The Laboratory's Role in Pain Management Testing

Frederick G. Strathmann, PhD, DABCC (CC, TC)

Medical Director, Toxicology
Associate Scientific Director of Mass Spectrometry
ARUP Laboratories
Assistant Professor
Department of Pathology
University of Utah
SLC, Utah

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

- Grant/Research Support: **Agilent Technologies**
- Salary/Consultant Fees: **None**
- Board/Committee/Advisory Board Membership: **None**
- Stocks/Bonds: **None**
- 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

Risk Category	Recommended Frequency of Testing (per year) - UDT
Low	≥ 1
Moderate	≥ 2
High	≥ 3 or 4
Aberrant Behavior	At visit

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

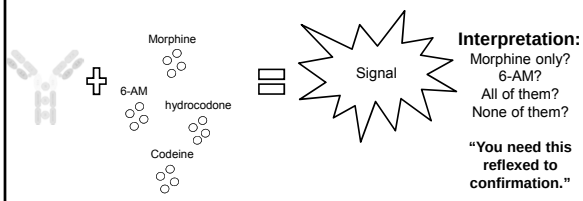
What is the difference between identification, quantitation and confirmation?

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?

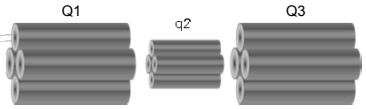
- Non-specific screening method used
  - e.g., immunoassay for opiates



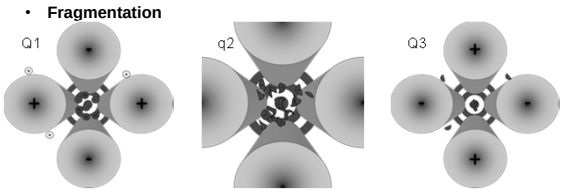
Interpretation:
Morphine only?
6-AM?
All of them?
None of them?

"You need this reflexed to confirmation."

Mass Spectrometry
Triple Quadrupoles

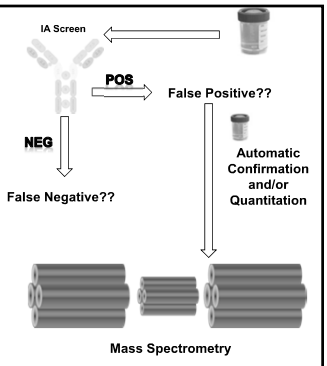


- Gas phase ions
- Mass-to-charge ratio (*m/z*)
- Flight stabilization
- **Fragmentation**



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?



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

Mass Spectrometry Screen
Mass Spectrometry Quantitation

1. 55 y/o male prescribed 7.5mg hydrocodone and clonazepam.

Hydrocodone	PRESENT	262 ng/mL
Norhydrocodone	PRESENT	254 ng/mL
Clonazepam	PRESENT	42 ng/mL
7-aminoclonazepam	PRESENT	652 ng/mL

Creatinine	286 mg/dL

2. 48 y/o male prescribed 7.5mg hydrocodone and clonazepam.

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

Visit #1

Oxycodone	PRESENT	657ng/mL
Noroxycodone	PRESENT	698 ng/mL
Lorazepam	PRESENT	58 ng/mL
Amphetamine	PRESENT	886 ng/mL
THC	PRESENT	432 ng/mL

Creatinine	154 mg/dL

Visit #2

Oxycodone	PRESENT	432 ng/mL
Noroxycodone	PRESENT	329 ng/mL
Lorazepam	PRESENT	43 ng/mL
Amphetamine	NOT DETECTED	
THC	PRESENT	59 ng/mL

Creatinine	156 mg/dL

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

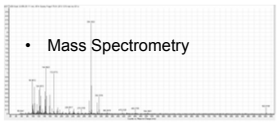
Recommendations: Quantitation

- 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?

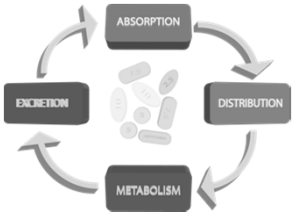
- Immunoassay



- 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.

Result A

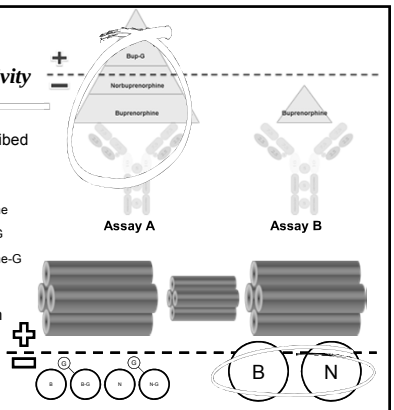
Oxycodone	PRESENT
Alprazolam	PRESENT

Result B

Oxycodone	PRESENT
- Noroxycodone	PRESENT
Alprazolam	PRESENT
- Alpha-OH-alprazolam	PRESENT

Metabolites:
Enhancing sensitivity

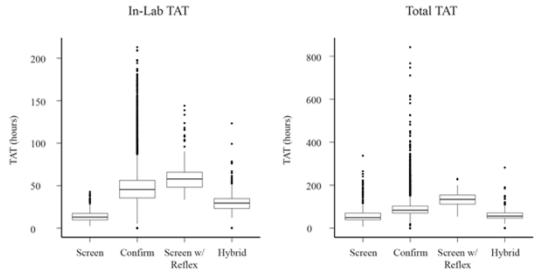
- 36 y/o female prescribed buprenorphine.
  - Buprenorphine
    - Norbuprenorphine
    - Buprenorphine-G
    - Norbuprenorphine-G
- Cross-reactivity in an immunoassay
- Hydrolysis for mass spectrometry



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

Screen Results	Confirmation Results
Opiate screen NEGATIVE	Oxycodone 2500 ng/mL, oxymorphone 1500 ng/mL
Amphetamine screen POSITIVE	Amphetamine 2500 ng/mL
Benzo screen NEGATIVE	Lorazepam 4000 ng/mL

Interpretation (Educational)

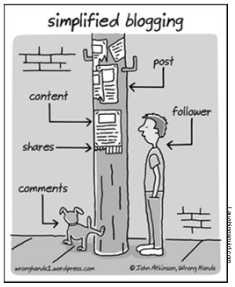
	Result	No. of Respondents	%
POS DMPM	Toxicology results are **inconsistent** with prescribed medication	49	59.8
	Toxicology results are **consistent** with prescribed medication	33	40.2
	Additional prescription drugs present	74	90.2
	Additional prescription drugs absent	8	9.8
	Illicit drugs present	40	48.2
	Illicit drugs absent	43	51.8

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 *Lab*
  - Provide interpretation to physician
  - Wait for a call



Example Interpretation: High Volume Test

Drugs Provided: Submitted with order
NORCO
ALPRAZOLAM Provided by Lab

Interpretation: Tells physician what and why
CONSISTENT with medications provided:
NORCO: based on hydrocodone, norhydrocodone, dihydrocodeine, hydromorphone
ALPRAZOLAM: based on alprazolam, alpha-OH-alprazolam

INCONSISTENT with medications provided: Indicates detection method if not definitive
THC: based on immunoassay detection

Drugs not included in this assay: Helpful co-formulation information
Acetaminophen

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

Frederick G. Strathmann, PhD, DABCC (CC, TC)
Medical Director, Toxicology
Associate Scientific Director of Mass Spectrometry
ARUP Laboratories
Assistant Professor
Department of Pathology
Associate Member
Interdepartmental Graduate Program in Neuroscience
University of Utah
frederick.g.strathmann@aruplab.com

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY

UNIVERSITY OF UTAH | DEPARTMENT OF PATHOLOGY

© 2014 ARUP Laboratories

ARUP IS A NONPROFIT ENTERPRISE OF THE UNIVERSITY OF UTAH AND ITS DEPARTMENT OF PATHOLOGY.

Example Physician Handout

1 Immunoassay

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

3 Spectrophotometry

Creatinine

2 Mass Spectrometry

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

Drug Name	Reported Drugs and Metabolites that Indicate Use*
Alprazolam	Alprazolam, Alpha-hydroxyalprazolam
Chlordiazepoxide	Nordiazepam, Oxazepam
Clorazepate	Nordiazepam, Oxazepam
Clonazepam	Clonazepam, 7-aminoclonazepam
Diazepam	Diazepam, Nordiazepam, Temazepam, Oxazepam
Lorazepam	Lorazepam
Midazolam	Midazolam
Oxazepam	Oxazepam
Temazepam	Temazepam, Oxazepam
Zolpidem	Zolpidem

*Not all drugs or metabolites may be present for each patient

Drug Name	Reported Drugs or Metabolites that Indicate Use*
Buprenorphine	Buprenorphine, Norbuprenorphine, Buprenorphine-glucuronide
Codeine	Codeine, Morphine
Fentanyl	Fentanyl, Norfentanyl
Hydrocodone	Hydrocodone, Norhydrocodone, Dihydrocodeine, Hydromorphone
Hydromorphone	Hydromorphone
Meperidine	Meperidine metabolite (Normeperidine)
Morphine	Morphine, Hydromorphone
Oxycodone	Oxycodone, Noroxycodone, Oxymorphone, Noroxymorphone
Oxymorphone	Oxymorphone, Noroxymorphone
Tapentadol	Tapentadol, Tapentadol-o-Sulfate

*Not all drugs or metabolites may be present for each patient

Drug Name	Example Trade Name	Reported Drugs or Metabolites that Indicate Use
Amphetamine	Adderall	Amphetamine
Methylphenidate	Ritalin	Ritalinic Acid
Phentermine	Adipex-P	Phentermine

Drug Name	Reported Drugs and Metabolites that Indicate Use*
MDMA (Ecstasy)	MDMA, MDA
MDEA (Eve)	MDEA, MDA
MDA	MDA
Heroin	Morphine, 6-acetylmorphine†, Codeine
Marijuana	9-carboxy-tetrahydrocannabinol (**detected by immunoassay**)
Methamphetamine	Methamphetamine, Amphetamine

*Not all drugs or metabolites may be present for each patient
†Presence required to accurately identify heroin use

Drug Name	Reported Drugs or Relevant Metabolites that Indicate Use*
Barbiturates	Butalbital†, amobarbital†, pentobarbital†, phenobarbital†
Carisoprodol	Carisoprodol†, Meprobamate†
Cocaine	Cocaine‡, Benzoylecgonine†
Ethanol	Ethyl-glucuronide†
Methadone	Methadone†, EDDP‡
PCP	PCP†
Propoxyphene	Propoxyphene†, Norpropoxyphene†
Tramadol	Tramadol†, O-desmethyl-Tramadol‡, N-desmethyl-Tramadol‡

*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