Appropriate utilization of drug tests for pain management patients

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Drug testing in pain management

- Baseline testing
- Routine testing
  - Periodic, based on patient risk assessment
  - To evaluate changes
    - Therapeutic plan (drugs, formulations, dosing)
    - Clinical response (poor pain control, toxicity)
    - Clinical events (disease, surgery, pregnancy)
    - Patient behavior
Objectives of drug testing

- Detect and encourage appropriate drug use
- Detect and discourage inappropriate drug use
Traditional approach

- Immunoassay-based screen
- Confirm positive results with a mass spectrometric method (GC-MS, LC-MS)

*Not appropriate for pain management*

- Need to confirm positive screen results is limited to certain drug classes
- Confirmation of negative screen results may be important
- Immunoassays are not useful for detection of all drugs of interest
Positivity rates in urine drug testing for pain management

- ~80% of urine specimens collected for the purpose of adherence testing are positive
- <5% of positive results fail to confirm, with the exception of amphetamine tests
- False negative results occur frequently
Positive results “missed” by immunoassay vs LC-MS/MS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Immunoassay cutoff (ng/mL)</th>
<th>LC-MS/MS cutoff (ng/mL)</th>
<th>% missed by immunoassay (total n ~8000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>300</td>
<td>50</td>
<td>29.6% (45)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>50</td>
<td>50</td>
<td>23.3% (701)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>50</td>
<td>50</td>
<td>69.3% (1878)</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>200</td>
<td>20</td>
<td>53.3% (646)</td>
</tr>
<tr>
<td>Nordiazepam</td>
<td>40</td>
<td>40</td>
<td>40.0% (320)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>40</td>
<td>40</td>
<td>66.1% (119)</td>
</tr>
</tbody>
</table>

Mikel et al., *TDM* 31(6):746-8, 2009
West et al., *Pain Physician* 13:71-8, 2010
Immunoassay detection

- Cutoff
- Calibrator
- Cross-reactivity profile of the immunoassay

SAMHSA cutoff: 2,000 ng/mL

Medical immunoassay cutoff: 300 ng/mL

Medical LC-MS/MS cutoff: 10 ng/mL
Concentrations (ng/mL) required to trigger a positive opiate (300 ng/mL cutoff)

<table>
<thead>
<tr>
<th>Drug</th>
<th>EMIT</th>
<th>CEDIA</th>
<th>Triage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Codeine</td>
<td>247</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>6-monoacetylmorphine</td>
<td>1088</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>364</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>498</td>
<td>300</td>
<td>500</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5,388</td>
<td>10,000</td>
<td>20,000</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>&gt;20,000</td>
<td>20,000</td>
<td>40,000</td>
</tr>
<tr>
<td>Noroxymorphone</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Concentrations (ng/mL) required to trigger a benzodiazepine positive \((300\text{ ng/mL cutoff})\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>EMIT</th>
<th>Nex Screen</th>
<th>Triage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>79</td>
<td>400</td>
<td>100</td>
</tr>
<tr>
<td>Alpha-OH-alprazolam</td>
<td>150</td>
<td>N/A</td>
<td>100</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>500</td>
<td>5,000</td>
<td>650</td>
</tr>
<tr>
<td>7-amino-clonazepam</td>
<td>11,000</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>7,800</td>
<td>8,000</td>
<td>13,000</td>
</tr>
<tr>
<td>Nordiazepam</td>
<td>140</td>
<td>500</td>
<td>700</td>
</tr>
<tr>
<td>Diazepam</td>
<td>120</td>
<td>2,000</td>
<td>200</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>350</td>
<td>300</td>
<td>3,500</td>
</tr>
<tr>
<td>Temazepam</td>
<td>210</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>890</td>
<td>4,000</td>
<td>200</td>
</tr>
</tbody>
</table>

False negatives likely
Drugs that could cause a false positive amphetamine test

- N-acetylprocainamide
- Chlorpromazine
- Phenylpropanolamine
- Brompheniramine
- Trimethobenzamide
- Pseudoephedrine
- Tolmentin
- Propylhexedrine
- Ranitidine
- Labetalol
- Perazine
- Promethazine
- Quinicrine
- Buflomedil
- Fenfluramine
- Mephentermine
- Phenmetrazine
- Tyramine
- Ephedrine
- Talmetin
- Nylidrin
- Isoxsuprime
- Chloroquine
- Isomethetime
- Mexiletine
- Phentermine
- Ritodrine

Adapted from: Broussard L, Handbook of Drug Monitoring Methods, Humana Press, 2007
Performance challenges

- Cutoff discrepancy
- Test not designed to detect drug

Poor specificity
- Cross-reactivity profile
- Calibrator

Poor sensitivity

Poor agreement
- Unexpected ("false") results
- Poor alignment of confirmation test
Impact of traditional approach

- Inappropriate selection and interpretation of screen results
- Inappropriate selection and interpretation of confirmation tests
- Unnecessary costs of testing associated with inappropriate testing
- Poor patient-provider-laboratory relationships
Evolving approach

- Understand needs
- Understand testing options and limitations
- Select best test
- Evaluate results
- Targeted testing for unexpected or inadequate results, or when quantitation is needed
Case Example 1

• Pharmacy history
  – Prescribed methadone and lisdexamfetamine dimesylate

• Screen results
  – **POSITIVE** for methadone, amphetamine, and THC
  – **NEGATIVE** for methamphetamine, oxycodone, opiates, and all other drug classes tested

• Patient history
  – Admits to occasional use of marijuana (THC)
Case Example 1 (cont)

• Interpretation based on expectations:
  
  *Results are consistent with expectations*

  – Confirmation tests not needed
  – Document results of investigation and final interpretation

• Reflex testing approach:

  – 3 confirmation tests would have been ordered
  – Additional office visit(s) may have been required

  *Unnecessary expenses!!!*
Case Example 2

• Pharmacy history
  – Prescribed oxycodone, hydrocodone, clonazepam, and methylphenidate

• Screen results
  – **POSITIVE** for oxycodone and opiates
  – **NEGATIVE** for benzodiazepines, amphetamines, and all other drug classes tested

• Patient history
  – Insists on adherence to prescribed therapy
Case Example 2 (cont)

• Interpretation based on expectations: results are NOT consistent with expectations

• Post-analytical investigation (laboratory):
  – Clonazepam sensitivity of the benzodiazepine screening test that was used is poor
  – Methylphenidate is not detected by the screen
Case Example 2 (cont)

• Interpretation based on expectations: 
  *results are consistent with expectations*

• Post-analytical investigation (laboratory):
  – Clonazepam sensitivity of the benzodiazepine screening test that was used is poor
  – Methylphenidate is not detected by the screen
Case Example 2 (cont)

Recommendation:
– Confirm periodically, if concern arises, and/or if results impact clinical management decisions
– Document results of investigation and final interpretation

• Reflex testing approach:
  – 1 confirmation test would have been ordered
  – 2 possible false negative results remain unresolved
  – Could compromise patient care and relationship between the physician and the laboratory
Is adulteration testing necessary?
Adulteration in urine drug testing

• Reduce signal/noise
  – Dilute specimen
  – Increase analytical noise

• Prevent drug-antibody interactions
  – Charge interactions (pH)

• Destroy drug analytes

• Mimic drug use
  – Urine substitution
  – Direct addition of drug to urine
Examples of urine substitutes

- Beverages
- Animal urine
- Synthetic urine
- Human urine
  - Purchased
  - Obtained from friend or relative
  - Archived by patient
Common forms of adulteration testing

- Temperature
- Visual inspection
- Creatinine
- Specific gravity
- Nitrates
- Oxidants

Will these tests detect urine substitution or direct addition of drug to the urine?
Substitution may not be detected

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample Check (%) Microgenics, CEDIA</th>
<th>Creatinine (mg/dL) Syva (Dade), EMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human urine</td>
<td>80-100</td>
<td>&gt; 5 (DOT)</td>
</tr>
<tr>
<td>Dog urine (n=7)</td>
<td>52 - 85</td>
<td>87 - 284</td>
</tr>
<tr>
<td>Horse urine (n=1)</td>
<td>92</td>
<td>104</td>
</tr>
<tr>
<td>Energy drinks (n=44)</td>
<td>72-103</td>
<td>0-63</td>
</tr>
<tr>
<td>Margarita mix (n=2)</td>
<td>73-74</td>
<td>71-76</td>
</tr>
<tr>
<td>Fruit juice (n=8)</td>
<td>39-81</td>
<td>0-62</td>
</tr>
</tbody>
</table>

Simplified metabolism of Suboxone® and proportions in urine

- 4% Buprenorphine
- <1% Naloxone (4:1)
- 39% Buprenorphine glucuronide
- 46% Norbuprenorphine glucuronide
- 11% Norbuprenorphine

4% Buprenorphine
<1% Naloxone (4:1)
Results suggest drug was added

<table>
<thead>
<tr>
<th></th>
<th>BUP (ng/mL)</th>
<th>NORBUP (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39,400</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>39,200</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>31,100</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>20,200</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>19,300</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>18,800</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>15,000</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>12,100</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>11,100</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>10,900</td>
<td>7</td>
</tr>
</tbody>
</table>

NOTES: Glucuronides were < 20 ng/mL

McMillin et al., JAT 36(2):81-7, 2012
Results suggest drug was added

<table>
<thead>
<tr>
<th></th>
<th>BUP (ng/mL)</th>
<th>NORBUP (ng/mL)</th>
<th>Naloxone (ng/mL)</th>
<th>BUP: Naloxone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39,400</td>
<td>24</td>
<td>6,690</td>
<td>5.9</td>
</tr>
<tr>
<td>2</td>
<td>39,200</td>
<td>36</td>
<td>9,560</td>
<td>4.1</td>
</tr>
<tr>
<td>3</td>
<td>31,100</td>
<td>20</td>
<td>8,500</td>
<td>3.7</td>
</tr>
<tr>
<td>4</td>
<td>20,200</td>
<td>23</td>
<td>5,160</td>
<td>3.9</td>
</tr>
<tr>
<td>5</td>
<td>19,300</td>
<td>11</td>
<td>4,470</td>
<td>4.3</td>
</tr>
<tr>
<td>6</td>
<td>18,800</td>
<td>31</td>
<td>4,430</td>
<td>4.2</td>
</tr>
<tr>
<td>7</td>
<td>15,000</td>
<td>7</td>
<td>2,300</td>
<td>6.5</td>
</tr>
<tr>
<td>8</td>
<td>12,100</td>
<td>14</td>
<td>3,110</td>
<td>3.9</td>
</tr>
<tr>
<td>9</td>
<td>11,100</td>
<td>12</td>
<td>2,920</td>
<td>3.8</td>
</tr>
<tr>
<td>10</td>
<td>10,900</td>
<td>7</td>
<td>3,010</td>
<td>3.6</td>
</tr>
</tbody>
</table>

McMillin et al., *JAT* 36(2):81-7, 2012

NOTES:

Expected ratio of BUP:Naloxone for Suboxone® = 4

Average ratio of BUP:Naloxone for these patients: 4.4
Why use blood for drug testing?

- Urine substitution is suspected
- Dialysis patients
- Evaluate pharmacokinetics
  - Unpredictable drug absorption (e.g. bariatric surgery, Crohn’s disease)
  - Suspicious drug delivery/bioavailability
  - Polypharmacy (drug-drug interactions)
  - Altered metabolic status
  - TDM
Conclusions

• Clinical laboratories are in an excellent position to actively participate, and/or consult, regarding the drug testing needs of chronic pain management patients.

• Utilization of testing should be based on the clinical needs and test performance characteristics, rather than traditional reflex testing approaches.