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

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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

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How much experience/training do you have with interpreting urine drug testing?

ⓘ Start presenting to display the poll results on this slide.

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What is your main specialty area?

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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

Demographic group	N (% of total)	Mean Correct (SD)	p (vs Lab PhD)
All respondents	911 (100%)	4.04 (1.33)	
Lab PhD	144 (15.8%)	4.63 (1.15)	Ref.
MD or equivalent	510 (56.0%)	4.14 (1.22)	0.001
Other clinical staff	51 (5.6%)	3.76 (1.26)	<0.0001
MDs by specialty	N (% of MDs)	Mean Correct (SD)	p (vs Toxicology)
Clinical or medical toxicology	28 (5.5%)	4.82 (1.31)	Ref.
Addiction medicine	39 (7.6%)	4.56 (0.94)	n.s.
Psychiatry	22 (4.3%)	4.55 (1.06)	n.s.
Pain management	23 (4.5%)	4.39 (1.03)	n.s.
Emergency medicine	121 (23.7%)	4.26 (1.29)	0.02
Pathology	43 (8.4%)	4.19 (1.28)	0.03
Occupational medicine	73 (14.3%)	4.18 (0.98)	0.01
Primary care and internal medicine	132 (25.9%)	3.66 (1.22)	<0.0001

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

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Which of the following can generally be detected using an opiate immunoassay screen?

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From the survey

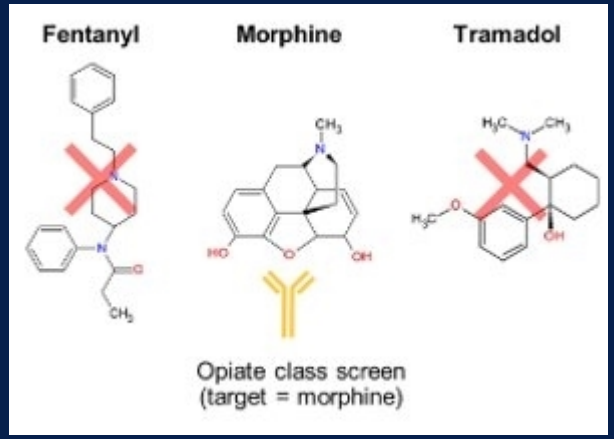
- Overall correct: 77%
- Addiction med correct: 72%

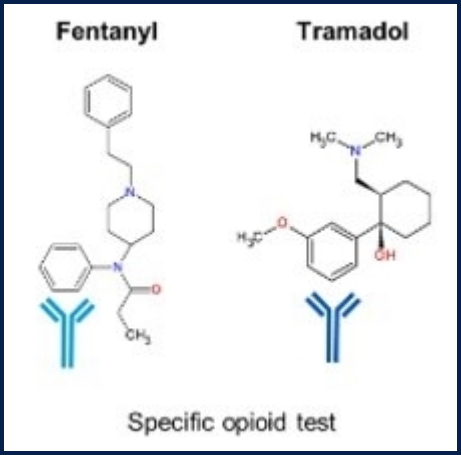
- Most common incorrect response: Fentanyl

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)

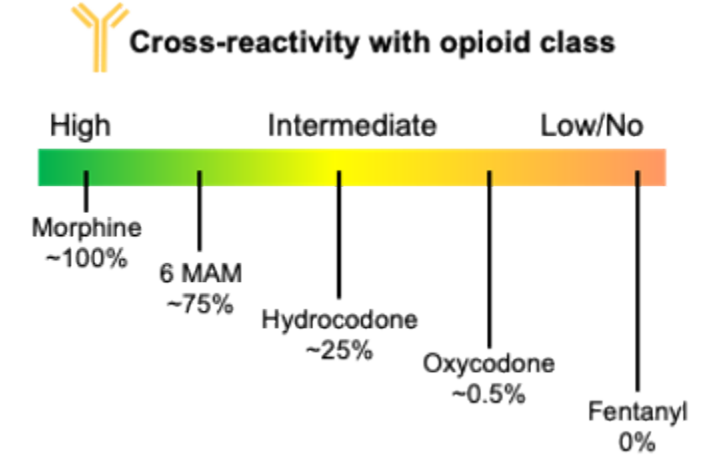




Delaney et al. *Crit Rev Clin Lab Sci* 2022 Aug;59(5):309-331

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



Drug	300 ng/mL cut-off	% Cross reactivity
6-MAM	386 ng/mL	78%
Codeine	224 ng/mL	134%
Hydrocodone	1,086 ng/mL	28%
Hydromorphone	1,425 ng/mL	21%
Oxycodone	>75,000 ng/mL	<0.4%

Delaney et al. *Crit Rev Clin Lab Sci* 2022 Aug;59(5):309-331

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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?

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From the survey

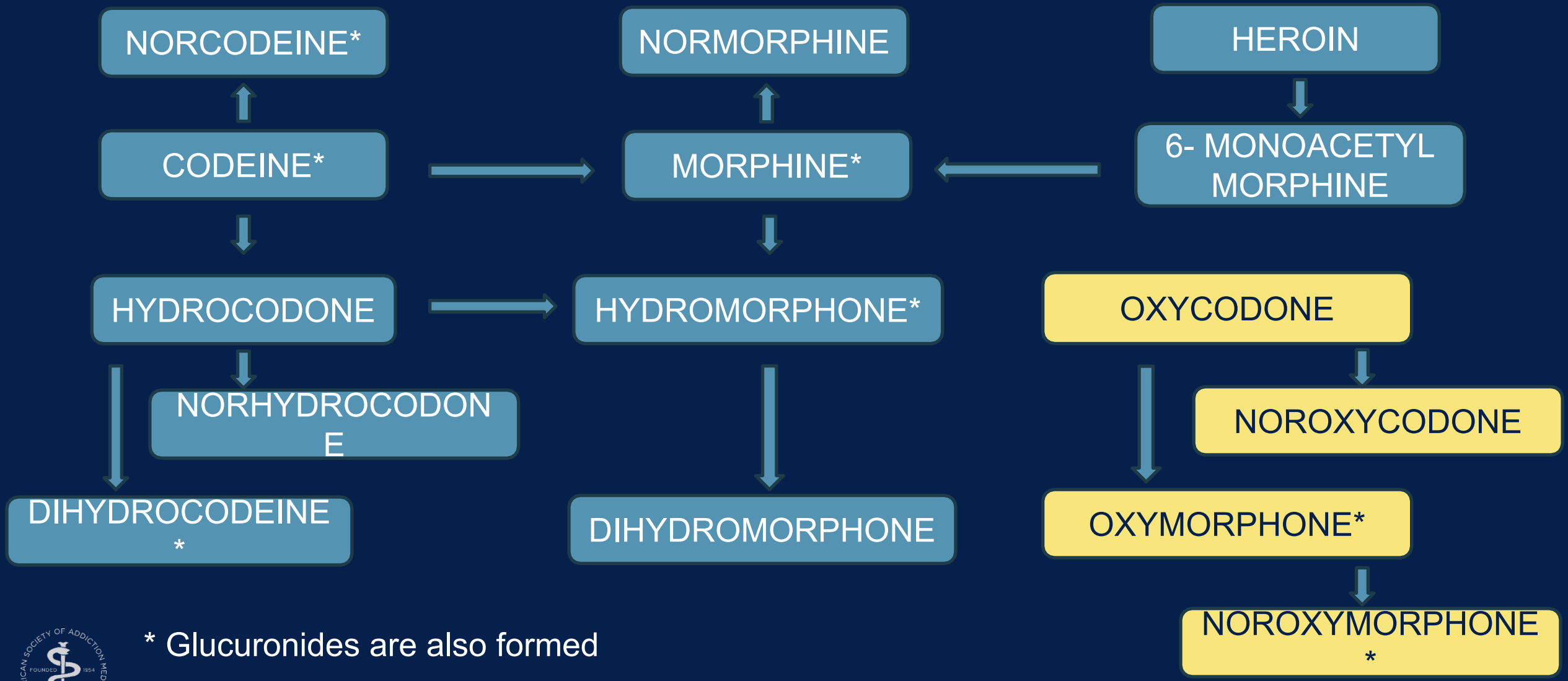
- Overall correct: 55%
- Addiction medicine correct: 63%

- 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



* Glucuronides are also formed

Modified from: Michael Gordon, Ph.D, Medical Pharmacology Chapter 13: Pain Management: Opioids

Opioid Screen General Rules of Thumb

- Standard Opiate Screen:
  - Detects well: Morphine, Codeine
  - Detects ok: Hydrocodone, Hydromorphone, Heroin
  - Does not detect: Oxycodone, Oxymorphone, Methadone, Buprenorphine, Tramadol, Tapentadol, Fentanyl

- Standard Oxycodone Screen:
  - Detects well: Oxycodone, Oxymorphone
  - Does not detect: All others

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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?

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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

Opium:
A mixture of
>25 alkaloids

Naturally occurring alkaloids	Example synthetic compounds
MORPHINE	HEROIN, HYDROMORPHONE
CODEINE	
THEBAINE	OXYCODONE, OXYMORPHONE, BUPRENORPHINE, NALOXONE
PAPAVERINE	

- 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

Lachenmeier DW et al., (2010). Ther. Drug Monit. 32 11–18.; Powers, D et al., (2018). J Forensic Sci, 63: 1229-1235; Dasgupta A, Crit Issues Alcoh Drugs Abuse Testing 2019, Ch 31. Opium Consumption. Lyon (FR): International Agency for Research on Cancer; IARC, 2021.

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

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From the survey

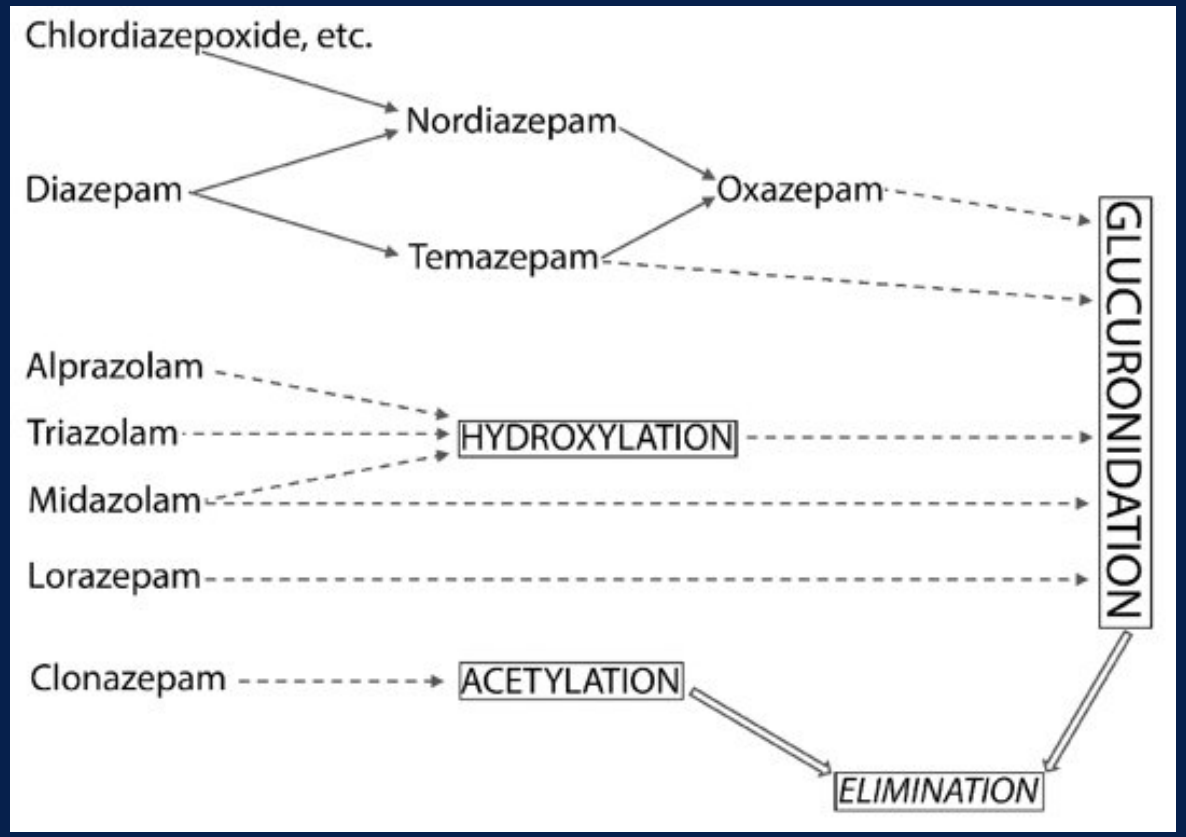
- Overall correct: 67%
- Addiction med correct: 81%

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

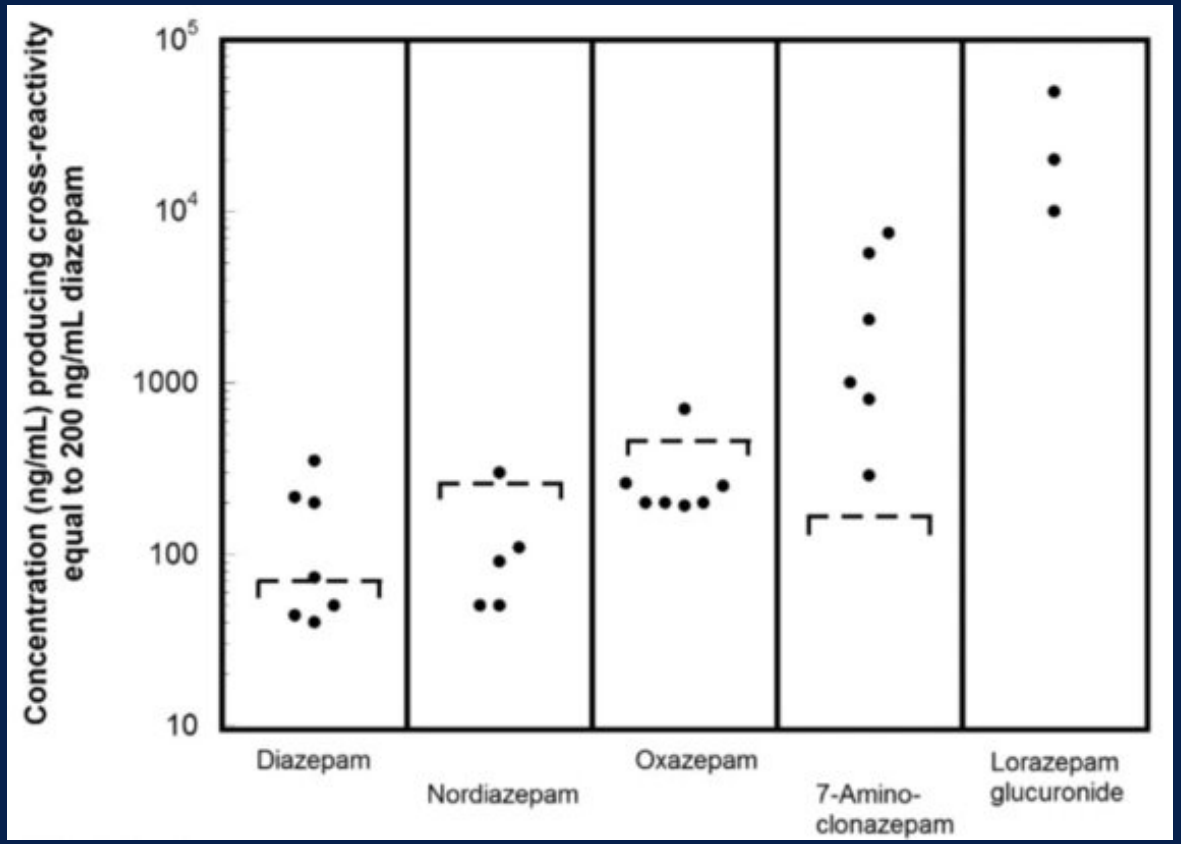
- Immunoassay screens should never be considered definitive

Snozek et al., submitted 2024

Benzo metabolism & assay X-reactivity



Toxicology 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

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Which sample type is best for distinguishing recent use from remote drug use?

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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

Characteristic	Urine	Oral fluid (saliva)	Hair
Observed collections	+	+++	+++
Detection window	++	+	+ to +++
Identify recent use	+/- (light vs remote heavy)	++	-
Identify infrequent use	++	+	++
Contamination risk	++	+	-
Availability of testing	+++	++	+

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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?

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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

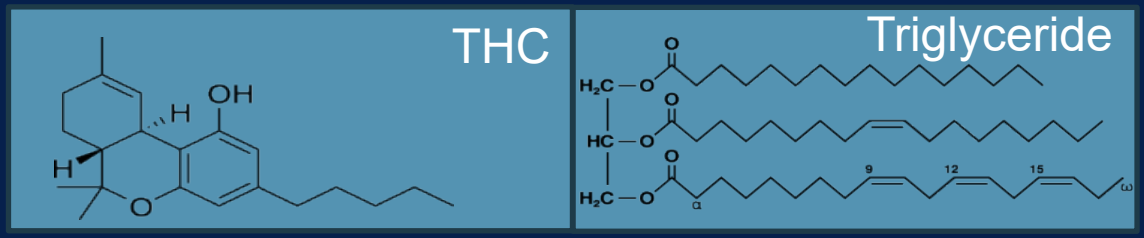
THC distribution

Underweight BMI: <18.5	Healthy 18.5-24.9	Overweight 25-29.9	Obese 30-39.9	Severely obese >40

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

Frequency of use	Detection window (days) at 3 ng/ml
Single use	3 days
Moderate (4 x/week)	5 days
Heavy (daily)	10 days
Chronic heavy use	30 -60 days



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Goodwin RS J Anal Toxicol. 2008 Oct; 32(8): 562–569
Moeller KE Mayo Clin Proc 83: 1, 66–76, 2008

Case comparisons

Case comparison #1: Patient A

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

Component	Result	Reference Range
Buprenorphine, screening	Positive	Not Detected

- 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?

Component	Result	Reference Range
Buprenorphine, Quantitative	>4,000 ng/mL	Not Detected
Norbuprenorphine, Quantitative	16 ng/mL	Not Detected
Naloxone, Quantitative	2,500 ng/mL	Not Detected

Case comparison #1: Patient B

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

Component	Result	Reference Range
Buprenorphine, screening	Positive	Not Detected

- You are reviewing the results of this case.
- What are your initial impressions?
- Would you want additional information?

Case comparison #1: Patient B

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

Component	Result	Reference Range
Buprenorphine, Quantitative	2,500 ng/mL	Not Detected
Norbuprenorphine, Quantitative	700 ng/mL	Not Detected
Naloxone, Quantitative	120 ng/mL	Not Detected

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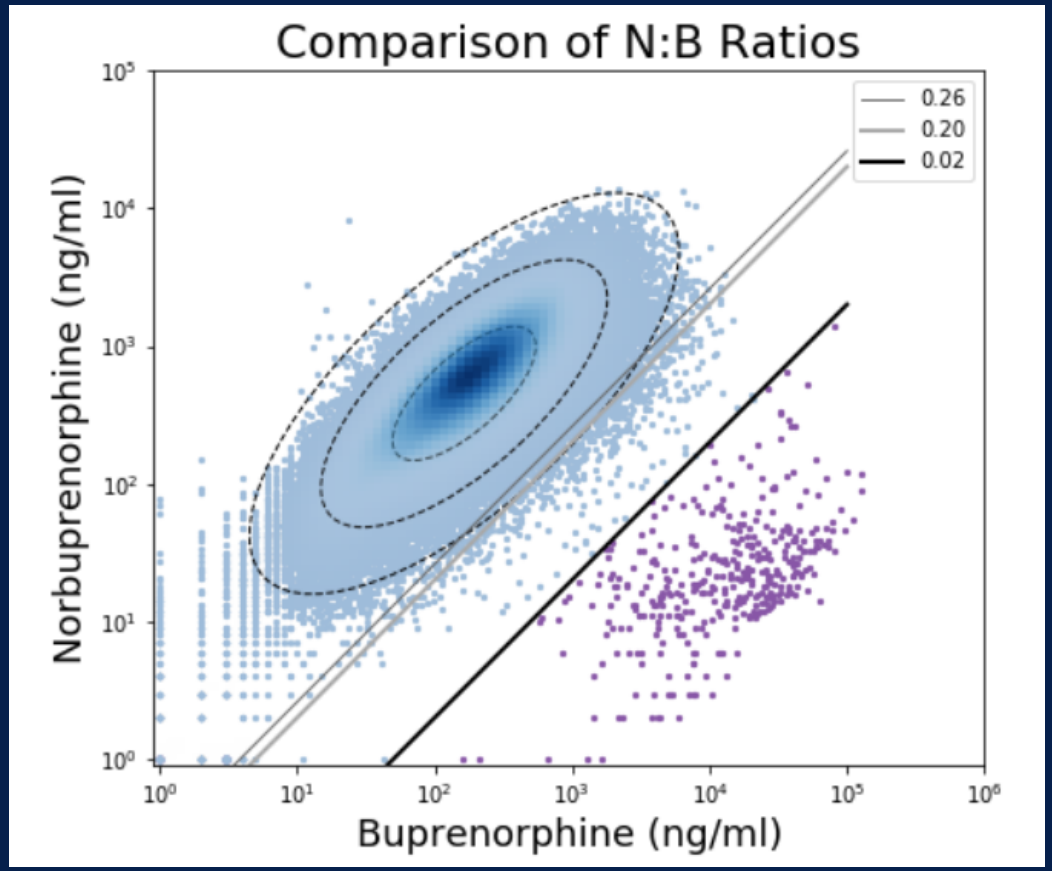
What is your diagnosis for patient A?
What is your diagnosis for patient B?

ⓘ 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



Warrington, JS. *et al.* Use of urinary naloxone levels in a single provider practice: a case study. *Addict Sci Clin Pract* **15**, 3 (2020); Warrington JS, et al. J Addict Med. 2020 Dec;14(6):e344-e349.

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:

	February 2017	March 2017	Cutoff
Codeine	Present	Present	25 ng/mL
Codeine-6-β-glucuronide	Present	Present	100 ng/mL
Morphine	Not detected	Present	25 ng/mL
Morphine-6-β-glucuronide	Present	Present	100 ng/mL
6-monoacetylmorphine	Not detected	Not detected	25 ng/mL
Hydrocodone	Present	Present	25 ng/mL
Norhydrocodone	Present	Present	25 ng/mL
Dihydrocodeine	Not detected	Present	25 ng/mL
Hydromorphone	Not detected	Not detected	25 ng/mL
Hydromorphone-3-β-glucuronide	Not detected	Present	100 ng/mL
Oxycodone	Not detected	Not detected	25 ng/mL
Noroxycodone	Not detected	Not detected	25 ng/mL

You are asked to consult on this case.

What are your initial impressions?

What additional information might you want?

Cervinski & Jannetto *Clin Chem* 65(2):236-240 2019

Case comparison #2: Patient B

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

Drug class	Immunoassay result
Amphetamines	Detected
Benzodiazepines	Not Detected
Barbiturates	Not Detected
Cocaine	Not Detected
Fentanyl	Not Detected
Opiates	Not Detected
Oxycodone	Not Detected
THC	Not Detected

AMP Confirmation	Result	Cut-off
Amphetamine	98,000 ng/mL	< 25 ng/mL
Methamphetamine	275 ng/mL	< 25 ng/mL
Phentermine	negative	< 25 ng/mL
MDA	negative	< 25 ng/mL
MDMA	negative	< 25 ng/mL

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

Adapted from Jemionek et al. *J Anal Tox*; 2009: 33(3):170 – 173

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What is your initial interpretation of these cases (select all that apply)?

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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?

Cervinski & Jannetto *Clin Chem* 65(2):236-240 2019

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?

Adapted from Jemionek et al. *J Anal Tox*; 2009: 33(3):170 – 173

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What is your interpretation of these cases given the additional information (select all that apply)?

ⓘ Start presenting to display the poll results on this slide.

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.)

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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

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