Bridge Over Troubled Waters: Crossing the Knowledge Gap in Drug Test Interpretation

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ASAM 55th Annual Conference, Dallas TX, April 6, 2024, 1:15-2:30 PM
Disclosure Information

 Presenter 1: Christine Snozek, PhD
  Presenter 1 Disclosures: No Disclosures

 Presenter 2: Jill S. Warrington, MD, PhD
  Presenter 2 Disclosures: Vermont Blue Cross Blue Shield, Community Advisory Council, member, reimbursement for time
Learning Objectives

- Introduce results of recent 900+ provider survey evaluating answers to common drug testing interpretative questions
- Review common misconceptions or misinterpretations with drug testing
- Break out into groups to discuss case scenarios
- Share ideas on how to broaden understanding of testing outside of specialty areas
Join us on Slido

🌟 https://app.sli.do/event/uzcRfzicnPNxRxhcZK2cFy

Event code: 3487389
How much experience/training do you have with interpreting urine drug testing?
What is your main specialty area?
Who are we, and why are we here?

- Clinical laboratorians with particular interest in toxicology
- Representatives from a team that led a large, multi-specialty, multi-institution survey of educational needs re DOA

The survey:

- 911 clinical and laboratory respondents (2020-2023)
- 510 (56%) physicians responded
- MDs included experts (toxicologists, addiction med, pain management) and areas with less DOA training (primary care, ED)
- Goals: address modern drug issues, identify knowledge gaps
<table>
<thead>
<tr>
<th>Demographic group</th>
<th>N (% of total)</th>
<th>Mean Correct (SD)</th>
<th>p (vs Lab PhD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All respondents</td>
<td>911 (100%)</td>
<td>4.04 (1.33)</td>
<td></td>
</tr>
<tr>
<td>Lab PhD</td>
<td>144 (15.8%)</td>
<td>4.63 (1.15)</td>
<td>Ref.</td>
</tr>
<tr>
<td>MD or equivalent</td>
<td>510 (56.0%)</td>
<td>4.14 (1.22)</td>
<td>0.001</td>
</tr>
<tr>
<td>Other clinical staff</td>
<td>51 (5.6%)</td>
<td>3.76 (1.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MDs by specialty</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
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Key educational gaps

- Compounds detected by typical drug screens (immunoassay)
- Opioid metabolism
- Impact of legal cannabinoids on THC testing
- Drug detection windows

- Recognizing simulated compliance was challenging for all groups except addiction medicine physicians
Our goals for today

- Provide intermediate / advanced level information regarding testing for drugs with misuse or recreational potential

- Focus on educational needs highlighted by the survey for addiction medicine & related specialties

- Discuss opportunities for knowledge sharing with other specialties managing similar patients, e.g. primary care
Which of the following can generally be detected using an opiate immunoassay screen?
From the survey

- Overall correct: 77%
- Addiction med correct: 72%
- Most common incorrect response: Fentanyl

Snozek et al., submitted 2024
Most drug screens (lab or point of care) are based on immunoassay

- Test antibodies target 1-2 key drugs:
  - Opiates = morphine
  - Barbiturates = secobarbital (can include others)
  - Benzos = (nor)diazepam, oxazepam
  - ATS = amphetamine and/or methamphetamine
  - Cocaine = benzoylecgonine
  - Methadone = methadone or EDDP (poor cross-reactivity)
  - Buprenorphine = parent (poor metabolite XR)

Immunoassay cross-reactivity

Detection of drugs within a class differs between test manufacturers / labs due to varied antibody specificity.

Example: concentrations required to trigger a “positive” opiate result for one assay.

<table>
<thead>
<tr>
<th>Drug</th>
<th>300 ng/mL cut-off</th>
<th>% Cross reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MAM</td>
<td>386 ng/mL</td>
<td>78%</td>
</tr>
<tr>
<td>Codeine</td>
<td>224 ng/mL</td>
<td>134%</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1,086 ng/mL</td>
<td>28%</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1,425 ng/mL</td>
<td>21%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>&gt;75,000 ng/mL</td>
<td>&lt;0.4%</td>
</tr>
</tbody>
</table>

A patient prescribed oxycodone is positive on her urine confirmation test for oxycodone (40,000 ng/mL) and hydrocodone (5000 ng/mL). What is the best interpretation?
From the survey

- Overall correct: 55%
- Addiction medicine correct: 63%

- Most common incorrect response: Hydrocodone is a metabolite of oxycodone; she is compliant

- Educational emphasis: Providers should recognize metabolic pathways for common opioids.

Snozek et al., submitted 2024
Opioid metabolism

- NORCODEINE
- CODEINE
- HYDROCODONE
- HYDROMORPHONE
- DIHYDROCODEINE
- NORMORPHINE
- MORPHINE
- OXICODONE
- OXYMORPHONE
- HEROIN
- 6-MONOACETYL MORPHINE

* Glucuronides are also formed

Modified from: Michael Gordon, Ph.D, Medical Pharmacology Chapter 13: Pain Management: Opioids
Opioid Screen General Rules of Thumb

ירהון Opiate Screen:

Detects well: Morphine, Codeine
Detects ok: Hydrocodone, Hydromorphone, Heroin
Does not detect: Oxycodone, Oxymorphine, Methadone, Buprenorphine, Tramadol, Tapentadol, Fentanyl

ירהון Oxycodone Screen:

Detects well: Oxycodone, Oxymorphine
Does not detect: All others
A patient prescribed oxycodone states that he ate a pastry with poppy seed filling for breakfast. If he is compliant, which drugs might reasonably be expected to be detected in his urine?
From the survey

- Overall correct: 47%
- Addiction medicine correct: 69%
- Most common incorrect response: Oxycodone and hydromorphone
- Educational emphasis: Codeine and morphine are naturally present in opium products; other semi-synthetic and synthetic opioids are not.

Snozek et al., submitted 2024
Poppy seeds

- Seeds develop in opium, a rich milky sap of the plant
- Washing removes >90% opium
- Usually ≤2,000 ng/mL in urine for morphine and codeine
- Seed wash or tea is exception and can be lethal

Opium: A mixture of >25 alkaloids

Naturally occurring alkaloids

- MORPHINE
- CODEINE
- THEBAINE
- PAPAVERINE

Example synthetic compounds

- HEROIN, HYDROMORPHONE
- OXYCODONE, OXYMORPHONE, BUPRENORPHINE, NALOXONE

---

A patient prescribed lorazepam has a negative urine immunoassay screen for benzodiazepines. Which is the best response?
From the survey

- Overall correct: 67%
- Addiction med correct: 81%

Most common incorrect response: No further testing needed, the screen proves noncompliance

Immunoassay screens should **never** be considered definitive
Benzo metabolism & assay X-reactivity

Toxidology Cases for the Clinical and Forensic Laboratory. DOI: https://doi.org/10.1016/B978-0-12-815846-3.00013-2

Krasowski et al. BMC Emerg Med 9, article 5 (2009)
Mass spectrometry in drug testing

- Questionable immunoassay screens should be confirmed
- Highly specific: individual drugs/metabolites, not class
- Highly sensitive: cutoffs are often <1/10th of immunoassay
- Previously, GC-MS was more common; LC-MS/MS or LC-HRMS predominate now
- Some labs now do ‘direct-to-definitive’ i.e., MS-based screen rather than historical immunoassay with MS confirmation
  - Note, MS screens are not always validated to same degree as confirmation (definitive), but are generally very good
Which sample type is best for distinguishing recent use from remote drug use?
Matrix pros & cons

- **Oral fluid**
  - Easily observed collections, low risk of adulteration
  - Relatively short detection window, reflects recent use only
  - Few clinical labs perform OF testing, limited POC offerings

- **Hair**
  - Easily observed collections, though might require body hair
  - Potentially very long detection window, but insensitive for recent use
  - Risk of external contamination, influence of hair color or texture
## Matrix pros & cons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Urine</th>
<th>Oral fluid (saliva)</th>
<th>Hair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed collections</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Detection window</td>
<td>++</td>
<td>+</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Identify recent use</td>
<td>+/-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>(light vs remote heavy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identify infrequent use</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Contamination risk</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Availability of testing</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
A patient with BMI >40 was told to cease his regular marijuana habit before surgery. Urine confirmation is positive for THC metabolites, 2 weeks after he claims to have stopped. What is the most likely explanation?
From the survey

- Overall correct: 60%
- Addiction medicine correct: 71%

- Most common incorrect response: THC metabolites are detectable for several months after last use

- Educational emphasis: Compounds with longer elimination (e.g. THC metabolites) can have quite prolonged detection windows.

Snozek et al., submitted 2024
THC distribution

Detection can depend on:

- **Body mass index (BMI)**
  - THC is lipophilic
  - Will accumulate in adipocytes
- **Patterns of use**
  - Dose
  - Mechanism of consumption
  - Timing of use
  - Regularity of use

<table>
<thead>
<tr>
<th>Frequency of use</th>
<th>Detection window (days) at 3 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single use</td>
<td>3 days</td>
</tr>
<tr>
<td>Moderate (4 x/week)</td>
<td>5 days</td>
</tr>
<tr>
<td>Heavy (daily)</td>
<td>10 days</td>
</tr>
<tr>
<td>Chronic heavy use</td>
<td>30 - 60 days</td>
</tr>
</tbody>
</table>

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<th>Detection window (days) at 3 ng/ml</th>
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<td>Single use</td>
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<tr>
<td>Moderate (4 x/week)</td>
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https://www.mayocliniclabs.com/test-catalog/Clinical-and+Interpretive/8898
Case comparisons
Case comparison #1: Patient A

34-year-old male is prescribed buprenorphine for Opioid Use Disorder

<table>
<thead>
<tr>
<th>Component</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine, screening</td>
<td>Positive</td>
<td>Not Detected</td>
</tr>
</tbody>
</table>

- You are reviewing the results of this case.
- What are your initial impressions?
- Would you want additional information?
**Case comparison #1: Patient A**

- Lab’s protocol is to perform reflex confirmation tests.
- What is your interpretation of these results?

<table>
<thead>
<tr>
<th>Component</th>
<th>Result</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine, Quantitative</td>
<td>&gt;4,000 ng/mL</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Norbuprenorphine, Quantitative</td>
<td>16 ng/mL</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Naloxone, Quantitative</td>
<td>2,500 ng/mL</td>
<td>Not Detected</td>
</tr>
</tbody>
</table>
Case comparison #1: Patient B

(primary) 43-year-old female is prescribed buprenorphine for Opioid Use Disorder

<table>
<thead>
<tr>
<th>Component</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine, screening</td>
<td>Positive</td>
<td>Not Detected</td>
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• You are reviewing the results of this case.
• What are your initial impressions?
• Would you want additional information?
Lab’s protocol is to perform reflex confirmation tests.

What is your interpretation of these results?

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<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine, Quantitative</td>
<td>2,500 ng/mL</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Norbuprenorphine, Quantitative</td>
<td>700 ng/mL</td>
<td>Not Detected</td>
</tr>
<tr>
<td>Naloxone, Quantitative</td>
<td>120 ng/mL</td>
<td>Not Detected</td>
</tr>
</tbody>
</table>
What is your diagnosis for patient A?
What is your diagnosis for patient B?

Start presenting to display the poll results on this slide.
Case comparison #1: Summary

- Treatment adherence vs. tampering

- Given individual variation in metabolism, this issue can be complex
- While quantitation in urine is problematic, values can assist in this assessment
- Norbuprenorphine: Buprenorphine ratios of <0.02 are suggestive of spiking
- Consider, however, episodic use and spiking can be difficult to distinguish

Case comparison #2: Patient A

60 yo F prescribed codeine 60 mg / acetaminophen 300 mg up to 4x/day for chronic pain & headache post TBI. Mass spectrometry results:

You are asked to consult on this case.

What are your initial impressions?

What additional information might you want?
Case comparison #2: Patient B

- 37 yo F prescribed amphetamine 20 mg/day with no previous history of SUD undergoes routine military UDT

```
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Immunoassay result</th>
<th>AMP Confirmation</th>
<th>Result</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>Detected</td>
<td>Amphetamine</td>
<td>98,000 ng/mL</td>
<td>&lt; 25 ng/mL</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Not Detected</td>
<td>Methamphetamine</td>
<td>275 ng/mL</td>
<td>&lt; 25 ng/mL</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Not Detected</td>
<td>Phentermine</td>
<td>negative</td>
<td>&lt; 25 ng/mL</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Not Detected</td>
<td>MDA</td>
<td>negative</td>
<td>&lt; 25 ng/mL</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Not Detected</td>
<td>MDMA</td>
<td>negative</td>
<td>&lt; 25 ng/mL</td>
</tr>
<tr>
<td>Opiates</td>
<td>Not Detected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Not Detected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC</td>
<td>Not Detected</td>
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<td></td>
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```

What are your initial impressions? Is there any information that might help explain what’s going on?

What is your initial interpretation of these cases (select all that apply)?
Case comparison #2: Patient A

🌟 Additional testing is performed:
- Codeine: >100,000 ng/mL
- Morphine: 25,992 ng/mL
- Hydrocodone: 605 ng/mL
- Norhydrocodone: 359 ng/mL
- Hydromorphone: 330 ng/mL

🌟 What is your interpretation of these results?
Case comparison #2: Patient B

- Further testing was performed:
  - Urine (d)-amphetamine: 75%
  - Urine (d)-methamphetamine: 83%

- What are the implications of these results?

- Does this change your initial interpretation?

What is your interpretation of these cases given the additional information (select all that apply)?
Case comparison #2: Summary

**Co-ingestion vs. metabolism vs. impurities**

- Quantitation of parent drugs & metabolites is essential
- Manufacturing impurities:
  - In most prescribed meds, impurities RARELY >1%, generally much lower
  - But quality does matter – brand-name vs Internet sourced
- Minor metabolism:
  - As assays get more sensitive & more testing is performed, atypical or minor metabolic pathways do appear
  - E.g., hydromorphone as morphine metabolite is ~10 yrs recognized
  - Stay current with literature and/or consult reputable lab resources
# How to share knowledge?

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How can we best educate colleagues who interpret drug testing? (ECHO, formal talks, etc.)
Final Takeaways/Summary

- Understand that laboratory testing is only one tool of many to support your patients
- Be familiar with the cross-reactivity of each laboratory test or get to know your lab staff
- Recognize the inherent flaws of immunoassay screens and the superiority of definitive/confirmation testing where needed
- Find opportunities to share your expertise with your colleagues
References

1. Snozek et al. Assessing knowledge gaps and educational needs in urine drug test interpretation among healthcare professionals. Submitted, 2024
5. Toxicology Cases for the Clinical and Forensic Laboratory, Garg & Ketha eds. Academic Press, 2020
11. https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/8898