URINE DRUG SCREENING
IN CHRONIC PAIN MANAGEMENT

Background

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

2. General Information
   o American Pain Society and American Academy of Pain Medicine recognize UDS as potential tool for monitoring chronic opioid therapy\textsuperscript{3,4}
     ▪ Purposes\textsuperscript{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
         o Referral to pain specialists
         o Referral to drug rehabilitation programs
     ▪ Benefits\textsuperscript{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\textsuperscript{1,6}
       • Varying thresholds for drug detection
         o Affected by individual’s absorption, nutrition status, body composition, dosage, duration of use, protein binding, and concentration thresholds of immunoassay\textsuperscript{4,7}
       • Many false positives and false negatives
       • No evidence that regular use of UDS acts as deterrent
         o 2010 systematic review of 11 observational studies
         o Practices routinely utilized the UDS
         o Resulted in non-statistically significant decrease in opioid misuse\textsuperscript{3}
Pathophysiology
1. Pathology
   o Opioids and drugs of abuse metabolized to products that can be detected in urine
2. Incidence, Prevalence
   o 1 in 4 chronic pain patients misuse opioids or abuse illicit drugs
   o Prescription medications are second most commonly abused drug category after marijuana
     ▪ Prescription drug abuse surpasses cocaine, heroin, and hallucinogen use combined
   o Retrospective studies found
     ▪ 10-24% of patients on chronic opioid therapy were using illicit drugs a
     ▪ Determined by combination of screening and confirmatory tests
     ▪ Most commonly used illicit drugs include marijuana, cocaine, and ecstasy
     ▪ Prevalence higher than general population
3. Risk Factors for Aberrancy
   o Illicit drug use
     ▪ Younger patients
     ▪ Workman’s compensation recipients
     ▪ Chronic pain secondary to motor vehicle crashes
   o Opioid misuse
     ▪ Young men
     ▪ History of drug or alcohol abuse
     ▪ History of criminal convictions
4. Morbidity / Mortality
   o Development of addiction
   o Opioid overdose may be lethal secondary to cardiac and respiratory effects
     ▪ Risk for fatality compounded by illicit drug use

Diagnostics
1. History
   o Risk stratification
   o Review prescription drug monitoring programs
2. Urine Drug Screening: Enzyme Immunoassay (EIA)
   o Point of care “dipstick” test most commonly used initial screen
   o Test should be compliant with Clinical Laboratory Improvement Advisory Committee (CLIAC) assurances
   o Suggested panel includes testing for opiates, marijuana, cocaine, amphetamine, and methadone
   o 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 opiates
     ▪ 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
  - Tested substances and potential sources of false positives
    - 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 opioids
  - 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 UDS
  - 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 screen
    - 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 tampering
    - 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 present
   ▪ 20-32% of urine drug screens produce unexpected result requiring follow-up confirmatory testing
   ▪ 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 serum
     ▪ 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
     ▪ Methods
       ▪ Gas chromatography with mass spectrometry (GC/MS)
         ▪ Considered gold standard
       ▪ Liquid chromatography tandem mass spectrometry (LC/MS/MS)
       ▪ High performance liquid chromatography (HPLC)
   ▪ Some drugs may cause multiple positive results due to production of metabolites
     ▪ 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
  - Hydroxybutorphanol, 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 aberrancy^5
2. Algorithm proposed by Christo et al^1
   - 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 UDS\(^5\)

- Decline in function
- Concerning behavior patterns or aberrancies\(^5\)
  - 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

References


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