The Laboratory’s Role in Pain Management Testing

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Learning Objectives

1. Explain the utility of quantitative and qualitative testing for medication compliance testing
2. Differentiate between compound identification, quantitation and confirmation
3. Compare the screen with reflex approach with targeted screening for pain management testing
4. Judge the utility of providing interpretations as part of laboratory testing for pain management
Speaker Financial Disclosure Information

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- Honorarium/Expenses: **None**
- Intellectual Property/Royalty Income: **None**
Important Points to Consider

- Client/patient demographics
- Available platforms
- Reimbursement challenges
- Technical competency
- Clinical competency
- IT competency
The Clinical Goal for Testing

Pain Management Context

- Minimizing risk to maximize patient benefit
  - Monitoring Compliance
  - Detecting illicit use

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended Frequency of Testing (per year) - UDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥ 2</td>
</tr>
<tr>
<td>High</td>
<td>≥ 3 or 4</td>
</tr>
<tr>
<td>Aberrant Behavior</td>
<td>At visit</td>
</tr>
</tbody>
</table>
The Laboratory’s Goal for Testing

Pain Management Context

• High quality testing
  – AMRs; Cross-reactivity (IA); TAT; QC; cutoffs; etc.

• Well-designed testing menu
  – Metabolites; Free vs. Conjugated vs. Total

• Easy to interpret reports
  – Data overload; Physicians are not pharmacologists

• Development of a test that actually gets ordered
  – Welcome to clinical mass spectrometry!
Dose and Time

*Helpful or not?*

- **Serum/Plasma**
  - Dose compliance can be determined
    - Absorption
    - $t_{1/2}$
  - Shorter window of detection

- **Urine**
  - Drug compliance
    - Yes or No
  - Longer window of detection
    - 1 to 3 days
What is the difference between identification, quantitation and confirmation?
Confirmation Testing

*Yes, no, maybe?*

- True confirmation testing means that the identity of a drug has been determined by two different methods
  - e.g., an immunoassay “screen” and then a mass spectrometry “confirm”
  - *Two independent sample preps are key*
- For routine clinical testing, absolute identification is needed – *but not usually by two different methods!*
Confirmation Testing

When?

• Non-specific screening method used
  – e.g., immunoassay for opiates

Interpretation:

- Morphine only?
- 6-AM?
- All of them?
- None of them?

“You need this reflexed to confirmation.”
Mass Spectrometry

*Triple Quadrupoles*

- Gas phase ions
- Mass-to-charge ratio \((m/z)\)
- Flight stabilization
- **Fragmentation**
Rethinking Past Strategies

• Screen w/ reflex to confirmation
  – Forensic concept
    • Prep and measure by Method 1
    • Prep and measure by Method 2
  – What are we after for compliance testing?
    – Yes or No
    – Absolute identification
    – Quantitation?

IA Screen

POSS

False Positive??

NEG

False Negative??

Automatic Confirmation and/or Quantitation

Mass Spectrometry
The Laboratory’s Role: Identification, Quantitation, Confirmation

- Decide what is needed for the clinical context
- Think absolute identification
- Definitive methods can be used for “screening” purposes
- Break free of the forensic workflow if possible
When, if ever, does quantitation make sense for pain management?
Quantitative vs. Qualitative

*When? Why?*

- Will the amount of drug detected in the urine change management?
  - Remember to take urine concentration into account!
  - Quantitative value adds little when testing for compliance
Case Study #1

1. 55 y/o male prescribed 5mg hydrocodone and clonazepam.

2. 48 y/o male prescribed 15mg hydrocodone and clonazepam.

<table>
<thead>
<tr>
<th>Mass Spectrometry Screen</th>
<th>Mass Spectrometry Quantitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>PRESENT</td>
</tr>
<tr>
<td>Norhydrocodone</td>
<td>PRESENT</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>PRESENT</td>
</tr>
<tr>
<td>7-aminoclonazepam</td>
<td>PRESENT</td>
</tr>
</tbody>
</table>

Creatinine 286 mg/dL

| Hydrocodone | PRESENT | 32 ng/mL |
| Norhydrocodone | PRESENT | 29 ng/mL |
| Clonazepam | NOT DETECTED | |
| 7-aminoclonazepam | PRESENT | 59 ng/mL |

Creatinine 16 mg/dL
### Case Study #2

- **39 y/o female prescribed oxycodone and lorazepam.**
  - Visit #1
    - Amphetamine
    - THC
  - Visit #2
    - 3 weeks later
      - Amphetamine NOT DETECTED
      - THC 59 ng/mL

<table>
<thead>
<tr>
<th></th>
<th>Visit #1</th>
<th>Visit #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>PRESENT</td>
<td>432 ng/mL</td>
</tr>
<tr>
<td>Noroxycodone</td>
<td>PRESENT</td>
<td>329 ng/mL</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>PRESENT</td>
<td>43 ng/mL</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>PRESENT</td>
<td>59 ng/mL</td>
</tr>
<tr>
<td>THC</td>
<td>PRESENT</td>
<td>154 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>156 mg/dL</td>
<td>154 mg/dL</td>
</tr>
</tbody>
</table>
Benefits of a Qualitative Assay

- Simpler testing strategy for multi-analyte tests
  - 67 drugs/metabolites with 67 calibration curves?
  - Negative, 1 @ cutoff, 1 @ 50% control, 1 @ 150% control
  - Analog ISTDs possible *if you can prove it*
- Reduced costs
- Addition of new analytes can be rapid
Limitations of a Qualitative Assay

- Quantitative results can be useful
- Accurate ratios may be lost
  - Methamp/amp
  - Pharmaceutical tolerances for impurities
- Makes many physicians nervous
- Platform can cause reimbursement challenges
Recommendations: Quantitation

- Quantitation should be available (in-house or Send Out)
- Eliminate it when it isn’t useful
  - Reduces cost, complexity and time
- Use AND report numbers wisely!
  - Always with creatinine
What is the best workflow for pain management testing?
Which Method is Best?

• Immunoassay

• Mass Spectrometry

• Situation dependent
  • Expecting negatives
    – IAs work well
    – Think “workplace drug testing”
  • Expecting positives
    – Depends on the class
    – Mass spectrometry more specific

• Immunoassays do have a role
  – POC
  – ER
  – Rapid screening
Metabolites are Key
Metabolites: Accurate compliance determination

- 46 y/o male patient with Hx of diversion. Current medications include oxycodone and alprazolam.
Metabolites: Enhancing sensitivity

- 36 y/o female prescribed buprenorphine.
  - Buprenorphine
    - Norbuprenorphine
    - Buprenorphine-G
    - Norbuprenorphine-G

- Cross-reactivity in an immunoassay
- Hydrolysis for mass spectrometry
Benefits of a MS Screen

- Sensitivity & Specificity on par with classic “confirmatory” methods
- Individual compound/metabolite identification
- Elimination of cross-reactivity complications
- Drug/metabolite pairs for interpretations
- Drug abuse testing conducted concurrently for high risk populations
- Relatively easy integration of new targets
- “Reflex to Quantitation” still possible when needed
Reduction in TAT with a MS Screen
Recommendations: Assay Design & Workflow

• Use the platform you know and have
• Keep things as simple as possible
• Know your client base and needs
• Flexibility
  – Reimbursement, new drugs
• Design an assay for what is needed – no more, no less
What level of interpretation should we offer and why?
Physicians are not pharmacologists!

*Common calls*

- “My patient is taking Klonopin but repeatedly screens negative for benzos.”
  - 7-aminoclonazepam vs. clonazepam
- “My patient is taking oxycodone but is negative for opiates. Is he diverting?”
  - Opiate IA vs. Oxycodone IA
- “My patient is taking Valium but is positive for 4 other drugs.”
  - Benzo metabolism
Interpreting Results

Easier said than done...

2013 DMPM Cap Survey Results

Dry Lab Challenge
Case Summary and Interpretation
A 41-year-old male with chronic low back pain came for a follow-up visit. The patient has a known right L5-S1 disc extrusion osteophyte complex and is being prescribed Roxicet (oxycodone + acetaminophen) and Percocet (oxycodone + acetaminophen).

Medication List
- LYRICA 150 mg p.o. b.i.d
- ROXICET/PERCOCET 5 per day p.r.n. pain
- VIAGRA p.r.n.

Test Results
<table>
<thead>
<tr>
<th>Screen Results</th>
<th>Confirmation Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate screen NEGATIVE</td>
<td>Oxycodone 2500 ng/mL, oxymorphone 1500 ng/mL</td>
</tr>
<tr>
<td>Amphetamine screen POSITIVE</td>
<td>Amphetamine 2500 ng/mL</td>
</tr>
<tr>
<td>Benzo screen NEGATIVE</td>
<td>Lorazepam 4000 ng/mL</td>
</tr>
</tbody>
</table>

Interpretation (Educational)

<table>
<thead>
<tr>
<th>Result</th>
<th>No. of Respondents</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicology results are inconsistent with prescribed medication</td>
<td>49</td>
<td>59.8</td>
</tr>
<tr>
<td>Toxicology results are consistent with prescribed medication</td>
<td>33</td>
<td>40.2</td>
</tr>
<tr>
<td>Additional prescription drugs present</td>
<td>74</td>
<td>90.2</td>
</tr>
<tr>
<td>Additional prescription drugs absent</td>
<td>8</td>
<td>9.8</td>
</tr>
<tr>
<td>Illicit drugs present</td>
<td>40</td>
<td>46.2</td>
</tr>
<tr>
<td>Illicit drugs absent</td>
<td>43</td>
<td>51.8</td>
</tr>
</tbody>
</table>
Two Paths for Supporting Interpretations

• Path 1
  – Provide all information to the physician
    • Results (qual and/or quant)
    • Guides (see appendix at the end)
  – Hope for the best
  – Wait for a call
Two Paths for Supporting Interpretations

• Path 2
  – Provide all information to the \textit{Lab}
  – Provide interpretation to physician
  – Wait for a call
Example Interpretation: High Volume Test

**Drugs Provided:**
- NORCO
- ALPRAZOLAM

**Interpretation:**
- **CONSISTENT** with medications provided:
  - NORCO: based on hydrocodone, norhydrocodone, dihydrocodeine, hydromorphone
  - ALPRAZOLAM: based on alprazolam, alpha-OH-alprazolam

- **INCONSISTENT** with medications provided:
  - THC: based on immunoassay detection

**Drugs not included in this assay:**
- Acetaminophen

- Submitted with order
- Provided by Lab
- Tells physician what and why
- Indicates detection method if not definitive
- Helpful co-formulation information
Recommendations: Providing Interpretations

• Prepare for future volumes
• Decide on a level of detail and standardize
• Understand IT limitations
• Educate physicians if interest exists
• Provide tools customized to your assay
Summary & Key Points

• Rethink the screen with reflex paradigm

• Compound identification is key – quantitation is a separate aspect

• Qualitative results are often all that is needed

• Design testing with both physicians AND the staff in mind
Contact Information

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### 1 Immunoassay
- Barbiturates
- Carisoprodol
- Cocaine
- Ethyl-glucuronide
- Marijuana metabolite
- Methadone
- PCP
- Propoxyphene
- Tramadol

### 2 Mass Spectrometry

<table>
<thead>
<tr>
<th>Substance</th>
<th>Metabolite</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-acetylmorphine</td>
<td>Hydromorphone</td>
<td>Noroxycodone</td>
</tr>
<tr>
<td>7-aminoclonazepam</td>
<td>Lorazepam</td>
<td>Noroxymorphone</td>
</tr>
<tr>
<td>Alpha-OH-alprazolam</td>
<td>MDA</td>
<td>Oxazepam</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>MDEA</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>MDMA</td>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Meperidine metabolite</td>
<td>Phentermine</td>
</tr>
<tr>
<td>Buprenorphine-glucuronide</td>
<td>Methamphetamine</td>
<td>Ritalinic Acid</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Midazolam</td>
<td>Tapentadol</td>
</tr>
<tr>
<td>Codeine</td>
<td>Morphine</td>
<td>Tapentadol-O-Sulfate</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Norbuprenorphine</td>
<td>Temazepam</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>Nordiazepam</td>
<td>Zolpidem</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Norfentanyl</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Norhydrocodone</td>
<td></td>
</tr>
</tbody>
</table>

### 3 Spectrophotometry
- Creatinine
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Reported Drugs and Metabolites that Indicate Use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Alprazolam, Alpha-hydroxyalprazolam</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Nordiazepam, Oxazepam</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Nordiazepam, Oxazepam</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Clonazepam, 7-aminoclonazepam</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Diazepam, Nordiazepam, Temazepam, Oxazepam</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Midazolam</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Oxazepam</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Temazepam, Oxazepam</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Zolpidem</td>
</tr>
</tbody>
</table>

*Not all drugs or metabolites may be present for each patient*
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Reported Drugs or Metabolites that Indicate Use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Buprenorphine, Norbuprenorphine, Buprenorphine-glucuronide</td>
</tr>
<tr>
<td>Codeine</td>
<td>Codeine, Morphine</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Fentanyl, Norfentanyl</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Hydrocodone, Norhydrocodone, Dihydrocodeine, Hydromorphone</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Meperidine metabolite (Normeperidine)</td>
</tr>
<tr>
<td>Morphine</td>
<td>Morphine, Hydromorphone</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxycodone, Noroxycodone, Oxymorphone, Noroxymorphone</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Oxymorphone, Noroxymorphone</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Tapentadol, Tapentadol-o-Sulfate</td>
</tr>
</tbody>
</table>

*Not all drugs or metabolites may be present for each patient*
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Example Trade Name</th>
<th>Reported Drugs or Metabolites that Indicate Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Adderall</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Ritalin</td>
<td>Ritalinic Acid</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Adipex-P</td>
<td>Phentermine</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Reported Drugs and Metabolites that Indicate Use*</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>MDMA (Ecstasy )</td>
<td>MDMA, MDA</td>
<td></td>
</tr>
<tr>
<td>MDEA (Eve)</td>
<td>MDEA, MDA</td>
<td></td>
</tr>
<tr>
<td>MDA</td>
<td>MDA</td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>Morphine, 6-acetylmorphine†, Codeine</td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>9-carboxy-tetrahydrocannabinol (detected by immunoassay)</td>
<td></td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Methamphetamine, Amphetamine</td>
<td></td>
</tr>
</tbody>
</table>

*Not all drugs or metabolites may be present for each patient
†Presence required to accurately identify heroin use
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Reported Drugs or Relevant Metabolites that Indicate Use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Butalbital†, amobarbital†, pentobarbital†, phenobarbital†</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>Carisoprodol†, Meprobamate†</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Cocaine‡, Benzoylecgonine†</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Ethyl-glucuronide†</td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone†, EDDP‡</td>
</tr>
<tr>
<td>PCP</td>
<td>PCP†</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Propoxyphene†, Norpropoxyphene†</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Tramadol†, O-desmethyl-Tramadol‡, N-desmethyl-Tramadol‡</td>
</tr>
</tbody>
</table>

*Listed compounds are not individually identified. Total absorbance for all detected compounds is used to report presence or absence.
†Detected by the immunoassay
‡Minimal detection or Not detected by the immunoassay