

URINE DRUG SCREENING IN CHRONIC PAIN MANAGEMENT

Background

1. Definitions

- Chronic non-malignant pain syndrome
 - Persistent pain not related to life-threatening condition
- Opioid misuse
 - Not taking opioids as prescribed:
 - Diversion or selling of opioids
 - Concomitant use of undisclosed controlled or illicit drugs^{1,2}
- Urine drug screen (UDS)
 - Rapid test for detection of metabolites from common drugs of abuse

2. General Information

- American Pain Society and American Academy of Pain Medicine recognize UDS is potential tool for monitoring chronic opioid therapy^{3,4}
 - Purposes^{1,2,5}
 - Evaluating appropriate use of prescribed opiates
 - Screening for use of undisclosed controlled drugs
 - Identifying illicit drug abuse
 - Allows primary care providers to risk stratify patients
 - Referral to pain specialists
 - Referral to drug rehabilitation programs
 - Benefits^{1,3}
 - Ease of use
 - Low cost
 - Rapid availability of results
 - Ability to detect recent usage of multiple drug classes
 - Limitations
 - Historically utilized for testing high risk patients in addiction treatment setting^{1,6}
 - Varying thresholds for drug detection
 - Affected by individual's absorption, nutrition status, body composition, dosage, duration of use, protein binding, and concentration thresholds of immunoassay^{4,7}
 - Many false positives and false negatives
 - No evidence that regular use of UDS acts as deterrent
 - 2010 systematic review of 11 observational studies
 - practices routinely utilized the UDS
 - resulted in non-statistically significant decrease in opioid misuse³

Pathophysiology

1. Pathology
 - Opioids and drugs of abuse metabolized to products that can be detected in urine
2. Incidence, Prevalence
 - 1 in 4 chronic pain patients misuse opioids or abuse illicit drugs⁴
 - Prescription medications are second most commonly abused drug category after marijuana⁴
 - Prescription drug abuse surpasses cocaine, heroin, and hallucinogen use combined⁴
 - Retrospective studies found
 - 10-24% of patients on chronic opioid therapy were using illicit drugs a
 - Determined by combination of screening and confirmatory tests^{1,2,8,9}
 - Most commonly used illicit drugs include marijuana, cocaine, and ecstasy^{1,2,6,9}
 - Prevalence higher than general population⁹
3. Risk Factors for Aberrancy
 - Illicit drug use^{6,9}
 - Younger patients
 - Workman's compensation recipients
 - Chronic pain secondary to motor vehicle crashes
 - Opioid misuse⁵
 - Young men
 - History of drug or alcohol abuse
 - History of criminal convictions
4. Morbidity / Mortality
 - Development of addiction
 - Opioid overdose may be lethal secondary to cardiac and respiratory effects
 - Risk for fatality compounded by illicit drug use

Diagnostics

1. History
 - Risk stratification
 - Review prescription drug monitoring programs
2. Urine Drug Screening: Enzyme Immunoassay (EIA)
 - Point of care "dipstick" test most commonly used initial screen
 - Test should be compliant with Clinical Laboratory Improvement Advisory Committee (CLIA) assurances¹
 - Suggested panel includes testing for opiates, marijuana, cocaine, amphetamine, and methadone^{1,9}
 - Utilizes enzyme-labeled antibodies to detect particular substance
 - Presence of drug metabolites results in formation of antigen-antibody complexes measured by enzymatic reactions
 - Detects only drug classes rather than specific opiates²
 - Many false positives and false negatives

- False positives
 - Due to structural similarities and cross-reactivity between drugs
 - Amphetamines and methamphetamines have the highest rate for false positives on urine drug testing
 - Also common for phencyclidine (PCP), benzodiazepines, and propoxyphene^{3,10}
 - Tested substances and potential sources of false positives^{1,3,5}
 - Alcohol
 - Isopropyl alcohol, asthma inhalers (rare)
 - Amphetamines/Methamphetamines
 - Amantadine, brompheniramine, bupropion, chlorpromazine, desipramine, ephedrine, fluoxetine, L-methamphetamine (in nasal decongestants), labetalol, methylphenidate, phentermine, phenylephrine, phenylpropanolamine, promethazine, pseudoephedrine, ranitidine, selegiline, thioridazine, trazodone, trimethobenzamide, trimipramine
 - Barbiturates
 - NSAIDs
 - Benzodiazepines
 - Oxaprozin, sertraline, some herbal agents
 - Cannabinoids
 - Dronabinol (Marinol), NSAIDs, pantoprazole
 - Cocaine
 - Topical anesthetics containing cocaine
 - Methadone
 - Clomipramine, chlorpromazine, diphenhydramine, doxylamine, quetiapine, thioridazine, verapamil
 - Opioids
 - Dextromethorphan, diphenhydramine, fluoroquinolones, poppy seeds, quinine, rifampin, verapamil
 - Phencyclidine
 - Chlorpromazine, dextromethorphan, diphenhydramine, doxylamine, ibuprofen, imipramine, ketamine, meperidine, thioridazine, tramadol, venlafaxine
- False negatives
 - Poor sensitivity to synthetic and semi-synthetic opioids⁴
 - Natural opioids: morphine, codeine
 - Semi-synthetic opioids: hydrocodone, hydromorphone, oxycodone
 - Synthetic opioids: fentanyl, meperidine, methadone, propoxyphene
 - Varying drug metabolite detection thresholds and detection times on UDS¹
 - Opioids
 - Morphine
 - Detection threshold 300 ng/mL
 - Detection time 3-4 days

- Codeine
 - Detection threshold 300 ng/mL
 - Detection time 1-3 days
- Hydrocodone
 - Detection threshold 300 ng/mL
 - Detection time 1-2 days
- Oxycodone
 - Detection threshold 100 ng/mL
 - Detection time 1-3 days
- Methadone
 - Detection threshold 300 ng/mL
 - Detection time 2-4 days
- Benzodiazepines
 - Detection threshold 200 ng/mL
 - Detection time up to 30 days
- Cocaine
 - Detection threshold 300 ng/mL
 - Detection time 1-3 days
- Marijuana
 - Detection threshold 50 ng/mL
 - Detection time up to 1-3 days for casual use; up to 30 days for chronic use
- Amphetamine
 - Detection threshold 1,000 ng/mL
 - Detection time 2-4 days
- Methamphetamine
 - Detection threshold 1,000 ng/mL
 - Detection time 2-4 days
- Heroin
 - Detection threshold 10 ng/mL
 - Detection time 1-3 days
- Phencyclidine
 - Detection threshold 25 ng/mL
 - Detection time 2-7 days for casual use; up to 30 days for chronic use
- Specimen Tampering
 - Common strategies to elude abnormal drug screen⁹
 - Volume loading to reduce drug metabolites below screening thresholds
 - Using urine concentrate to which water is added
 - Substituting with clean specimen
 - Adding adulterant products
 - Methods to reduce specimen tampering⁵
 - Same-sex observation of collection

- Analysis of sample
 - Findings suggestive of tampered sample
 - Temperature <90°F or >100°F
 - Unusual appearance (e.g., bubbly, cloudy, clear, dark)
 - pH <4.5 or >8.5
 - Nitrite concentration >500 mg/dL (4.2 mmol/L)
 - Specific gravity ≤1.0010 or ≥1.0200

3. Confirmatory Testing

- Recommended if patient denies cause for discrepancy
- Positive screening for opioids may optionally be sent for confirmatory testing to establish specific opioid metabolites present⁷
- 20-32% of urine drug screens produce unexpected result requiring follow-up confirmatory testing¹
- May be performed on urine or serum; however, urine testing frequently utilized due to higher drug metabolite concentration of and longer detection times compared to serum¹
 - Order as panel for metabolites of specific drug
- Up to 10% of patients known to be taking opioids have negative confirmatory testing, likely related to factors in drug metabolism and testing thresholds^{9,11}
 - Methods
 - Gas chromatography with mass spectrometry (GC/MS)
 - Considered gold standard⁷
 - Liquid chromatography tandem mass spectrometry (LC/MS/MS)
 - High performance liquid chromatography (HPLC)
- Some drugs may cause multiple positive results due to production of metabolites¹²
 - Hydrocodone
 - Hydromorphone, dihydrocodeine, normorphine, norhydrocodone, hydrocodol
 - Oxycodone
 - Oxymorphone, noroxycodone, oxycodols and their respective oxide
 - Morphine
 - Hydromorphone (minor), morphine-3-glucuronide, morphine-6-glucuronide, normorphine
 - Methadone
 - 2-Ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine, 2-ethyl-5-methyl-3, 3-diphenylpyrrolidine
 - Hydromorphone
 - Dihydromorphone, hydromorphone-3-glucuronide
 - Oxymorphone
 - Oxymorphone-3-glucuronide, oxymorphol
 - Codeine
 - Hydrocodone (minor), norcodeine, morphine
 - Propoxyphene
 - Norpropoxyphene

- Fentanyl
 - Norfentanyl
- Tramadol
 - O-desmethyl-tramadol
- Butorphanol
 - Hydroxylbutorphanol, norbutorphanol
- Buprenorphine
 - Norbuprenorphine, norbuprenorphine-3-glucuronide, buprenorphine-3-glucuronide
- Heroin
 - Morphine, codeine (contaminant), 6-monoacetylmorphine (latter metabolite only detected for 6 hours)

4. Recommendations

- Inform patients about random UDS upon initiation of chronic opioid therapy (SOR:C)⁴
- Consider random UDS for both high and low risk patients (SOR:C)⁴
- Enzyme immunoassay recommended as initial urine drug screening test (SOR:C)⁵
- Exercise caution in UDS interpretation as it cannot reliably detect all opioids (SOR:C)⁴
- Abnormal immunoassay results should be followed by confirmatory testing with GC/MS or HPLC (SOR:C)⁵
- Appropriate collection techniques and tests of urine integrity may reduce risk of tampering (SOR:C)⁵

Follow-Up

1. Universal approach recommended
 - Decreases stigma of testing
 - Less than 50% of chronic pain patients misusing opioids display clear signs of aberrancy⁵
2. Algorithm proposed by Christo et al¹
 - Obtain baseline UDS at onset of therapy
 - Repeat UDS in 1-3 months
 - Appropriate or explained results on UDS
 - Repeat every 6-12 months
 - Inappropriate or unexplained results on UDS
 - Confirmatory testing
 - Appropriate results
 - Repeat UDS in 1-3 months
 - Follow appropriate result algorithm
 - Inappropriate results
 - Consider continued monitoring
 - Education with continued opioid therapy
 - Or discontinue opioid therapy

- Other indications for repeating UDS⁵
 - Decline in function
 - Concerning behavior patterns or aberrancies⁵
 - Taking controlled substance for long period of time (new patients)
 - Refusing permission to obtain old records or communicate with previous physicians
 - Reluctance to undergo comprehensive history, physical examination, or diagnostic testing
 - Requesting specific drug (often because of the higher resale value of a brand name)
 - Professing multiple allergies to recommended medications
 - Resisting other treatment options
 - Issuing threats or displaying anger
 - Targeting appointments at end of day or during off hours (nights or weekends)
 - Giving excessive flattery
 - Calling and visiting physician's associates
 - Repeatedly losing prescriptions
 - Requesting dose escalation
 - Demonstrating noncompliance with prescription instructions
 - Demonstrating other evidence of alcohol or illicit drug misuse
 - Prior to dose increase
 - Upon referral to a pain specialist

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