is using methamphetamine…right?

Not necessarily

Case Example 3 Teaching Points

- POC UDS vs confirmatory UDT results
  - Why was MAMP (-) on POC UDS when the confirmatory UDT was (+) for MAMP and AMP?
  - AMP cutoff
    - POC UDS → 1,000 ng/mL
    - LC-MS/MS → 100 ng/mL (actual result 3,376 ng/mL)
  - MAMP cutoff
    - POC UDS → *d*-MAMP 8,000 ng/mL, *l*-MAMP 10,000 ng/mL
    - LC-MS/MS → 100 ng/mL (actual result 269 ng/mL)

Case Example 3 Teaching Points

- Interpreting urinary methamphetamine (MAMP) results with confirmatory testing:
  - Routine LC-MS/MS testing does not distinguish between isomers detected following licit and illicit use
    - *Levo (l)* isomer – present in (OTC) Vicks® nasal inhaler and metabolite of selegiline
    - *Dextro (d)* isomer – metabolite of illicit MAMP, but also benzphetamine (CIII) and *d*-methamphetamine (CII)
- Isomer analysis *can often* rule out illicit use…

Case Example 3 Teaching Points

- Isomer analysis
  - Expressed as a percentage of the *d*-MAMP relative to total amount of MAMP present
  - Federal workplace drug testing programs established a threshold of 20% *d*-MAMP to distinguish between sources
    - Isomer result ≥20% *d*-MAMP would indicate use of benzamphetamine, *d*-methamphetamine, or illicit methamphetamine
    - Isomer result of <20% *d*-MAMP (or ≥80% *l*-MAMP) indicates use of Vicks® or selegiline

Case Example 3 Teaching Points

Are results from the case study consistent with licit or illicit MAMP?

Methamphetamine (MAMP)	269 ng/mL
Amphetamine (AMP)	3,376 ng/mL
% *d*-isomer	4%

Licit…Isomer result of <20% *d*-MAMP indicates use of Vicks® or selegiline

Case Example 3 Teaching Points

Substances known to test (+) for methamphetamine on POC UDS:

- Dextroamphetamine/ amphetamine
- Phenylpropanolamine
- Ephedrine
- Pseudoephedrine
- Ranitidine
- Phentermine
- Brompheniramine
- Bupropion
- Trazodone
- Chlorpromazine
- Promethazine
- Vicks® Nasal Inhaler (Pt's Visit Survey showed nasal congestion; pt reported using this med)

Case Example 4

37 yo male laborer with phantom limb pain s/p occupational injury, managed with oxymorphone ER and s/p spinal cord stimulator implant. He denies taking other controlled substances.

- POC UDS (+) for oxycodone
- PMP consistent with his prescribed/reported medications

Case Example 4

Confirmatory UDT Results

✓	Oxymorphone	15,159 ng/mL
?	Oxycodone	296 ng/mL

Does oxymorphone metabolize into oxycodone?

No…oxycodone metabolizes into oxymorphone, but not vice versa.

Case Example 4 Teaching Points

- Oxycodone was detected, but not matched to any of the reported prescriptions.
- Oxycodone is also a ***known impurity*** in various commercial preparations of oxymorphone.
  - Quantitative value should be small, ≤40 ng/mL

Are the case study results consistent with impurity or aberrancy?

Aberrancy (>40 ng/mL oxycodone)…Patient acknowledged taking brother's Rx

Case Example 5

25 yo female student with hx of chronic pelvic pain is treated with hydrocodone bitartrate ER.

- POC UDS positive for opiates and THC (?)
- PMP consistent with her prescribed/reported medications

Case Example 5

Confirmatory UDT Results

✓	Hydrocodone	6,201 ng/mL
✓	Norhydrocodone	2,444 ng/mL
✓	Hydromorphone	358 ng/mL
?	cTHC	Negative

Why is THC (+) on POC UDT, yet (-) on confirmatory UDT?...

Case Example 5 Teaching Points

- Substances known to cause a false positive result for THC on POC UDS
  - Omeprazole
  - Pantoprazole
  - Efavirenz
  - NSAIDs
- Case study pt had a h/o GERD and was actively taking omeprazole

Case Example 6

38 yo male executive on oxycodone/acetaminophen PRN for chronic neck pain.

- POC UDS (+) for oxycodone; however, the urine sample was noted to have a pinkish hue (?). Specimen temperature was <90 ˚F (normal range 90-100 ˚F within 4 min window)
- Obtains medication through military pharmacy, which does not report to PMP

Case Example 6

What would be an appropriate course of action?

Patient was asked to provide second urine sample, and complete oral fluid drug test

– Specimen #2 had appearance and temperature (between 90-100 ˚F) more consistent with urine

Case Example 6

Confirmatory Results

Specimen #1 - Urine

✓	Oxycodone	1,924 ng/mL	
✘	Noroxycodone	Negative	
✘	Oxymorphone	Negative	

Specimen Validity

✘	Creatinine	0 mg/dL	(>20 mg/dL)
✘	Specific Gravity	0.999	(1.003-1.050)

Case Example 6

Confirmatory Results

Specimen #2 - Urine

✓	Oxycodone	204 ng/mL
✓	Noroxycodone	177 ng/mL
✓	Oxymorphone	286 ng/mg
✗	cTHC	50 ng/mL

Specimen Validity

✓	Creatinine	27 mg/dL	(>20 mg/dL)
✓	Specific Gravity	1.003	(1.003-1.050)

Case Example 6

Confirmatory Results

Specimen #3 – Oral Fluid

✓	Oxycodone	128 ng/mL
✓	Noroxycodone	8 ng/mL*
✓	Oxymorphone	1 ng/mL*
✗	THC	75 ng/mL

Oral fluid testing cutoffs are lower compared to urine testing

Case Example 6 Teaching Points

- Validity results for urine include evaluation of temperature, creatinine, oxidant, pH, and specific gravity.
- Creatinine levels in single digits presents concerns for specimen tampering
- Creatinine level of 0 → not urine
- Metabolites should be present in specimen
- Finally…Given result variances from two UDTs during same encounter/same patient specimen → circumstances are consistent with **pill shaving**

Specimen Tampering

- Whole industry devoted to individuals trying to manipulate urine drug testing
- Urine for sale including synthetic and animal urine, body concealment of old urine, pill shavings in non-urine liquid
- Secondary gain from both addictive and monetary perspectives

Additional POC UDS False (+)

- Barbiturates → ibuprofen, naproxen
- Benzodiazepines → oxaprozin, sertraline
- Methadone → verapamil, quetiapine, diphenhydramine, doxylamine, chlorpromazine
- Oxycodone → codeine, morphine, hydrocodone, hydromorphone
- PCP → venlafaxine, dextromethorphan, diphenhydramine, ibuprofen, tramadol
- TCA → cyclobenzaprine, carbamazepine, diphenhydramine

Questions?

References

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