

Urine toxicology testing to support pain management and treatment for substance use disorder

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Learning Objectives and Presentation Outline

- Describe the general analytical workflow of urine drug testing
- Understand the testing approaches for medication compliance in pain management and treatment for substance use disorder (SUD) settings
- Recognize the utilities and limitations of qualitative and quantitative test results
- Discuss case-based unexpected urine drug testing results and considerations for results interpretation

Urine toxicology testing to support controlled substance prescription and monitoring

- Pain management and SUD treatment
 - Long-term prescription of controlled substances
 - Various opiates: hydrocodone, oxycodone, etc. at various doses
 - Buprenorphine, with naloxone (Suboxone)
 - Co-medication with benzodiazepines, heroin, and other opiates can increase risk for over-dose
- Urine toxicology testing is recommended:
 - Baseline testing prior to prescription
 - Annual monitoring (minimal), interval up to clinician discretion
 - Detect undisclosed medication use
 - Confirm expected medication use

Urine toxicology testing is used to confirm the presence of prescribed medications

- Drug presence prevalence:
 - High positivity rate
 - Patients are mostly taking medications
- Appropriate positive cutoffs are needed for effective detection
 - Sensitivity requirement is high
 - Metabolites of parent drugs are often used to confirm compliance
- Assays should be able to differentiate and identify specific medication (specificity):
 - Hydrocodone (Norco) vs. oxycodone (Oxycotin)
 - Amphetamine vs. Methamphetamine

Urine toxicology test is used to detect non-disclosed substance use

- Critical to examine undisclosed exposure to other co-medications
 - Co-medication can increase overdose risk
 - Benzodiazepines and opiates
 - Multiple classes of opiates drugs
 - Alcohol use and opiates medication
 - Appropriate positive cutoffs are required for efficient detection and to minimize false positive
- Use of certain illicit substances use predict treatment failure for SUD
 - Heroin, cocaine, methamphetamine

Traditional urine drug of abuse testing: Screening assay reflexed to confirmation testing

- Immunoassays screens to detect different classes of drugs
 - Urine Opiates, Benzodiazepines, etc.
 - Assays normally adopt a high cutoff to optimize specificity
 - Immunoassays are traditionally designed for low prevalence, low positivity setting (work place drug testing)
- Confirmation assay is performed following a specific class produces a positive results
 - Urine opiates immunoassay screen: positive (detected)
 - Urine opiates confirmation assay is performed accordingly
 - Confirmation assay detects urine morphine at 4345 ng/mL

Common questions based on traditional reflex testing mechanism

- Low sensitivity (false negative)
 - Common question: My patient is taking lorazepam, why the urine benzodiazepine immunoassay is negative?
- Poor specificity (false positive)
 - Common question: My patient has a positive result for urine amphetamine/methamphetamine immunoassay, but he/she denies use. Is this a false positive?

Common questions based on traditional reflex testing mechanism

- Low sensitivity (false negative)
 - Common question: My patient is taking lorazepam, why the urine benzo immunoassay is negative?
 - Immunoassay has different sensitivities to drugs belonging to the same class

Table 7— Concentrations (ng/mL) of Benzodiazepine Compounds That Produce a Result Approximately Equivalent to the 200 ng/mL and 300 ng/mL Lorazepam Cutoffs

Compound	Concentration (ng/mL) at 200 ng/mL Cutoff	Concentration (ng/mL) at 300 ng/mL Cutoff
Alprazolam	65	79
7-Aminoclonazepam	5300	8600
7-Aminoflunitrazepam	930	1400
Lorazepam	600	890
Lorazepam glucuronide [†]	>20000	>20000

- Poor specificity (false positive)
 - Common question: My patient has a positive result for urine amphetamine/methamphetamine immunoassay, but he/she denies use. Is this a false positive?
 - Multiple drugs/metabolites have shown to cause false positive for urine amphetamine immunoassays
 - Ranitidine based on case report

Siemens Syva urine benzodiazepine assay package insert

Confirmation assay uses definitive techniques to improve sensitivity and specificity

- Definitive Techniques:
 - Gas Chromatography (GC) or Liquid Chromatography (LC) as separation technique
 - Tandem Mass Spectrometry (MS/MS) or High Resolution Mass Spectrometry (HRMS) as detection and identification
- Highly Specific and sensitive based on multiple identification criteria
 - Molecular mass over charge (m/z)
 - Retention time (RT)
 - Internal standards
 - Ion ratios

Diversified urine drug testing approaches are designed to meet different clinical needs

- Screen only testing:
 - Drug of abuse screening panel
 - Presumptive positive requires confirmation testing based on different methodology
- Screen with reflex confirmation testing:
 - Drug of abuse screening panel with reflex to confirmation
- Point of Care Drug of Abuse Screen:
 - “Urine cups”
 - Presumptive positive requires confirmation testing based on different methodology
- Direct order of confirmation panels:
 - Quantitative, class based
 - High sensitivity and quantified results reported

Other considerations for test selections

- Results turn-around-time need:
 - Screen results are fast
 - Additional confirmation requires additional testing time (1-4 days)
- Cost of testing:
 - Screen test is low and confirmation can be expensive
 - Presumptive positive results need to be reflex to confirmation testing
- Drugs of interest:
 - Tramadol, methadone and fentanyl are not included in regular opiates immunoassays
 - Certain benzodiazepines and metabolites have poor reactivity to immunoassays

Direct and definitive testing is better suited for pain management and SUD treatment population

- A hybrid approach: LC-MS/MS (definitive techniques) and immunoassays are both adopted
- A hybrid approach can be adopted based on drug classes monitored:
- Qualitative test results reported:
 - “Present”, “Not detected”, or “interference”
- Maximize quality of results and minimize costs of testing

Analytes determined by LC-MS/MS definitive technique

- Opioids

- Heroin metabolite (6-AM)
- Codeine, Morphine
- Hydrocodone, Hydromorphone & metabolites
- Oxycodone, Oxymorphone & metabolites
- Buprenorphine & metabolite
- Fentanyl & metabolite
- Tapentadol & metabolite
- Meperidine metabolite

- Zolpidem

- Benzodiazepines

- Clonazepam & metabolite
- Alprazolam & metabolite
- Midazolam & metabolite
- Lorazepam
- Diazepam, Nordiazepam, Temazepam, Oxazepam

- Stimulants

- Methamphetamine
- Amphetamine
- Methylphenidate
- MDMA & metabolites
- Phentermine

Immunoassays are adopted to detect defined drug/metabolites

- Poor physical and chemical fit in the LC-MS/MS assay
 - Marijuana (THC) metabolite
 - Barbiturates
 - Tramadol
 - Ethyl glucuronide
- Good performing immunoassays with high specificity and comparable sensitivity
 - Methadone
 - Cocaine metabolite (Benzoylecgonine): illicit drug
 - Carisoprodol/Meprobamate
- Drugs rarely observed (false positive rate reflects low positivity rate in patient population)
 - Phencyclidine (PCP)
 - Propoxyphene

The “Hybrid” approach benefits from advantages from both testing modalities

- Qualitative and definitive LC-MS/MS approach:
 - Highly sensitive cutoffs for direct detection
 - High specific approach to differentiate drugs in the same class
- Qualitative results are sufficient for most clinical needs
 - Quantitative results can be over-interpreted to make correlations with dose or drug use patterns
 - Exceptions (discuss later)

The “Hybrid” approach benefits from advantages from both testing modalities

- Results reporting turn-around-time (TAT)
 - One LC-MS/MS method + additional immunoassays (random access)
 - Shortened TAT compared to presumptive positive samples needing confirmation
- Costs of testing
 - Quantitative tests are more costly than qualitative tests
 - Multiple quantitative confirmation tests are costly

Analytical differences of qualitative and quantitative methods

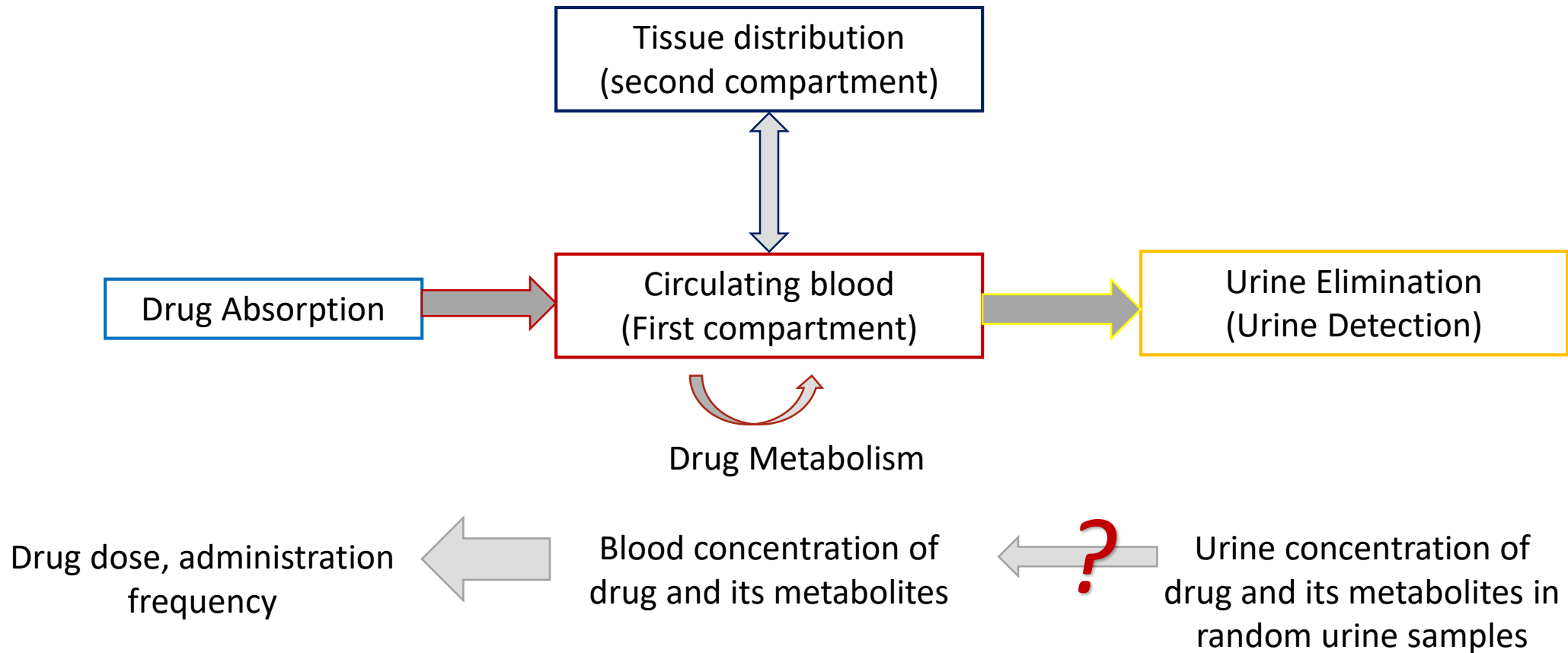
- Qualitative Testing Principles

- One calibrator at the cutoff concentration for each drug/metabolite detected
- Quality control checked at 50% and 150% cutoff concentrations
- Results are reported as present or not detected
- *Certain relative concentrations information can be extracted from qualitative assay (needs toxicologist interpretation)*

- Quantitative Testing Principles

- Multiple calibrator curve is adopted
- Defined analytical measuring range
- Multiple levels of quality control check
- Results are reported as a quantified number, below or above quantification range
 - Below Lower limit of quantification:
 - <LLOQ

Urine drug concentrations can be misleading for clinical interpretation

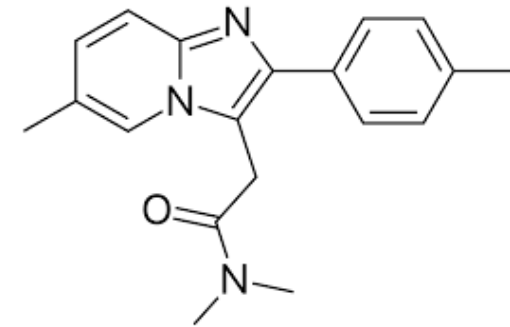


Quantitation of certain drug and its metabolites may provide useful information

- Distinguish pharmaceutical impurities from poly drug use
 - Oxycodone present with low hydrocodone
- Document drug elimination and abstinence
 - Concentration can be further normalized by urine creatinine
- Characterize unusual drug metabolism patterns in individual patients
- Identify addition of drug directly to urine to mimic adherence with therapy
 - Large amount of parent drug present without metabolite present

Case 1: missing zolpidem (unexpected negative)

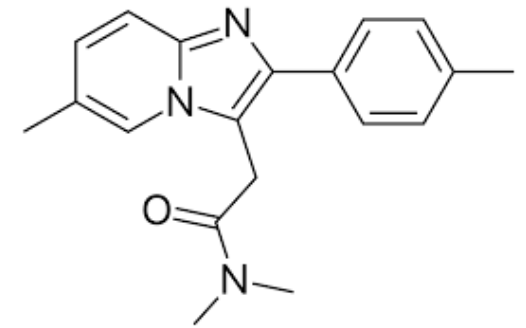
- Drug prescribed: Ambien (zolpidem), 5 mg, PRN at night
- Drug found: none above cutoff (20 ng/mL)
- Question: Is my patient taking Ambien?



Zolpidem

Case 1: missing zolpidem

- Drug prescribed: Ambien (zolpidem), 5 mg, PRN at night
- Drug found: none above cutoff (20 ng/mL)
- Question: Is my patient taking Ambien?



Interpretation consideration:

- Zolpidem is usually used only at night
- Half-life in serum/plasma ~2-3 hrs, urine detection window varies
- Frequently missed:
 - most laboratory tests are either not designed to detect zolpidem, or because methods don't detect metabolites,
 - most urine samples are not first morning collections, missed detection window

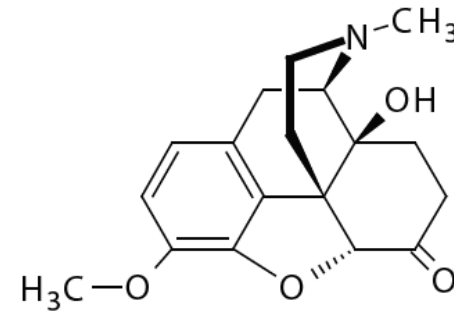
Case 2: unexpected hydrocodone (unexpected positive)

- Drug prescribed: oxycodone, 10 mg, QID
- Drug analytes found in the assay:
 - Oxycodone
 - Noroxycodone
 - Oxymorphone
 - Noroxymorphone
 - Hydrocodone
- Questions: is the patient taking non-disclosed hydrocodone containing medication?

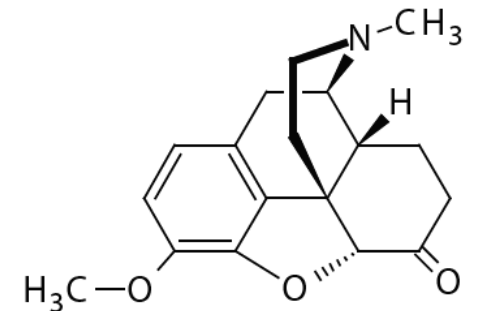
Case 2: unexpected hydrocodone

- Drug prescribed: oxycodone, 10 mg, PRN
- Drug analytes found in the assay:
 - Oxycodone, Noroxycodone, Oxymorphone, Noroxymorphone
 - Hydrocodone
- Interpretation Consideration:
 - Oxycodone and its metabolites are present
 - Could hydrocodone presence be due to impurity?

Oxycodone



Hydrocodone



Case 2: unexpected hydrocodone

10/22/2018

Interpretation of Urine Drug Testing in Pain Patients | Oxford Academic

Table 3

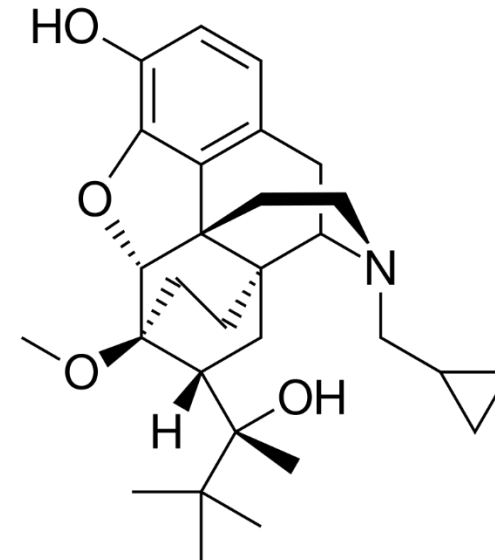
Known impurities in medication formulations

Formulation	Process Impurities	Allowable Limit (%)	Typically Observed (%)
Codeine	Morphine	0.15	0.01–0.1
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	0.02–0.12
Oxymorphone	Hydromorphone	0.15	0.03–0.1
	Oxycodone	0.5	0.05–0.4

- Assay cutoff 20 ng/mL
 - Oxycodone: 1546 ng/mL
 - Noroxycodone: 1423 ng/mL
 - Oxymorphone: 456 ng/mL
 - Noroxymorphone: 2140 ng/mL
- Hydrocodone: 23 ng/mL
- Concentration ratio is consistent with hydrocodone being impurities from oxycodone

Case 3: unexpected noroxymorphone (unexpected positive)

- Drug prescribed: Suboxone (buprenorphine 12 mg + naloxone 3 mg)
- Drug analytes found:
 - Buprenorphine
 - Norbuprenorphine
 - Noroxymorphone
- Question: is noroxymorphone detected due to undisclosed medication?

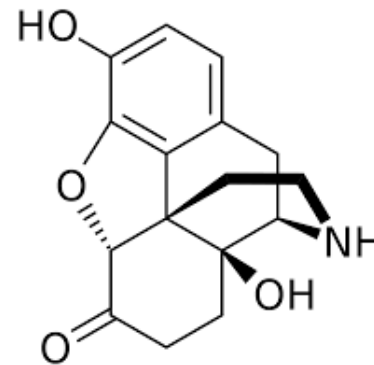


Buprenorphine

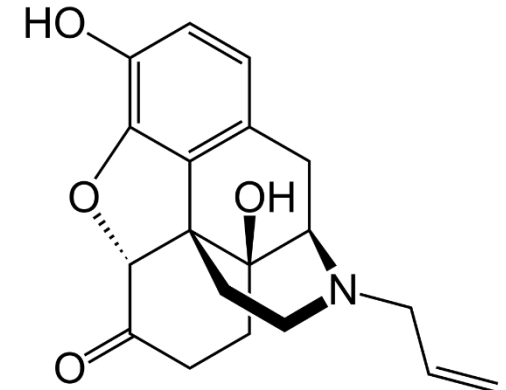
Case 3: unexpected noroxymorphone

Interpretation consideration:

- Noroxymorphone is chemically identical to nornaloxone (naming convention)
- Naloxone can be taken up through Suboxone sublingual film and further metabolized to nornaloxone



Noroxymorphone
(Nornaloxone)

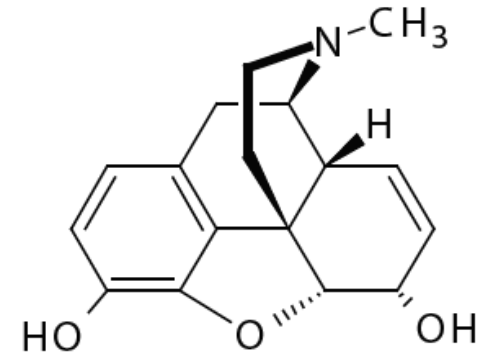


Naloxone

Drug analytes found:
Buprenorphine
Norbuprenorphine
Noroxymorphone

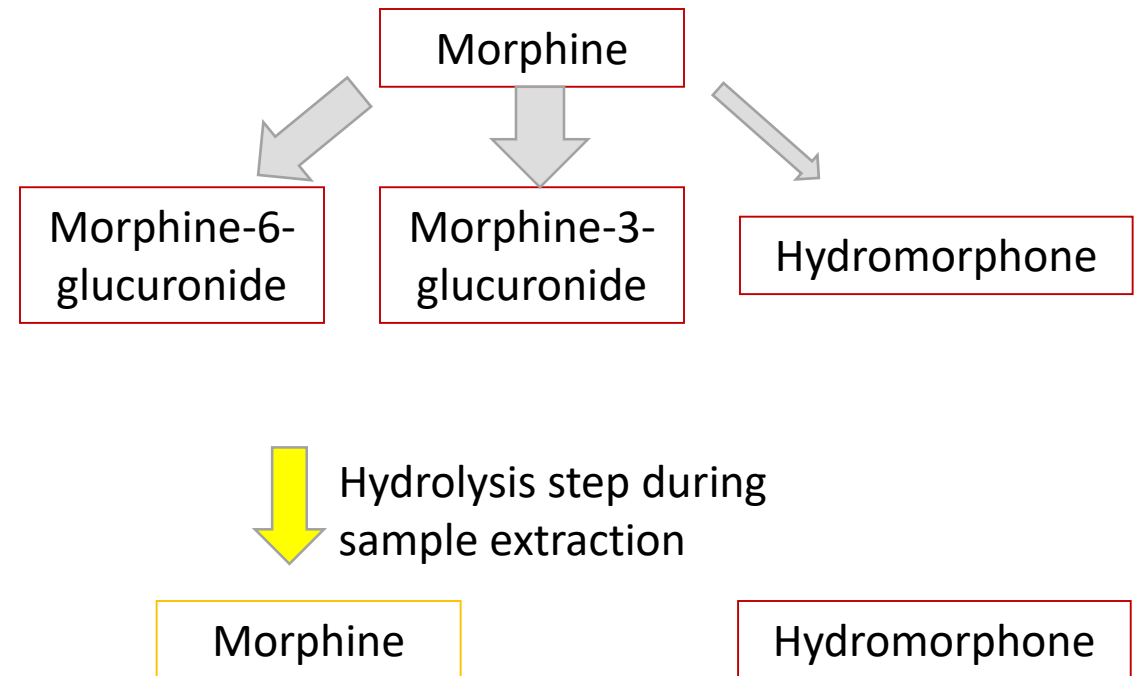
Case 4: no metabolite for morphine

- Drug Prescribed: MS Contin (morphine sulfate) extended release
 - 40 mg, BID
- Drug analytes detected:
 - Morphine
- Question: Is the patient compliant with the medication?
 - No supporting metabolite detected
 - Is the sample adulterated?



Case 4: no metabolite for morphine

- Interpretation Consideration:
 - Hydromorphone is only minor metabolite of morphine
 - Majority of morphine is eliminated by glucuronide conjugation
 - Hydrolysis reaction adopted in assay extraction can convert all conjugated morphine to free morphine
- No hydromorphone could not support sample adulteration



Interpretation to resolve unexpected results

- Unexpected positive(s) result
 - Unexpected drug was taken recently
 - Unusual patient pharmacokinetics
 - Drug detected is a metabolite
 - Drug detected is a pharmaceutical impurity
 - Drug was added to urine
 - Test limitations/errors
 - Specimen mixup
- Unexpected negative(s)
 - Expected drug was not taken recently
 - Unusual patient pharmacokinetics
 - Specimen quality prevented detection
 - Drug metabolites not detected
 - Test was not designed to detect the drug of interest
 - Test limitations/errors
 - Specimen mix-up

Summary and discussion

- Toxicology testing is widely adopted in pain management and treatment of SUD
 - Patient population differs from traditional drug of abuse screening
 - Appropriate urine toxicology tests should be used
- Analytical workflows and techniques are diversified to meet different clinical needs
- Urine drug and metabolites concentrations have limited utility to correlate medication dose and frequency



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