Drug Testing in the Pain Management Setting

September 27, 2011

Gwen McMillin, PhD, DABCC
University of Utah, ARUP Laboratories
Disclosure

Laboratory director consultant for Clinical Lab Consulting, LLC
Application of drug testing

MEDICAL:
- Intoxications/ED
- TDM
- Surgery qualification
- Drug abuse monitoring

FORENSIC:
- Death investigations
- Crime/accidents
- Employment
- Competitive sports
- Military, DOT

SOCIAL:
- Child custody
- Sobriety testing
- Licensures

Pain Management
Objectives

- Compare strengths and limitations of screening and confirmation testing for drugs used in the pain management setting

- List scenarios that could explain both positive and negative drug testing results

- Understand the limitations of urine drug testing for evaluating dose adherence
Pain is the #1 reason people seek medical care

Prevalence of chronic non-cancer pain (>3 months) in the US is estimated at 20-60%, over a lifetime

Chronic non-cancer pain is expensive
- Leading cause of health-related absenteeism
- Increased risk of depressive and anxiety disorders
- Estimated medical costs in the US up to $635 billion/yr (Reuters US Online Report Health News June, 2011)

Pain is a major health and social issue
Pain management is a medical specialty (American Board of Pain Medicine, >2200 diplomates, 2011)

Treatment approach is multi-disciplinary; primary goals to diagnose and treat the underlying cause of pain, restore/maintain function and well-being

Commonly used medications include opioids, benzodiazepines, antidepressants, anticonvulsants, THC, and muscle relaxants
Drugs in “Top 200” US scripts (2010)

- **Opioid analgesics**
  - Hydrocodone (#1, 3, 34, 147)
  - Oxycodone (#39, 54, 128, 141)
  - Tramadol (#33, 122)
  - Codeine (#66)
  - Propoxyphene (#98, 169)
  - Buprenorphine (#163)

- **Benzodiazepine-like**
  - Alprazolam (#46, 57, 88, 119)
  - Clonazepam (#47, 116)
  - Lorazepam (#78, 200)
  - Diazepam (#106)
  - Zolpidem (#24, 134, 186)

- **Non-opioid analgesics**
  - Ibuprofen (#21, 113)
  - Naproxen (#132, 187)
  - APAP (#1, 3, 34, 39, 54, 66, 98, 147, 169)

- **Other medications**
  - Gabapentin (#87, 112, 140)
  - Pregabalin (#74)
  - Carisoprodol (#100)
  - Antidepressants (#13, 20, 29, 35, 56, 77, 83, 89, 103, 120, 138, 161, 184, 198)

Rank #s from
Pain relievers are misused

- Pain relievers are the #1 new illicit drug in the U.S. National Survey on Drug Use in Health (NSDUH), 2009

- It is estimated that 20% of Americans have used prescription drugs for nonmedical reasons; including 15% of 12th graders www.drugabuse.gov

- 60% of people who use pain relievers for nonmedical reasons obtain the drug from a friend or relative SAMHSA, 2006
### Estimates of profitability

<table>
<thead>
<tr>
<th>Drug</th>
<th>“Street” Price (per pill)</th>
<th>Retail Price Estimate (per pill)</th>
<th>Potential “Profit” (per pill)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>$12 - 40</td>
<td>$6</td>
<td>$34</td>
</tr>
<tr>
<td>Oxycontin®</td>
<td>$50 - 80</td>
<td></td>
<td>$74</td>
</tr>
<tr>
<td>Percocet®</td>
<td>$10 - $15</td>
<td></td>
<td>$9</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>$5 - 20</td>
<td>$1.50</td>
<td>$18.50</td>
</tr>
<tr>
<td>Vicodin®</td>
<td>$5 - 25</td>
<td></td>
<td>$23.50</td>
</tr>
</tbody>
</table>

CNN Money; June 1, 2011
Efforts to minimize drug trafficking

• US Department of Justice, Drug Enforcement Administration, Office of Diversion Control: www.deadiversion.usdoj.gov

• Hotline for illicit pharmaceutical activity: 877-RX-ABUSE (792-2873)

• Focus Topics
  – Diversion awareness
  – Drug disposal (Secure and Responsible Drug Disposal Act of 2010)
  – Internet pharmacy control
  – Current cases, and rulings, against doctors
Unintentional US deaths, drug-related

www.cdc.gov/HomeandRecreationalSafety/Poisoning/brief.htm
REMS = Risk Evaluation and Mitigation Strategies intended to

“protect patients from serious harm”

“ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes”

Sponsors/manufacturers of select long-acting or extended release opioid formulations will be required to provide training to prescribers for safe use, storage, and disposal of opioids.

Monitoring patients for misuse and abuse

Post-Approval REMS Notification, Appendix A, accessed 9/11/11

Prescription monitoring programs

Urine drug testing

Screening and referrals for substance abuse treatment
Clinical Practice Guidelines for Opioid Prescribers

- VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain, 2010
- Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain Parts A and B, 2010
- [Washington State] Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An Educational Aid to Improve Care and Safety With Opioid Treatment, Updated 2010
- Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain, 2009
- APS-AAPM Clinical Guidelines For the Use of Chronic Opioid Therapy in Chronic Noncancer Pain, 2009
Objectives of drug testing

1. Detect drug use
   - Verify adherence to prescribed medications
   - Identify use of undisclosed drugs

2. Discourage drug misuse
   - Reduce likelihood of diversion
   - Reduce likelihood of abuse
The “10 P’s

Protect the patient
Protect the practitioner
Protect the pain therapy plan
Protect the community
Protect society
Promote cost-effectiveness
Protect resources
Practice safe and effective medicine
Practice and fulfill ethics in medicine
Preserve access to therapy

How do patients perform???
Urine drug testing (UDT) results

Reference lab study, representing 938,586 results

- Expected drug: 26%
- Illicits: 11%
- Unexpected prescription drug: 29%
- Missing drug: 38%

Another example of UDT results

- Clinic-based study, retrospective, 470 patients
- Urine drug testing results confirmed by GC-MS
- All results reviewed/verified vs. patient charts for appropriateness of test results

- Expected opioid 55% (vs. 26%)
- Illicits 20% (vs. 11%)
- Unexpected opioid 15% (vs. 29%)
- Missing opioid 10% (vs. 38%)

Sources of variation in UDT

- Pharmacokinetic variability of drugs, drug formulations, and patients
- Limitations of urine
- Testing methods involved
- Inappropriate interpretation of results
“Take-home” message #1

Drug testing for pain management REQUIRES synchronization between the clinic and the lab!

- Little standardization exists among laboratory tests today
- Drugs used in pain management have complicated pharmacokinetics, interactions, and some are not “pure”
- Patients are often “high risk”
- Consequences of false positive or false negative results are severe, for all involved
**Screen**: a qualitative (positive/negative) test; usually designed to detect many drugs or drug classes; confidence in results may be poor, but depends on the assay. Commonly based on immunoassay; may be accomplished with “point of care tests” (POCT).

**Confirmation**: a test designed to provide a high degree of confidence in identification of individual drugs/compounds; may be qualitative or quantitative (reports the amount of drug present). Commonly based on a combination of chromatography and mass spectrometry.
Selecting the best drug test

*Drug testing for pain management purposes should NOT mirror traditional drugs of abuse testing*

- Objectives of testing are different
- Testing needs vary based on:
  - Patient population
  - Specific drug(s) of interest
  - Specimen
  - Sensitivity (cutoff)
  - Need for quantitative results
  - Specificity
SPECIFICITY

Defined by: Antibody, Cutoff, and Calibrator

Poor = FALSE negative result

Good (for wrong drug) = FALSE positive result

TRUE result, negative or positive
### Drug class
- Marijuana
- Amphetamines
- Benzodiazepines
- Methadone
- Opiates

### Compounds not detected
- Spice, K2
- Methylphenidate
- Clonazepam, Zolpidem
- EDDP
- Oxycodone, Fentanyl, Tramadol, Buprenorphine

*Possible FALSE negative*

**Substances with good cross-reactivity**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Compounds detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoids</td>
<td>NSAIDs, Pantoprazole</td>
</tr>
<tr>
<td>Opioids</td>
<td>Chlorpromazine, Fluoroquinolones</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Oxaprozin, Sertraline</td>
</tr>
<tr>
<td>Methadone</td>
<td>Propoxyphene, Seroquel</td>
</tr>
<tr>
<td>PCP</td>
<td>Dextromethorphan, Meperidine</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Vicks, Desipramine, Trazodone</td>
</tr>
</tbody>
</table>

*Possible FALSE positive*

Detection limits reflect

Assay method and cutoff
Drug and formulation
Patient pharmacokinetics
Sample
  – Type
  – Timing of collection
  – Quality of specimen (e.g. dilution)
Example: effect of urine dilution on drug screen

Assume opiate cutoff of 300 ng/mL
Samples contain 428 ng morphine/mg creatinine

Sample 1: positive
- morphine: 856 ng/mL
- creatinine: 200 mg/dL

Sample 2: negative
- morphine: 214 ng/mL
- creatinine: 50 mg/dL

\[
\frac{\text{Drug} \times 100}{\text{Creatinine}} = \text{ng drug/mg creatinine}
\]
Substitution may not be detected

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample Check (%)</th>
<th>Creatinine (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Microgenics, CEDIA</td>
<td>Syva (Dade), EMIT</td>
</tr>
<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>

UDT in Pain Management

Confirmation testing was required for ~35% of POCT results in the Manchikanti 2011 studies.
## POCT in pain patients

<table>
<thead>
<tr>
<th>Drug/Drug Class</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine, Codeine, Hydrocodone, Hydromorphone</td>
<td>92.2%</td>
<td>93.1%</td>
<td>92.5%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>75.4%</td>
<td>92.3%</td>
<td>90.0%</td>
</tr>
<tr>
<td>Methadone</td>
<td>96.1%</td>
<td>98.8%</td>
<td>98.7%</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>74.7%</td>
<td>98.0%</td>
<td>87.4%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>90.9%</td>
<td>98.0%</td>
<td>97.8%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>25.0%</td>
<td>100%</td>
<td>99.4%</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>40.0%</td>
<td>98.8%</td>
<td>98.5%</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>47.0%</td>
<td>99.1%</td>
<td>98.2%</td>
</tr>
</tbody>
</table>

When to “confirm” a result

2nd immunoassay

1. Screen results are inconsistent with clinical expectations
2. Screen used does not detect the drug(s) of interest
3. Quantitative results are necessary for interpretation

Chromatography

Mass spectrometry: GC-MS, LC-MS/MS, LC-MS/TOF
Interpretation:

Evaluating negative and positive results
Reasons for a negative result

- **Drug was not taken/administered**
- Drug was taken incorrectly (less than prescribed or less frequently than prescribed)
- Drug delivery was variable
- Drug was not absorbed
- Accelerated metabolism/elimination
- Specimen was collected too late
- Specimen was dilute, or adulterated
- Clinic or lab mixup
- Test performed is not designed to detect drug

✔ Drug
✔ Patient
✔ Sample
✔ Test
“False” negatives for oxycodone common

<table>
<thead>
<tr>
<th>Drug (ng/mL)</th>
<th>Abbott FPIA</th>
<th>Dade Behring (Syva) EMIT II</th>
<th>Roche CEDIA DAU</th>
<th>BIOSITE Triage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>100</td>
<td>300</td>
<td>364</td>
<td>300</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1000</td>
<td>5,388</td>
<td>10,000</td>
<td>20,000</td>
</tr>
</tbody>
</table>

The Clinical Toxicology Laboratory, AACC Press, 2003, pp. 491-2
Reasons for a positive result

- **Drug was taken/administered**
- Drug detected is an expected metabolite of a prescribed drug
- Drug detected is a process impurity
- Incorrect prescription filled
- Prescription obtained elsewhere
- Non-prescribed drug was used
- Drug was added to urine after collection
- Clinic or lab mixup
- Result is a false positive (e.g., test specificity)
Patient results

2033 ng/mL Morphine
15 ng/mL Hydromorphone

- Morphine is metabolized to hydromorphone (minor pathway, <3% expected)

- Thresholds for independent use of hydromorphone are not well established

Patient Rx

MS Contin® (morphine sulfate)

Patient results

2033 ng/mL Morphine
15 ng/mL Hydromorphone
8 ng/mL Codeine

Patient Rx

MS Contin® (morphine sulfate)
Simplified opioid metabolism

- Poppy seeds
  - Codeine → Morphine
  - Hydrocodone → Hydromorphine
- Heroin
  - 6-Monoacetylmorphine (6-AM)

* Not specifically detected by most assays
Interpreting concentrations (cont.)

Patient results

2033 ng/mL Morphine
15 ng/mL Hydromorphone
8 ng/mL Codeine

Codeine is not a metabolite of morphine or hydromorphone

Codeine can be an impurity in some morphine preparations; up to 0.5% is allowed

Patient Rx

MS Contin® (morphine sulfate)

MRO Alert XXI, No. 3, 2010
West et al, TDM 31(6):776-8, 2009
## Opioid process impurities

<table>
<thead>
<tr>
<th>Active pharmaceutical compound</th>
<th>Process impurities</th>
<th>Allowable pharmaceutical impurity limit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Morphine</td>
<td>0.15</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Hydromorphine</td>
<td>Morphine</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td>0.1</td>
</tr>
<tr>
<td>Morphine</td>
<td>Codeine</td>
<td>0.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Hydrocodone</td>
<td>1.0</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Hydromorphine</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td>0.5</td>
</tr>
</tbody>
</table>

MRO Alert XXI, No. 3, 2010
Interpretation:

Detecting adulteration intended to *mimic* adherence to prescribed medications
Results suggesting drug was added to urine

<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, 2011, in press

**NOTES:**

Glucuronides were < 20 ng/mL

Expected ratio of BUP:Naloxone for Suboxone® = 4

Average ratio of BUP:Naloxone for these patients: 4.4
Adulteration possible?

- 2 mg buprenorphine (tablet):
  \[ \frac{2,000,000 \text{ ng}}{100 \text{ mL}} = 20,000 \text{ ng/mL buprenorphine} \]

- 0.5 mg naloxone companion (Suboxone):
  \[ \frac{500,000 \text{ ng}}{100 \text{ mL}} = 5,000 \text{ ng/mL naloxone} \]
“Take-home” message #2

Drug testing results should ALWAYS be interpreted based on the clinical scenario, including, but not limited to, the drug, the patient, the sample, and the test.
Interpretation:
Drug adherence vs. dose and dosing adherence
UDT cannot reliably evaluate dosing

- Dose delivery may vary with formulation
- Pharmacokinetics will vary by patient
- Time of specimen collection vs. drug dosing is usually NA
  - Drug administration may or may not be timed
  - UDT specimens are not usually timed (prior + collected void)
- Urine varies based on hydration status, other medications, renal function, urine pH, etc.
- Not all drug is eliminated in urine
- UDT is based primarily on measurement of drug metabolites which can arise from more than one drug
- Routine/chronic administration of a drug affects the amount of drug and drug metabolites observed in the urine
- Laboratory methods vary
### Expected urine findings

<table>
<thead>
<tr>
<th>Parent drug</th>
<th>% of a dose eliminated in the urine within 72 hrs</th>
<th>% of a dose eliminated as FREE parent drug</th>
<th>% of a dose eliminated as glucuronide conjugate of parent drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>~87%</td>
<td>~10%</td>
<td>~75%</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>~26%</td>
<td>~12%</td>
<td>NA</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>~50%</td>
<td>~6%</td>
<td>~30%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>~72%</td>
<td>~5%</td>
<td>NA</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>~49%</td>
<td>~2%</td>
<td>~44%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>~27%</td>
<td>~1%</td>
<td>~9.4%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>~85%</td>
<td>~6%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Baselt RC, *Disposition of Toxic Drugs and Chemicals in Man*, 8th Ed, 2008
## Hydrolysis efficiency for morphine

### Percent (%) recovery of opioids using different hydrolysis methods

<table>
<thead>
<tr>
<th>Morphine Metabolite</th>
<th>Chemical (acid)</th>
<th>Enzyme <em>(P. vulgata, 2 hrs)</em></th>
<th>Enzyme <em>(H. pomatia, 16 hrs)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine-3-glucuronide</td>
<td>100 ± 4</td>
<td>94 ± 2</td>
<td>50 ± 13</td>
</tr>
<tr>
<td>Morphine-6-glucuronide</td>
<td>98 ± 5</td>
<td>12 ± 1</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Patient urine</td>
<td>100 ± 0</td>
<td>64 ± 19</td>
<td>35 ± 20</td>
</tr>
</tbody>
</table>

### Urine concentrations with Duragesic®

<table>
<thead>
<tr>
<th></th>
<th>25 µg/h</th>
<th>50 µg/h</th>
<th>75 µg/h</th>
<th>100 µg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fentanyl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ng/mL)</td>
<td>32</td>
<td>58</td>
<td>95</td>
<td>79</td>
</tr>
<tr>
<td>Range of central 90%</td>
<td>0-167</td>
<td>0-250</td>
<td>4-444</td>
<td>0-350</td>
</tr>
<tr>
<td><strong>Norfentanyl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ng/mL)</td>
<td>173</td>
<td>251</td>
<td>285</td>
<td>327</td>
</tr>
<tr>
<td>Range of central 90%</td>
<td>0-980</td>
<td>0-860</td>
<td>4-1330</td>
<td>0-1670</td>
</tr>
<tr>
<td>Number of samples</td>
<td>142</td>
<td>184</td>
<td>85</td>
<td>135</td>
</tr>
</tbody>
</table>

Poklis and Backer, *JAT* 28:422-5, 2004
End of dose failure

- ~1000 outpatients prescribed transdermal fentanyl patches for pain management
- ~50% needed more analgesia before the end of the standard 72 hour dose period
- Average pain control was ~63 hrs

Kim et al, Support Care Cancer 19(2):297-301, 2010

Suggests variation in actual drug delivery and/or patient pharmacokinetics
Suggests random UDT may not verify adherence
“Take-home” message #3

UDT cannot reliably determine the dose taken, or the frequency at which a dose was taken
Conclusions

- UDT has become an important part of routine pain management practices
- UDT offers many useful opportunities to identify and evaluate recent drug use
- Testing technologies and frequency of testing should be aligned with clinical needs/expectations
- Results should be interpreted in the context of the test, drug(s), patient, and sample(s) tested
- Unexpected positive or negative results should be discussed with the patient, and confirmed if needed
- Dose and dosing of a drug cannot be reliably determined by UDT