Making Sense of Numbers and Ratios

The Laboratory's Role in Pain Management Result Interpretation

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

AACC Mass Spectrometry in the Clinical Laboratory
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Contact Information

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

Medical Director, Toxicology
ARUP Laboratories

Assistant Professor
Department of Pathology
Associate Member
Interdepartmental Graduate Program in Neuroscience
University of Utah

frederick.g.strathmann@aruplab.com

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- University of Utah
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Objectives

- Explain the differences between quantitative and qualitative testing
- Differentiate between compound identification, quantitation and confirmation
- Compare the screen with reflex approach with targeted screening for pain management testing
- Judge the utility of urine drug testing for compliance in the pain management setting

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

NY Non-Acute Pain Medical Treatment Guidelines – April 3, 2013 1st Edition

The Laboratory's Goal for Testing

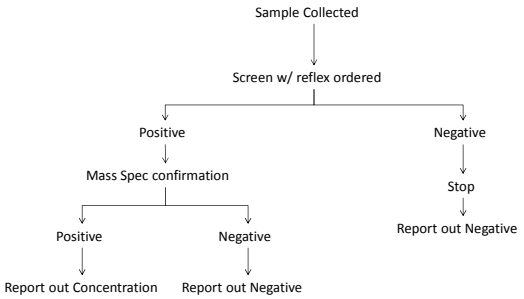
Pain Management Context

- 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!

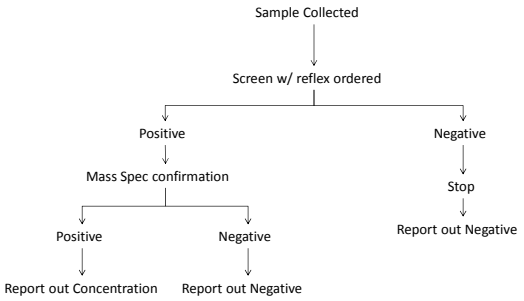
Outline

- Quantitative and qualitative testing
- Compound identification, quantitation and confirmation
- Screen with reflex versus targeted
- Urine drug testing for compliance in the pain management setting

Screen w/ Reflex Workflow



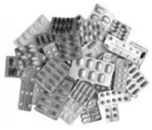
Screen w/ Reflex: Expectations



Positivity Rates: Clinical vs. Workplace Testing

Clinical Testing

- Nov – Dec 2011
- 77% positivity rate
- < 5% false positives

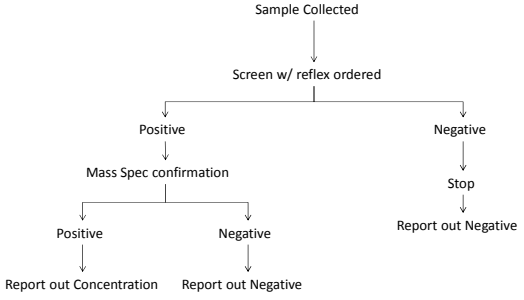


Workplace Testing

- Typical estimates
  - < 5% positivity rate

DATA: Dr. Gwendolyn McMillin; IMAGES: dietchange.com; confirmbiosciences.com

Screen w/ Reflex: Pain Management Reality



Traditional Screening Assay Design

SAMHSA Cutoffs

- Marijuana – 50 ng/mL
- Cocaine – 150 ng/mL
- Opiates – 2000 ng/mL
- 6-AM – 10 ng/mL
- PCP – 25 ng/mL
- AMP/MAMP – 500 ng/mL
- MDMA – 500 ng/mL

Factors not considered

- Appropriate cutoffs
- Drugs of interest
- TAT
- Quantitative vs. Qualitative results
- Population

SAMHSA.gov

Negative Screen Result: Poor Population Resolution

High Risk Patient		Pain Management Patient	
AMPHETAMINE	NEGATIVE	AMPHETAMINE	NEGATIVE
BARBITURATES	NEGATIVE	BARBITURATES	NEGATIVE
BENZODIAZEPINES	NEGATIVE	BENZODIAZEPINES	NEGATIVE
COCAINE	NEGATIVE	COCAINE	NEGATIVE
OPIATES	NEGATIVE	OPIATES	NEGATIVE
OXYCODONE	NEGATIVE	OXYCODONE	NEGATIVE
PCP	NEGATIVE	PCP	NEGATIVE
PROPOXYPHENE	NEGATIVE	PROPOXYPHENE	NEGATIVE
THC	NEGATIVE	THC	NEGATIVE

Negative Screen Result: Poor Population Resolution

High Risk Patient		Pain Management Patient	
AMPHETAMINE	NEGATIVE	AMPHETAMINE	NEGATIVE
BARBITURATES	NEGATIVE	BARBITURATES	NEGATIVE
BENZODIAZEPINES	NEGATIVE	BENZODIA	VE
COCAINE	ATIVE	COCAINE	ATIVE
OPIATES	EGATIVE	OPIATES	EGATIVE
OXYCODONE	NEGATIVE	OXYCODONE	ATIVE
PCP	NEGATIVE	PCP	VE
PROPOXYPHENE	NEGATIVE	PROPOXYPHENE	NEGATIVE
THC	NEGATIVE	THC	NEGATIVE

Positive Screen Result: Poor Analyte Resolution

- Rx:
  - Hydrocodone
  - Oxycodone
- Interpretations
  - Compliant?
  - Diversion?
  - Heroin?

AMPHETAMINE		NEGATIVE
BARBITURATES		NEGATIVE
BENZODIAZEPINES		NEGATIVE
COCAINE		NEGATIVE
OPIATES	H	POSITIVE
OXYCODONE	H	POSITIVE
PCP		NEGATIVE
PROPOXYPHENE		NEGATIVE
THC		NEGATIVE

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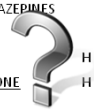

Screen with Reflex Summary

- One-size-fits-all solution that doesn't fit
- Delayed TAT
- Initial screen result that is often useless
- Unnece$$ary confirmation te$ting

Outline

- Quantitative and qualitative testing
- Compound identification, quantitation and confirmation
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Confirmation Testing

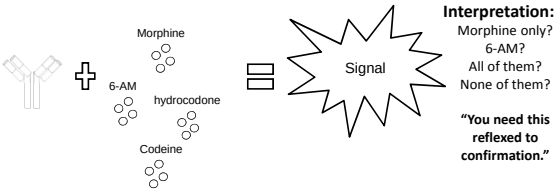
Yes, no, maybe?

- 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"
- 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."

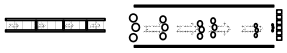
A Sensitive, Qualitative (Targeted) Screen by LC-TOF/MS

- Broad range of compounds
- Adequate sensitivity
  - on par with current confirmatory methods
- Parent drug and metabolites to aid interpretation
- TAT less than classic screen w/ reflex
- One and done (no need for confirmation)

Confirmation Testing

With LC-TOF this is not required!!

- Drugs are individually identified
  - Absolute identification with the ***first*** test



Interpretation:

Morphine	NOT FOUND
6-AM	NOT FOUND
Hydrocodone	PRESENT
Codeine	NOT FOUND

"Positive for hydrocodone. No need for further testing."

Benefits of an LC-TOF/MS Targeted Screen

- Sensitivity & Specificity on par with classic confirmatory methods
- Individual compound 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

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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

Prescriptions:
Klonopin
Lortab

LC-TOF (Qualitative):

Clonazepam	PRESENT
7-aminoclonazepam	PRESENT
Hydrocodone	PRESENT

LC-MS/MS (Quantitative):

Clonazepam	64 ng/mL
7-aminoclonazepam	820 ng/mL
Hydrocodone	120 ng/mL

Q: Would the interpretation differ if clonazepam was 35 ng/mL?
A: Not likely.

Q: What if hydrocodone was 250 ng/mL?
A: Both values indicate compliance.

Quantitative vs. Qualitative

When? Why? cont.

- Quantitation can help – sometimes
  - long $t_{1/2}$ for marijuana metabolites in a patient claiming to have abstained but still positive
    - Result 1 = 826 ng/mL (creatinine of 86 mg/dL)
    - Result 2 = 278 ng/mL (creatinine of 92 mg/dL)
    - Trend is downward = good!
- <u>Quantitation is still available when needed</u>

Q: Can't I extrapolate back from a urine concentration and predict compliance with dose?
A: Unfortunately this has not proven to be reliable with routine testing in large and diverse populations.

Benefits of a Qualitative Assay

- Simpler testing strategy for multi-analyte tests
  - 67 drugs with 67 calibration curves??
- Reduced costs
- Addition of new analytes can be rapid

Limitations of a Qualitative Assay

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

Quant vs. Qual Summary

- Absolute identification is required and can be done qualitatively
- Quantitation can be useful in select scenarios
- Quantitation in urine will not allow for partial vs. full compliance in the general population

Outline

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Interpreting Results

Easier said than done…

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)

DMPM404

Result	No. of Respondents	%
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

2013 DMPM Cap Survey Results

Physicians make mistakes too

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 opioids. Is he diverting?"
  - Opiate IA vs. Oxycodone IA
- "My patient is taking Valium but is positive for 4 other drugs."
  - Benzo metabolism

How can the lab help physicians?

- Open dialogue
- Tests designed to meet the needs of the population served
- Inclusion of metabolites and conjugates
- Enhanced reports – if you dare!

How can the lab help itself?

- Inclusion of metabolites
  - Enhances confidence in identification
    - Oxycodone
    - Oxycodone, oxymorphone, noroxycodone, noroxymorphone
  - Allow for higher LOQs
- Staff education
  - Instrumentation, metabolite patterns, interferences
  - Continued education

Key Points

- Rethink the screen with reflex paradigm
- Com ion is a se
- Qua ded
- Design testing with both physicians AND the staff in mind

Contact Information

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

Medical Director, Toxicology
ARUP Laboratories

Assistant Professor
Department of Pathology
Associate Member
Interdepartmental Graduate Program in Neuroscience
University of Utah

frederick.g.strathmann@aruplab.com