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Mayo Medical Laboratories

Why is Laboratory Testing for Pain Management so Painful?



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Disclosure

- Relevant Financial Relationships:
 - None
- Off Label Usage:
 - None

Objectives

- Recognize the clinical utility and limitations of the following urine drug tests used to support pain management:
 - Immunoassays
 - Mass spectrometry-based assays
- Define the metabolic profiles of common classes of pain management medications and how to interpret screening/confirmatory test results.
- Assess the role of adulterant/specimen validity testing in pain management and the use of alternative specimen types.

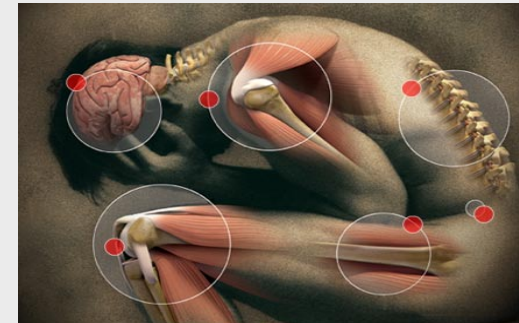
Pain Management Over the Past 25 Years

- 1990's inadequate pain treatment was recognized as a growing public health issue
- Congress passed, President Clinton signed into law a bill declaring 2001-2010 the “Decade of Pain Control and Research”
- The Joint Commission standards require the country's 18,000 hospitals, nursing homes, and other care facilities need to assess, manage, and if necessary treat pain.
- Pain is considered the “fifth vital sign”



Pain is Still a Major Public Health Issue

- Pain is cited as the most common reason Americans access the health care system
- Pain affects more Americans than diabetes, heart disease and cancer combined
- 1 in every 4 Americans have suffered from pain that lasts >24 hours and millions more suffer from acute pain
- Pain is a major contributor to health care costs (~\$635 billion/year in medical treatment and lost productivity)
- Sale of opioid pain relievers (OPR) quadrupled between 1999 and 2010
- Enough OPR were prescribed in 2010 to medicate every American adult around the clock (q4h) for a month
- Large number of patients (>40%) still report being inadequately treated for pain



How Do Physicians Manage Pain?

Nonpharmacologic

- Conventional
 - Physical therapy
 - Electrical stimulation
 - Surgery
- Alternative
 - Massage
 - Acupuncture
 - Herbals

Pharmacologic

- Nonopioids
 - Aspirin, acetaminophen, ibuprofen
 - Adjuvant medications
 - Anti-depressants (amitriptyline, nortriptyline, paroxetine, etc)
 - Anti-epileptic drugs (Carbamazepine, gabapentin, pregabalin, etc)
 - Benzodiazepines (clonazepam, diazepam, lorazepam, etc...)
- Opioids
 - Morphine, oxycodone, hydrocodone, hydromorphone, etc

Role of Opioids in Pain Management

Acute pain

- Extremely useful
- Used in combination with anti-inflammatory agents (Ibuprofen, Aspirin, etc)
- Can taper dosage and stop as source/cause heals

Chronic pain

- Sometimes useful
- Used in combination with other medications (anti-depressants, anti-epileptic drugs, etc)
- Length of time and dosage varies greatly

Issues with opioids

- Narrow therapeutic index
- Large interpatient variability in dosage
- Abuse, misuse, addiction/diversion potential

Walking the Tightrope

“Using Opioids for Pain Management”

Prescribe opioids

- Patient’s needs (Quality of Life)
- Clinical goal to manage pain
- Ethical obligation to prevent, diagnose, and treat pain
- Legal/regulatory obligation to manage and if needed treat pain

Don’t prescribe opioids

- Abuse/misuse potential
- Limited objective measures of pain
- Limited tools to follow patients
- Lack of adequate prescription monitoring information
- Regulatory scrutiny

Clinical Approach to Pain Management



Clinical evaluation of the patient

- Med Hx, Physical exam
- Characterization of pain
- Past Hx of substance abuse



Written plan/informed consent

- Serum/urine med levels/screening
- No. and frequency of prescription refills
- Reason therapy may be discontinued



Ongoing review/consultation

- Monitor activities of daily living/VAS
- Signs of addiction/abuse/ADRs
- Lab tests as needed

Why Do Physicians Use UDTs to Monitor Pain Management Patients?

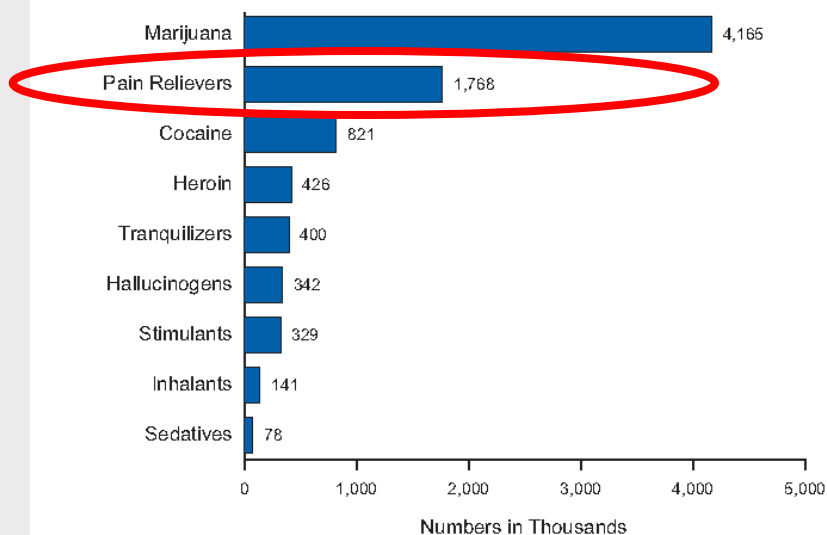
1. Clinical Practice Guidelines:

- American Society of Interventional Pain Physicians (ASIPP) Guidelines
 - Urine drug testing (UDT) must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy (Evidence: Good)
 - Verify adherence/compliance to prescribed medications
 - Identify undisclosed drugs
 - Discourage drug misuse, abuse, diversion

The Abuse Potential for Opioids is High

- 13.3 % (~34 million) Americans ≥ 12 years used a pain reliever non-medically at least once in their lifetime
- 4.3% (~11 million) Americans ≥ 12 years used a pain reliever non-medically at least once in the past year

**2011 DSM-diagnosable Drug Dependence/Abuse
in the Past Year Among Persons Aged 12 or Older**



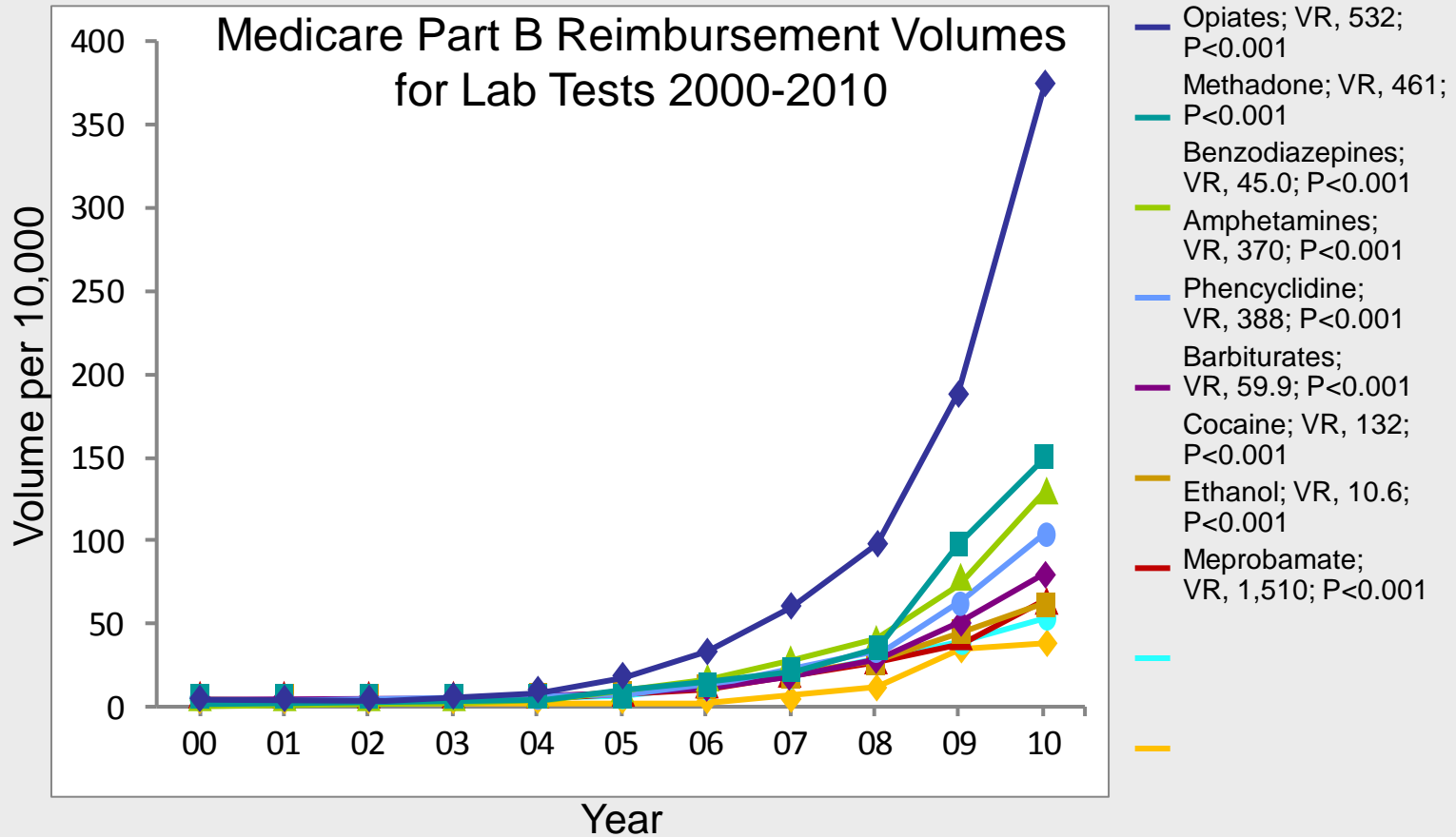
Why Do Physicians Use UDTs to Monitor Pain Management Patients?

1. Clinical Practice Guidelines:
2. Financial Reasons:
 - Non-adherence to opioid therapy leads to increased healthcare utilization and costs
 - Early monitoring of opioid adherence using UDTs may provide substantial cost savings associated with health care issues incurred in non-adherent chronic pain patients

Why Do Physicians Use UDTs to Monitor Pain Management Patients?

1. Clinical Practice Guidelines:
2. Financial Reasons:
3. Regulatory Scrutiny (State and Federal Regulations):
 - State Level:
 - Physicians can prescribe controlled substances w/ state board issued medical license.
 - Some states may require additional registration
 - Most states also have a regulation, guideline, or policy statement for prescribing opioid analgesics for pain
 - Some states discourage or prohibit physicians from prescribing opioids to patients whom they know or should know are using controlled substances for nontherapeutic purposes
 - Federal Level:
 - Must first satisfy state requirements of licensure and registration
 - DEA issues a federal controlled substances registration
 - Federal laws/regulations do NOT prohibit the use of opioids to treat pain if a patient is abusing controlled substances

Are Physician's Ordering UDTs?



Issues With Laboratory Testing for Pain Management

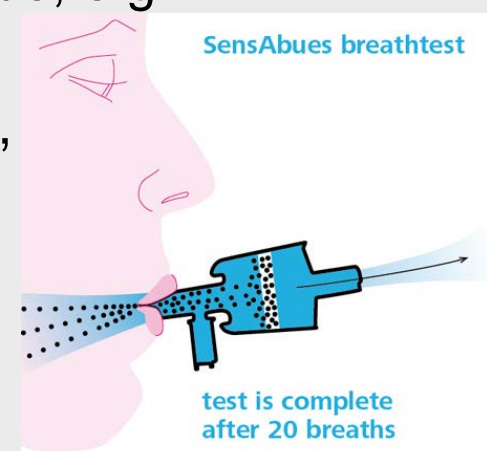
- Where are tests done?
 - Office vs. lab
- What specimen should be used?
- Qualitative vs. Quantitative Tests?
- Interpretation of test results
 - Screen vs. confirmatory/targeted assays
 - Complicated metabolic pathways/metabolite ratios
 - Compliance vs. more information (dose)
- Follow-up testing
 - To “confirm” or “not to confirm” screening assays
- Regulatory/reimbursement issues

What Specimen is Best?

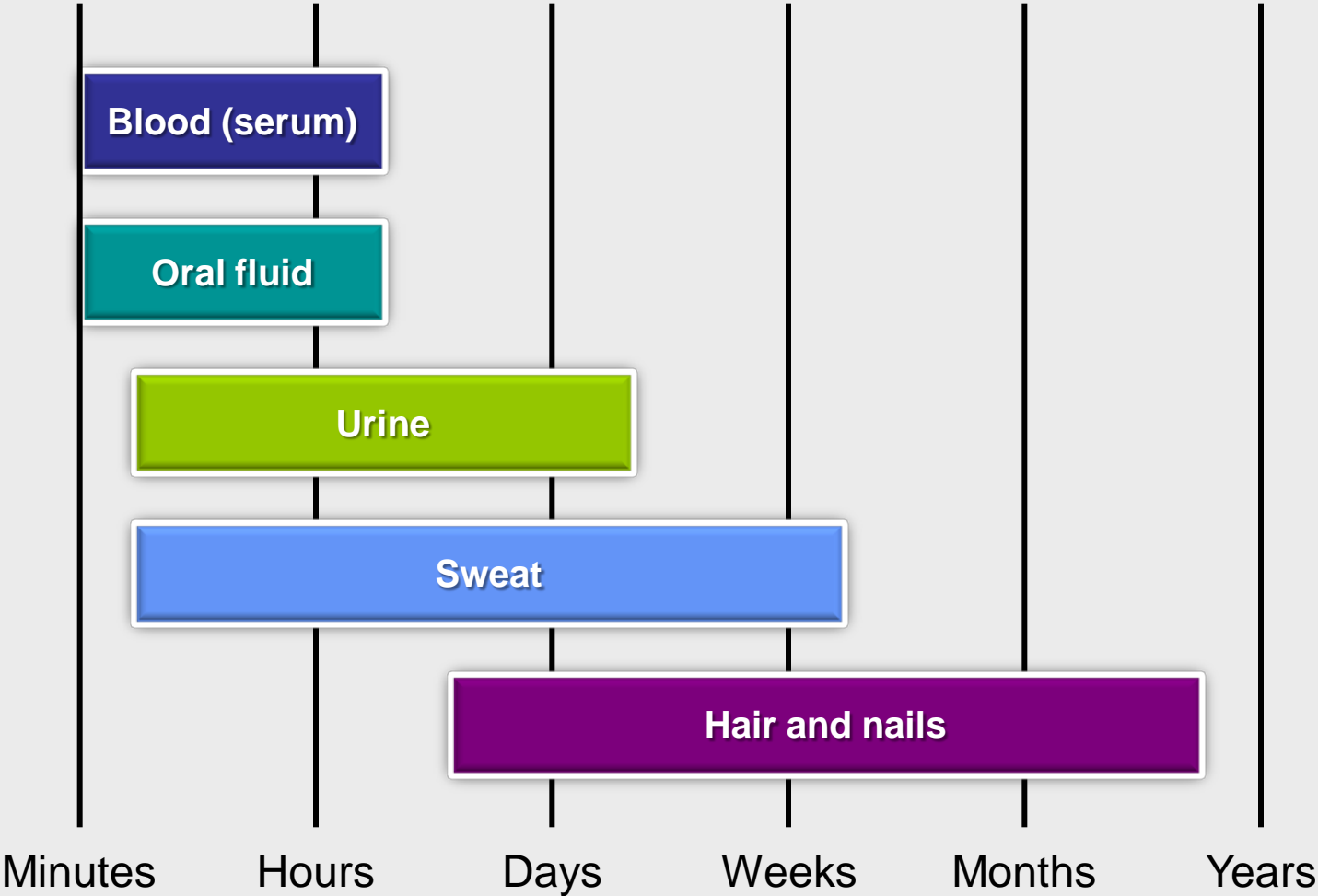
Specimen	Advantages	Disadvantages
Urine	Ease of collection Good detection window Testing widely available	Easy to adulterate Doesn't identify frequency of dosing Doesn't reliably estimate dose taken
Blood (serum/plasma)	Recent usage Difficult to adulterate Correlates better to dose/clinical symptoms	Invasive Short detection window Limited availability
Oral fluid (saliva)	Recent usage Noninvasive Ease of collection	Low concentrations Limited availability \$\$\$ Mainly parent drug
Hair	Long detection time	Limited availability \$\$\$

Breath: The Next Frontier?

- SensAbues:
 - During normal breathing microparticles are formed from the airway liquid fluid by the closure and opening of bronchioles.
 - These particles form a bioaerosol that is carried out in the exhaled breath.
 - Collected particles can be used for drugs of abuse detection by analysis with high sensitivity technique, e.g. LC-MS/MS
- Possible to detect amphetamine, methamphetamine, THC, cocaine, MDMA, buprenorphine, methadone, heroin, benzodiazepines, nicotine and more.



Approximate Detection Times By Specimen Type



Types of UDTs

Screening assays

- Identify drugs and/or drug metabolites with variable specificity often by drug class
- Typically immunoassay-based
- POC or laboratory-based
- Economical
- Quick TAT (<24 hours)
- Qualitative/semi-quant results
- Limited sensitivity and specificity
- Higher cutoffs

Quantitative/Confirmatory assays

- Identify and quantify the drug and/or drug metabolite with high specificity
- Typically GC/MS or LC-MS/MS
- Laboratory-based
- More labor intensive (higher cost)
- Longer TAT (2-7 days)
- Quantitative results
- Optimal sensitivity and specificity
- Lower cutoffs

Screening Assays



Types

- Traditional screening assays
 - Point-Of-Collection Tests (POCT)
 - Laboratory-based (commercial immunoassays)
- Targeted screening assays
 - Laboratory-Developed-Tests (LDT) using TOF-MS or other MS/MS analyzers

Test	Advantages	Disadvantages
POCT	Fastest TAT	Limited sensitivity
	CLIA-waived versions available	Higher cutoffs
	Instant result to review/discuss with patient	Limited specificity
	Great if patient resides far from care	Maintain inventory/regulatory compliance
	Good for high-risk patient	Higher cost
Immunoassay-lab based	Automated	Limited sensitivity
	CLIA environment	
	Most economic	Limited specificity
	Larger test menu	
Targeted screen	Better sensitivity	Limited availability
	Better specificity	
	Broadest test menu	

Cross-Reactivity Issues With Immunoassays

- Urine Opiate immunoassay target:
 - Morphine
- Concentration required to trigger a “positive” Opiate result:

Drug	300 ng/mL cutoff	2,000 ng/mL cutoff
6-acetylmorphine	435 ng/mL	4,182 ng/mL
Codeine	102-306 ng/mL	660-1,980 ng/mL
Hydrocodone	247 ng/mL	1,545 ng/mL
Hydromorphone	498 ng/mL	5,349 ng/mL
Oxycodone	1,500 ng/mL	48,000 ng/mL
Oxymorphone	9,300 ng/mL	>100,000 ng/mL

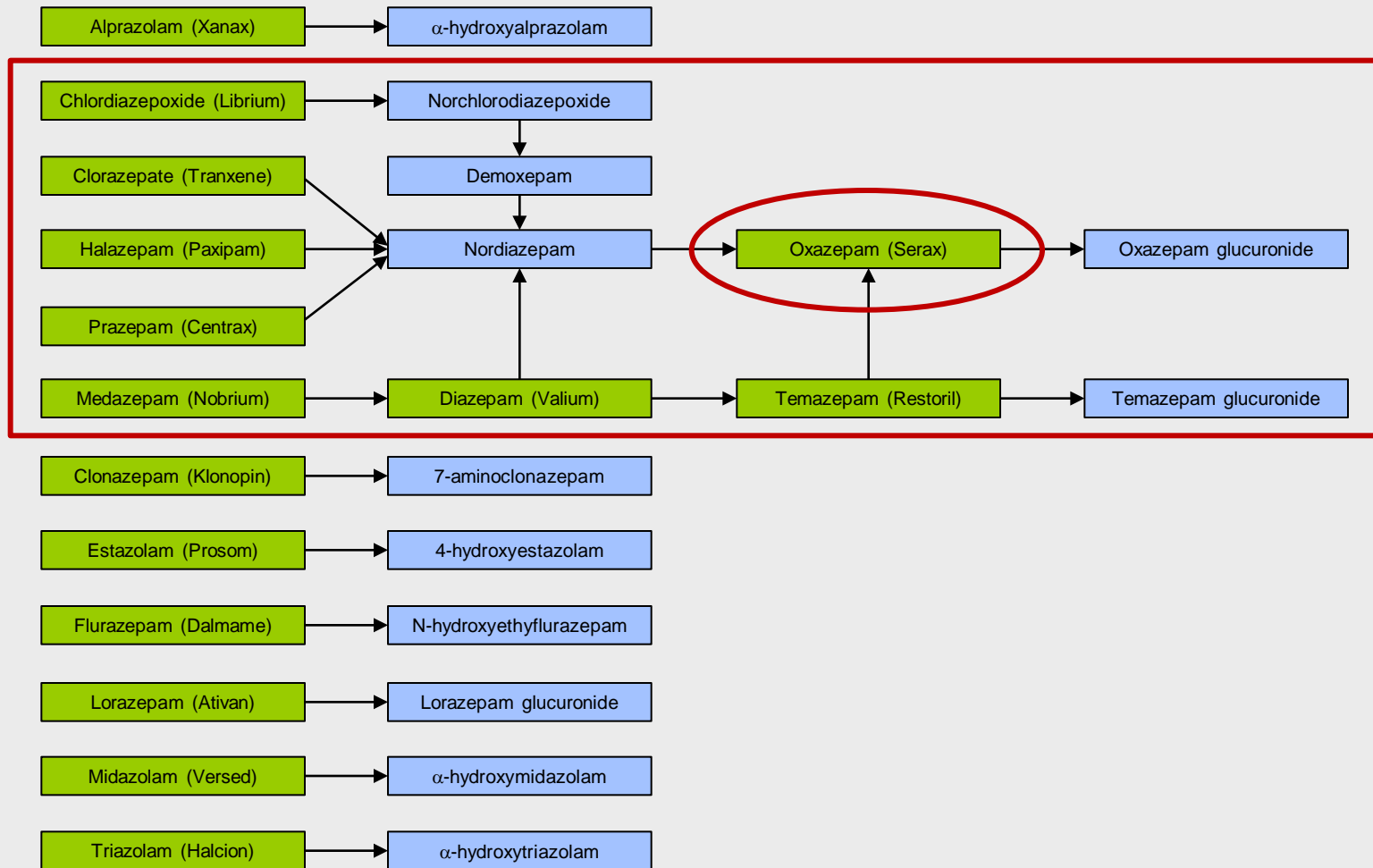
Cross-Reactivity Issues with Immunoassays

- Common Benzodiazepine immunoassay targets:
 - Oxazepam
 - Nordiazepam
 - Lormetazepam

Concentration required to trigger a “Positive” Benzodiazepine result

Drug	200 ng/mL cutoff
7-aminoclonazepam	5,700 ng/mL
α -hydroxyalprazolam	100 ng/mL
Diazepam	44 ng/mL
Lorazepam glucuronide	>10,000 ng/mL
Medazepam	150 ng/mL
Midazolam	130 ng/mL
Temazepam	140 ng/mL

Simplified Benzodiazepine Metabolism



What Does a Positive Urine Drug Screen (Immunoassay) Result Really Mean?

- Patient is compliant/adherent (took the prescribed drug as directed)
- Patient added drug to the urine after collection
- Patient took one dose prior to collection (partial compliance)
- Patient took another drug which also cross-reacts with the test
- Collection or laboratory error/mix-up
- False-positive result



Limitations of Immunoassays

False Positives

Screening test (drug class)	Agents that can give a positive result
Amphetamine/Methamphetamine	Phentermine Pseudoephedrine Adderall Selegiline Benzphetamine Vicks inhaler
Benzodiazepine	Oxaprozin Sertraline
Opiates	Poppy seeds Naloxone
PCP	Chlorpromazine Dextromethorphan

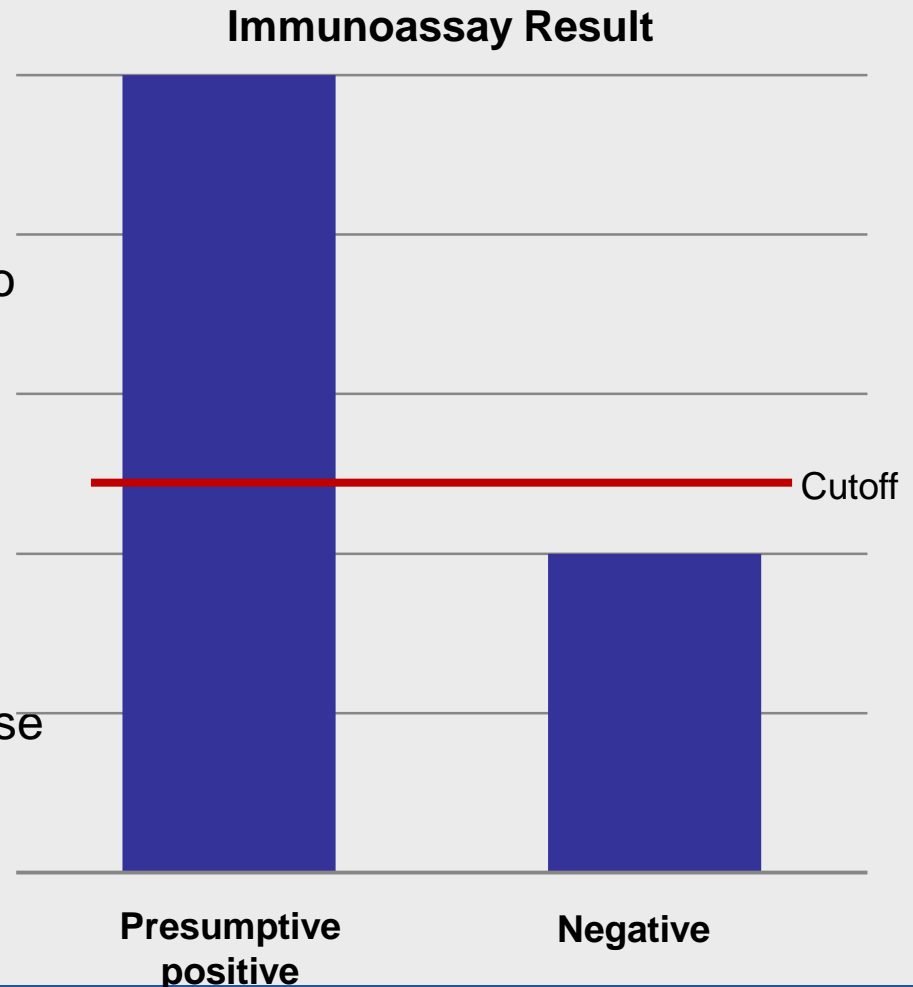
What Does a Negative Urine Drug Screen (Immunoassay) Result Really Mean?

- Patient is NOT compliant/adherent
- Patient took the drug incorrectly (i.e., less frequently/lower dosage)
- Altered pharmacokinetic variables
 - Drug wasn't absorbed
 - Altered metabolism or elimination
- Dilute or adulterated urine
- Test doesn't cross-react with drug of interest (i.e., opiate assay and Methadone; wrong test for the drug of interest)
- Collection or laboratory error/mix-up
- Drug present, but below the cutoff/detection limit (false-negative result)

Limitations of Immunoassays

False Negatives and Detection Limits

- Important variables that need to be considered
 - Assay cutoff
 - Assay vendor
 - Drug formulation/dose
 - Patient pharmacokinetics
 - Sample type
 - Collection time from last dose
 - Specimen integrity/quality



Limitations of Immunoassays

False Negatives

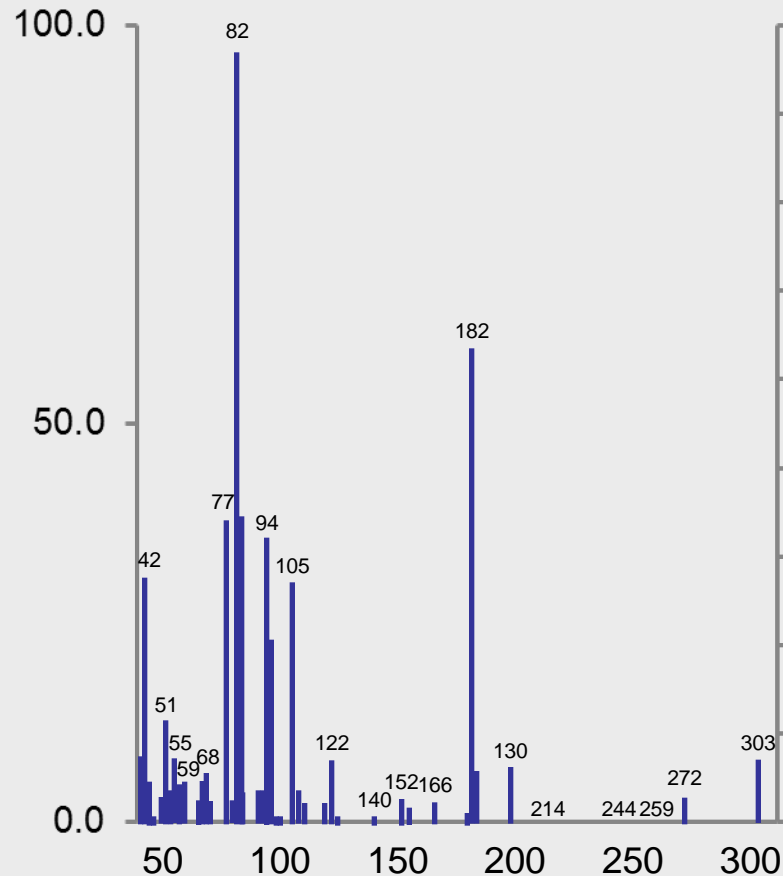
Drug	Immunoassay	Immunoassay cutoff	LC/MS/MS cutoff	Samples missed (%)
Codeine	Opiates	300 ng/mL	50 ng/mL	~30%
Hydrocodone				~23%
Hydromorphone				~69%
Morphine				~12%
Oxycodone	Oxycodone	100 ng/mL	50 ng/mL	~5%
Oxymorphone				~10%
Alprazolam (α -hydroxyalprazolam)	Benzodiazepine	200 ng/mL	20 ng/mL	~53%
Lorazepam			40 ng/mL	~18%

Proposed Urine Cutoffs

Drug/drug class	Current cutoff (ng/mL)	Proposed cutoff (ng/mL)
Amphetamines	500 ng/mL	50 ng/mL
Benzodiazepines		
<ul style="list-style-type: none"> • 7-aminoclonazepam • Alphahydroxyalprazolam 	200 ng/mL	10 ng/mL
Opiates/opioids		
<ul style="list-style-type: none"> • Codeine • Morphine • Hydrocodone • Hydromorphone 	2,000 ng/mL (300 ng/mL)	25 ng/mL
Oxycodone		
Oxymorphone	100 ng/mL	25 ng/mL
Methadone	300 ng/mL	50 ng/mL

Quantitative/Confirmatory Testing

- Chromatography-based
 - GC/MS
 - LC/MS/MS
 - UPLC/MS
- Advantages
 - Sensitivity:
 - Lower cutoffs compared to Immunoassay screens
 - Specificity
 - Can identify specific parent drug and/or metabolites
 - Quantitative
- Disadvantages
 - More expensive, time-consuming



When is Quantitative (Confirmatory) Testing Indicated?



- Unexpected qualitative (screening) results
- Drug prescribed doesn't cross-react with qualitative screen
- Legal/Forensic implications
- Evaluate patient pharmacokinetics and dose (blood/serum preferred)
- Concentrations may be required to interpret the results or make management decisions
 - Helps determine what drug(s) was taken
 - May identify drug-drug interactions or changes in pharmacokinetics
 - May help interpret serial monitoring for an individual patient
 - May identify adulteration
 - May identify pharmaceutical impurities

Another Consideration When Interpreting UDTs = Pharmaceutical Impurity

Allowable Pharmaceutical Impurities Found in Opioids

Drug (generic name)	Pharmaceutical process impurities (Note: These are not metabolites)	Allowable pharmaceutical impurity limit (%)*
Hydrocodone	Codeine	0.15
Hydromorphone	Morphine Hydrocodone	0.15 0.1
Morphine	Codeine	0.5
Oxycodone	Hydrocodone	1.0
Oxymorphone	Hydromorphone Oxycodone	0.15 0.5

What Does UDT Result Mean?

Differential Diagnosis Based on UDT Result

Prescribed drug not found	Illicit drug found	Nonprescribed drug found
Noncompliant	Supplemental pain relief	Supplemental pain relief
Diversion	Addiction	Addiction
Hoarding	Lab error	Lab error
Lab error	Deliberate use	Doctor shopping
Timing issue (specimen collection to last dose)	Trading prescription for illicit drug	Metabolite of prescribed drug
Binge use		Uncoordinated care
Taking med prn		Deliberate use
Rapid metabolizer		
Drug-drug interaction		

Clinical Case Studies

Patient #1 Patient #2



Oxycodone 20 mg/day



Patient #1
Negative

Urine Opiate Screen
Cutoff: 300 ng/mL

Patient #2



Is Patient 1 noncompliant?
Is it a false-negative result?

Clinical Case Studies

Patient #1 Patient #2



Oxycodone 20 mg/day



Patient #1
Negative

Urine Opiate Screen
Cutoff: 300 ng/mL

Patient #2
Positive

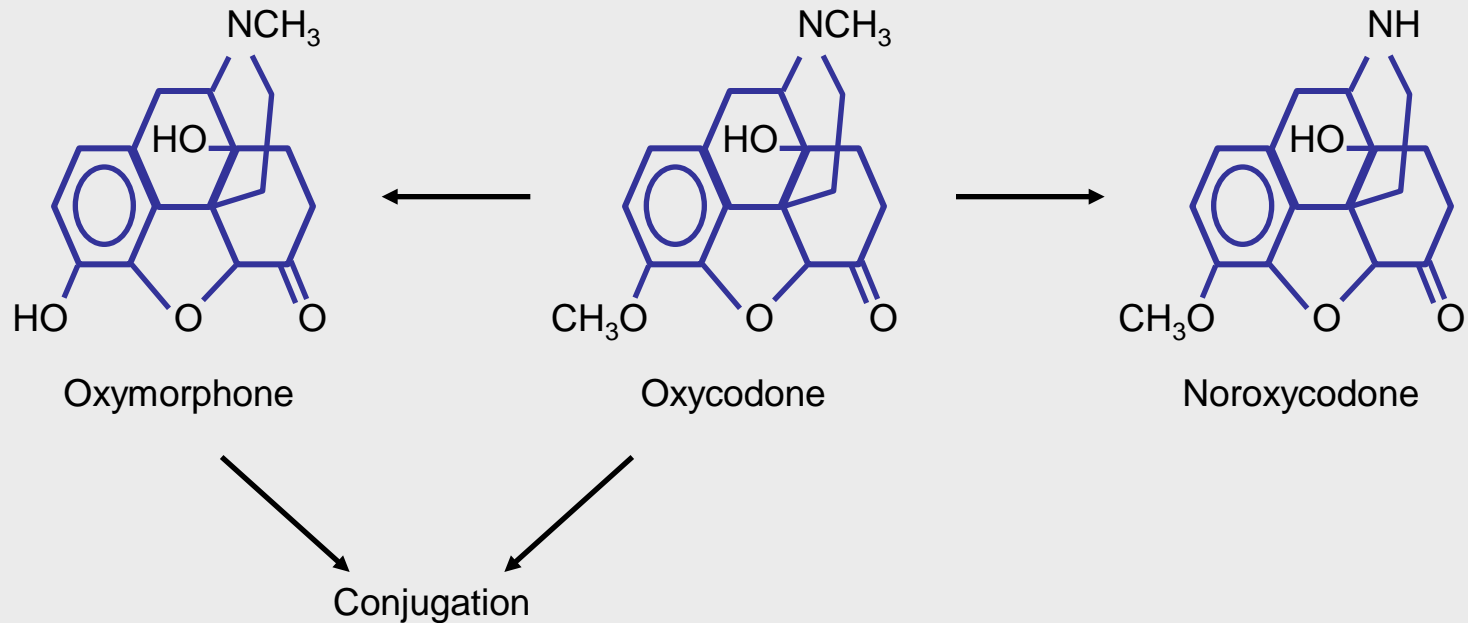


Urine Opiate Confirmation

Codeine: Not Detected
Morphine: Not Detected
Hydrocodone: Not Detected
Hydromorphone: Not Detected
Oxycodone: 1,235 ng/mL
Oxymorphone: 746 ng/mL

Where Did the Oxymorphone (Opana[®], Numorphan[®]) Come From?

Oxycodone metabolism



Why was the Urine Opiate Immunoassay Negative?

Concentration required to trigger a “Positive” urine opiate result:

Drug	300 ng/mL Cutoff	2,000 ng/mL Cutoff
6-Acetylmorphine	435 ng/mL	4,182 ng/mL
Codeine	102-306 ng/mL	660-1,980 ng/mL
Hydrocodone	247 ng/mL	1,545 ng/mL
Hydromorphone	498 ng/mL	5,349 ng/mL
Oxycodone	1,500 ng/mL	48,000 ng/mL
Oxymorphone	9,300 ng/mL	≥ 100,000 ng/mL

Patient #1 Results:

- Oxycodone: 1,235 ng/mL
- Oxymorphone: 746 ng/mL

Final Interpretation:

- Patient #1 is likely compliant and taking the prescribed oxycodone.

Clinical Case Studies

Patient #1 Patient #2



Oxycodone 20 mg/day



Patient #1
Negative

Urine Opiate Screen
Cutoff: 300 ng/mL

Patient #2
Positive



Urine Opiate Confirmation

Codeine: Not Detected
Morphine: Not Detected
Hydrocodone: Not Detected
Hydromorphone: Not Detected
Oxycodone: 1,235 ng/mL
Oxymorphone: 746 ng/mL

**Is Patient #2 compliant?
Is this patient using any
other opiates?**

Clinical Case Studies

Patient #1 Patient #2



Oxycodone 20 mg/day



Patient #1
Negative

Urine Opiate Screen
Cutoff: 300 ng/mL

Patient #2
Positive

Urine Opiate Confirmation

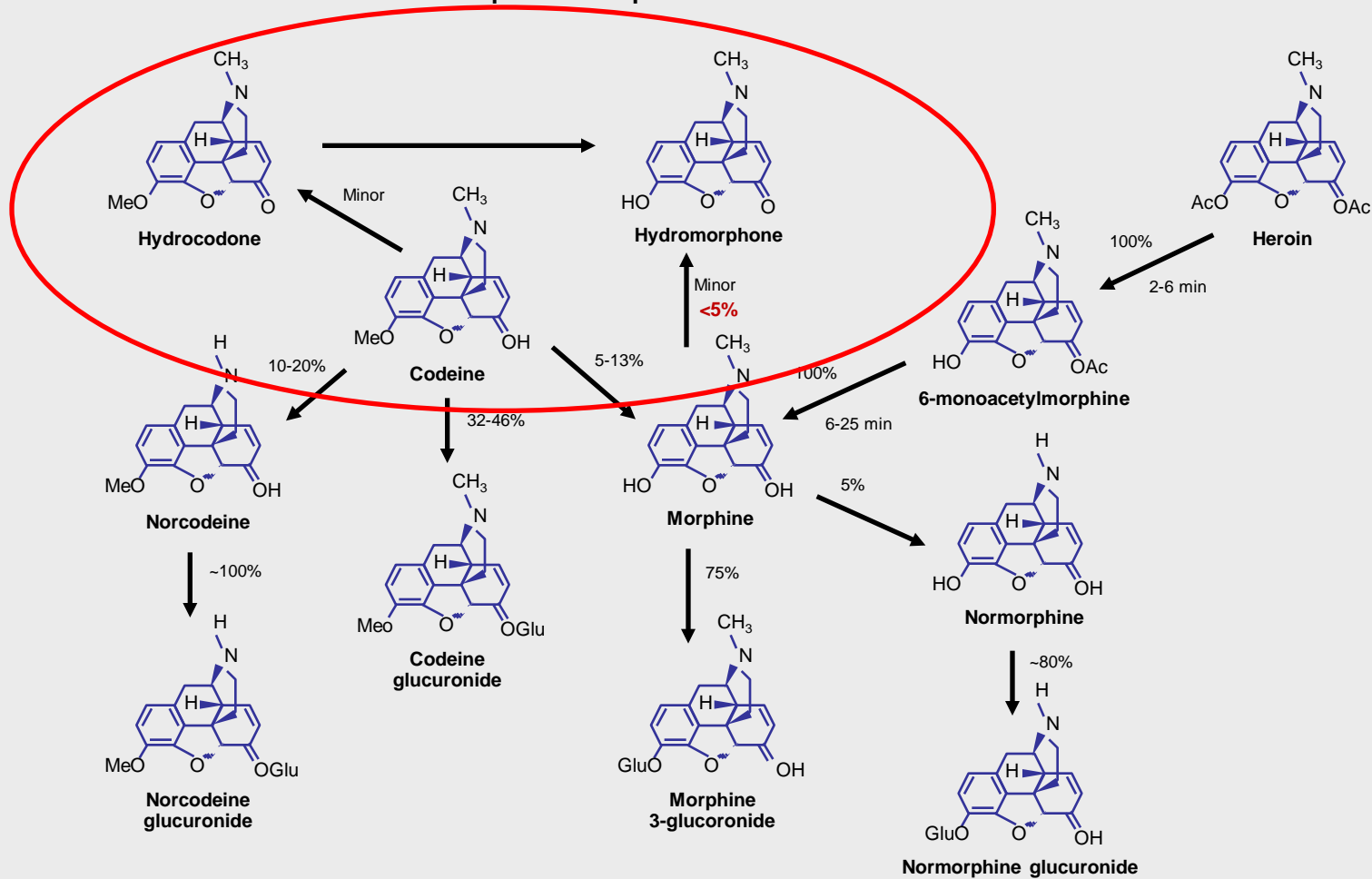
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Hydrocodone: Not Detected
Hydromorphone: Not Detected
Oxycodone: 1,235 ng/mL
Oxymorphone: 746 ng/mL

Urine Opiate Confirmation

Codeine: Not Detected
Morphine: Not Detected
Hydrocodone: 2,504 ng/mL
Hydromorphone: 2,013 ng/mL
Oxycodone: 2,407 ng/mL
Oxymorphone: 1,836 ng/mL

Where did the Hydrocodone/Hydromorphone Come From?

Simplified Opioid Metabolism



Other Considerations Include Pharmaceutical Impurities

Allowable Pharmaceutical Impurities Found in Opioids

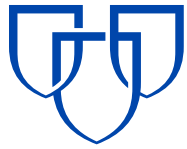
Drug (generic name)	Pharmaceutical process impurities (NOTE: These are NOT metabolites)	Allowable pharmaceutical impurity limit (%)*
Hydrocodone	Codeine	0.15
Hydromorphone	Morphine	0.15
	Hydrocodone	0.10
Morphine	Codeine	0.50
Oxycodone	Hydrocodone	1.00
Oxymorphone	Hydromorphone	0.15
	Oxycodone	0.50

Patient #2 Results:

- Hydrocodone: 2,504 ng/mL
- Hydromorphone: 2,013 ng/mL
- Oxycodone: 2,407 ng/mL
- Oxymorphone: 1,836 ng/mL

Final Interpretation:

- Patient #2 most likely taking oxycodone (prescribed) and hydrocodone (not prescribed).



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Adulteration



Ways to Adulterate Urine

1. Substitution
2. In vivo adulterants
3. In vitro adulterants



Substitution

Single Use Frozen Urine



\$59.95 + S/H

PROCEED TO SECURE
CHECKOUT ▶

Contents:

- 1 - I.V. bag filled with 2 fluid ounces of real human urine.
- 1 - heating element
- 1 - elastic belt
- 1 - temperature strip
- 1 - instructions

Single Use Dehydrated Urine



\$59.95 + S/H

PROCEED TO SECURE
CHECKOUT ▶

Contents:

- 1 - I.V. bag filled with 2 fluid ounces of distilled water.
- 1 - dehydrated urine vial
- 1 - heating element
- 1 - temperature strip
- 1 - syringe
- 1 - elastic belt
- 1 - instructions

Dehydrated Urine Kit



\$99.95 + S/H

PROCEED TO SECURE
CHECKOUT ▶

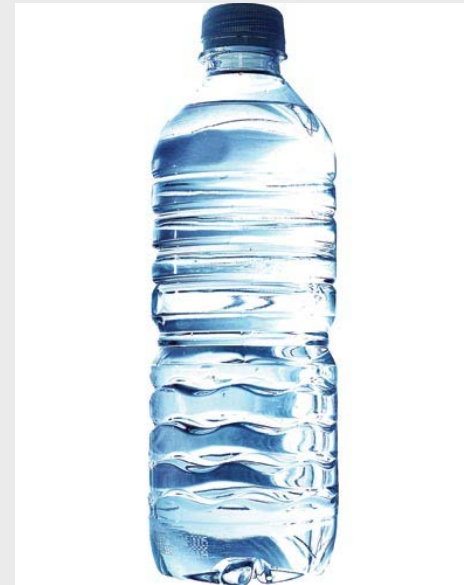
Contents:

- 1 - I.V. bag filled with 4 fluid ounces of distilled water
- 2 - dehydrated urine vials
- 2 - heating elements
- 1 - temperature strip
- 1 - syringe
- 1 - elastic belt
- 1 - instructions

[Click here to see Frozen Kit](#)

In vivo adulterants

- Excess water ingestion
- “Flushing” or “Detoxification” products
 - Naturally Klean Herbal Tea
 - Golden Seal root
 - Hydrochlorothiazide



In Vitro Adulterants

Purpose:

- Interfere with Immunoassay's

History:

- Originally found in bathrooms, purses, pockets, etc., as last minute adulterants
- Lemon juice, vinegar, detergents, soaps, can alter pH to affect conditions for optimum immunoassay screening
- Bleach, Drano, etc. oxidize drugs to other compounds
- Visine interfere with THC by forming micelle bodies

Commercial Adulterants

Whizzies, Klear:

- Contains nitrite (850 mg) for use in 30–50 mL water
- Oxidizes THC and THC internal standard at acid pH conditions
- No interference for immunoassay screening. Low recovery of IS following GC/MS procedures

Commercial Adulterants (Urine Luck, Sweet Pee's Spoiler, Klear II)

- Pyridinium chlorochromate (200 mmol/L)
- Slowly oxidizes THC and morphine under neutral or slightly acid conditions
- Low recovery of internal standards
- Urine Luck II: potassium chromate



Are Witnessed Collections the Solution?



Countermeasures

Collection

- DOT/SAMHSA collection site
 - Household solvents/cleaners removed from urinals/bathroom
 - Sources of water removed; bluing agent in toilet
- Direct observed collection

Immediate post-collection

- Temperature checks performed within minutes of collection
- Color and unusual odor noted

Other specimen validity tests

- Creatinine: <20 mg/dL = dilute specimen; ≤ 5 mg/dL = specimen substituted)
- Specific gravity: <1.003 = dilute; ≤ 1.001 or ≥ 1.020 = specimen substituted
- pH
- Nitrite
- Oxidants (bleach/PCC)
- Glutaraldehyde

Summary

- Objective measures like laboratory tests will be needed to:
 - Identify and evaluate recent drug use/abuse
 - Set and monitor clinical goals/expectations
- UDT results need to be interpreted in the context of the test, drug(s) prescribed, specimen type, specimen validity test results, and the patient
- Unexpected/unexplained results should be discussed with the patient/laboratory, and additional testing performed if needed

Future Laboratory Guidelines

- Development of Guidelines:
 - National Academy of Clinical Biochemistry (NACB):
 - Pain Management Laboratory Medicine Practice Guideline
 - Evidence-based
 - 2013-2015

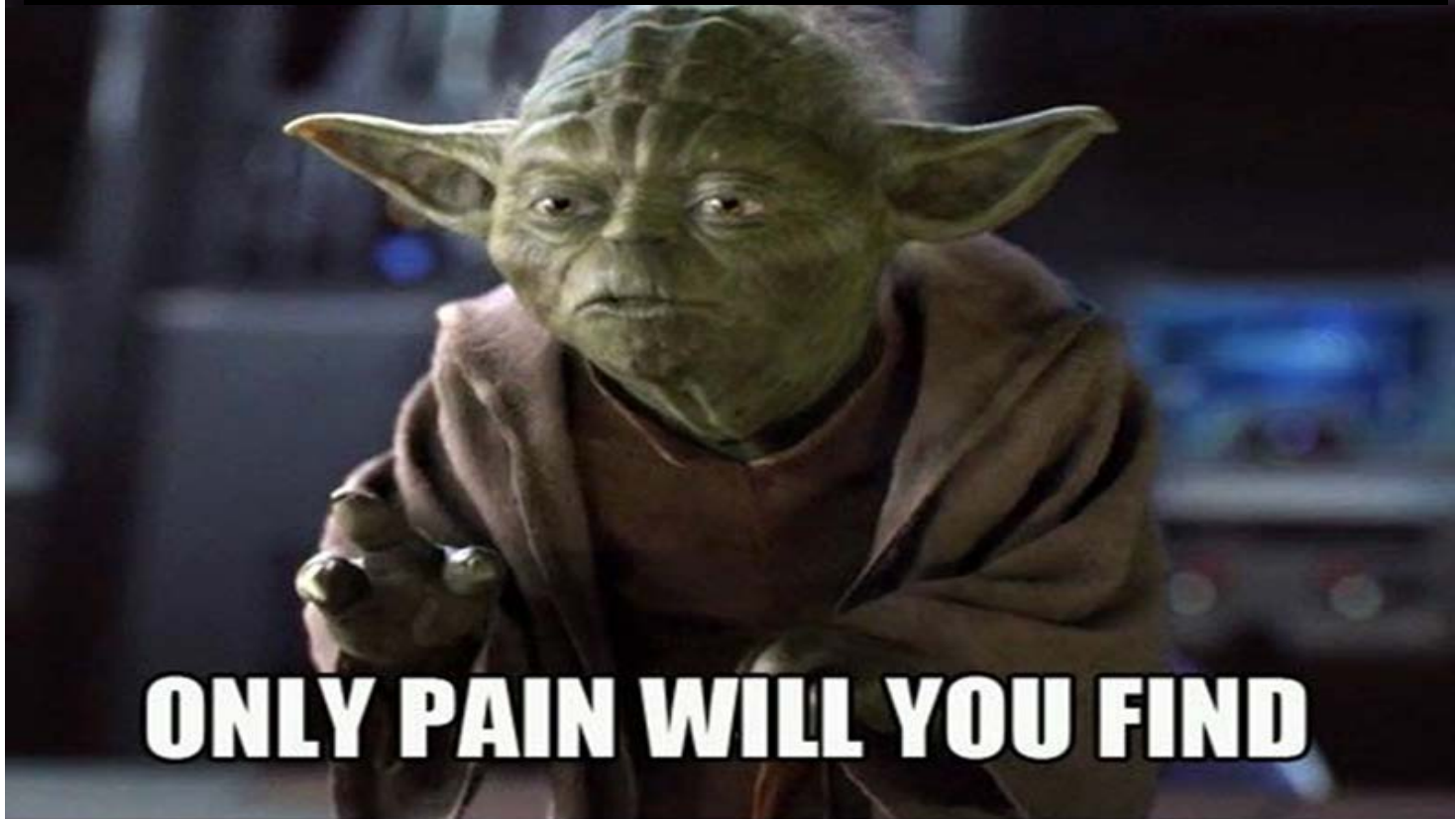


- Clinical and Laboratory Standards Institute (CLSI):
 - Pain Management Guideline
 - Consensus-based
 - 2013-2015



In the Mean Time...

If Lab Tests for Pain Management Order Do You...



More pics on www.imfunny.net



Questions & Discussion