Drug Testing in the Pain Management Setting

September 27, 2011

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Disclosure

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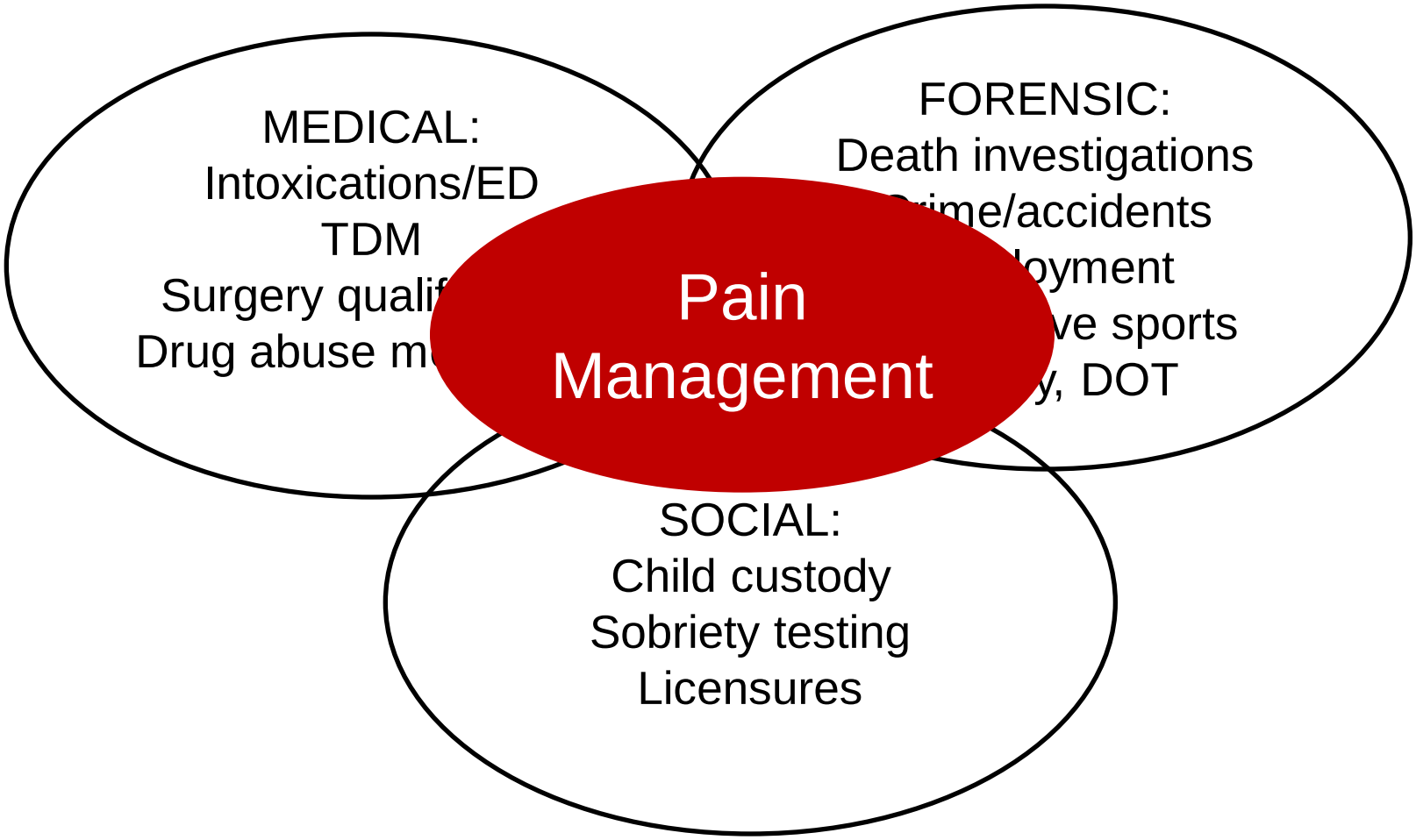
Application of drug testing



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 a major health and social issue

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 management in medicine

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)
- Non-opioid analgesics
  - Ibuprofen (#21, 113)
  - Naproxen (#132, 187)
  - APAP (#1, 3, 34, 39, 54, 66, 98, 147, 169)
- Benzodiazepine-like
  - Alprazolam (#46, 57, 88, 119)
  - Clonazepam (#47, 116)
  - Lorazepam (#78, 200)
  - Diazepam (#106)
  - Zolpidem (#24, 134, 186)
- 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
http://www.pharmacytimes.com/publications/issue/2011/May2011/Top-200-Drugs-of-2010

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

Drug	"Street" Price (per pill)	Retail Price Estimate (per pill)	Potential "Profit" (per pill)
Oxycodone	$12 - 40	$6	$34
Oxycontin®	$50 - 80		$74
Percocet®	$10 - $15		$9
Hydrocodone	$5 - 20	$1.50	$18.50
Vicodin®	$5 -25		$23.50

CNN Money; June 1, 2011

Efforts to minimize drug trafficking

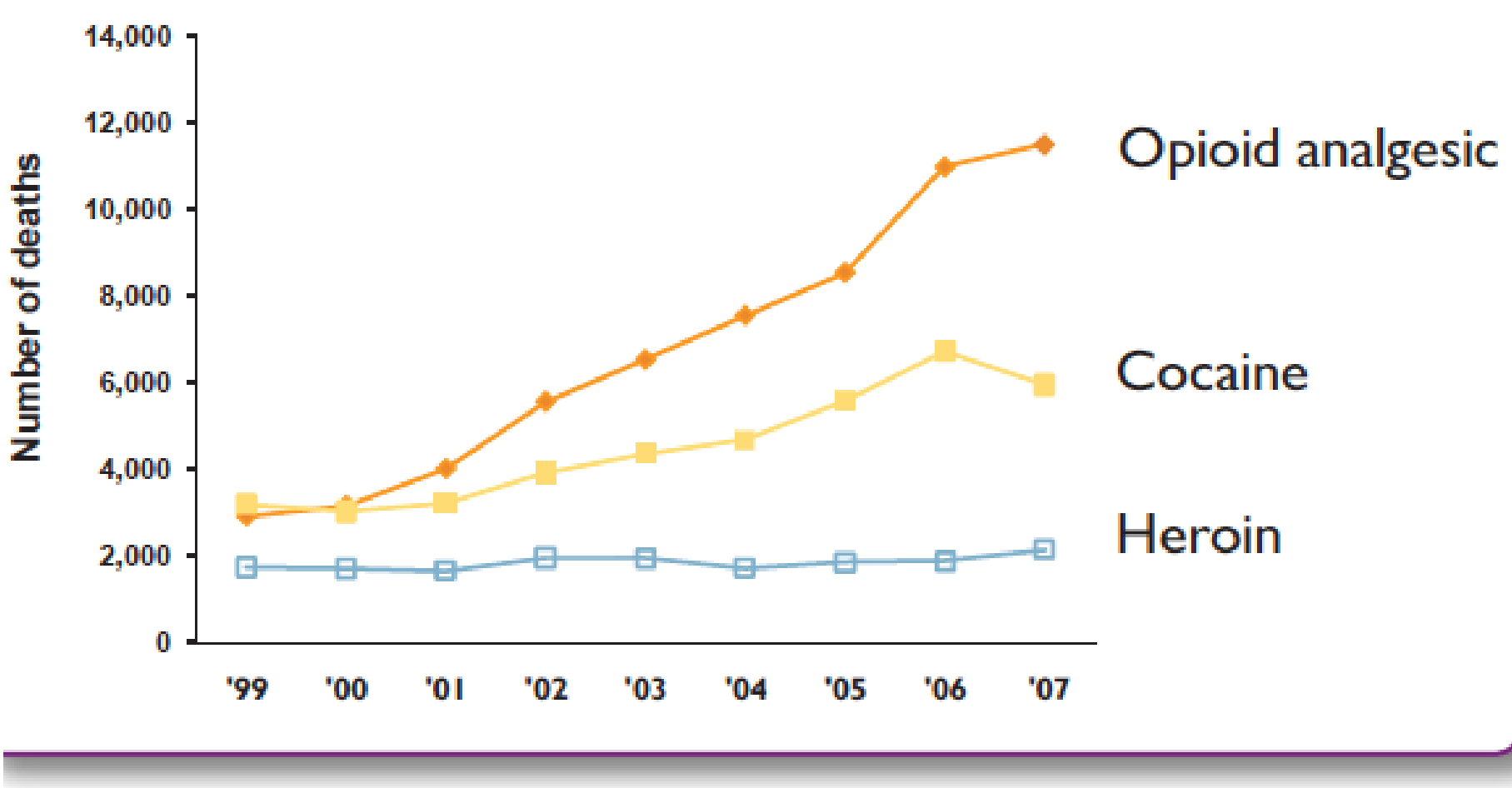
- US Department of Justice, Drug Enforcement Administration, Office of Diversion Control: www.deadiversion.usdoj.gov

- 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” requirements by the FDA

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.

http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm

Monitoring patients for misuse and abuse

Post-Approval REMS Notification, Appendix A, accessed 9/11/11
http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM251595.pdf

Prescription monitoring programs

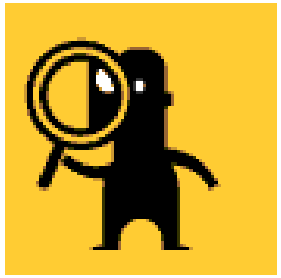
Urine drug testing

Screening and referrals for substance abuse treatment

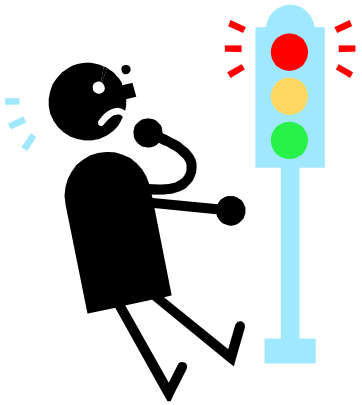
Clinical Practice Guidelines for Opioid Prescribers

- 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
- ASIPP Guideline: Opioids in the Management of Chronic Non-Cancer Pain — an Update of American Society of the Interventional Pain Physicians' Guidelines, 2008

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

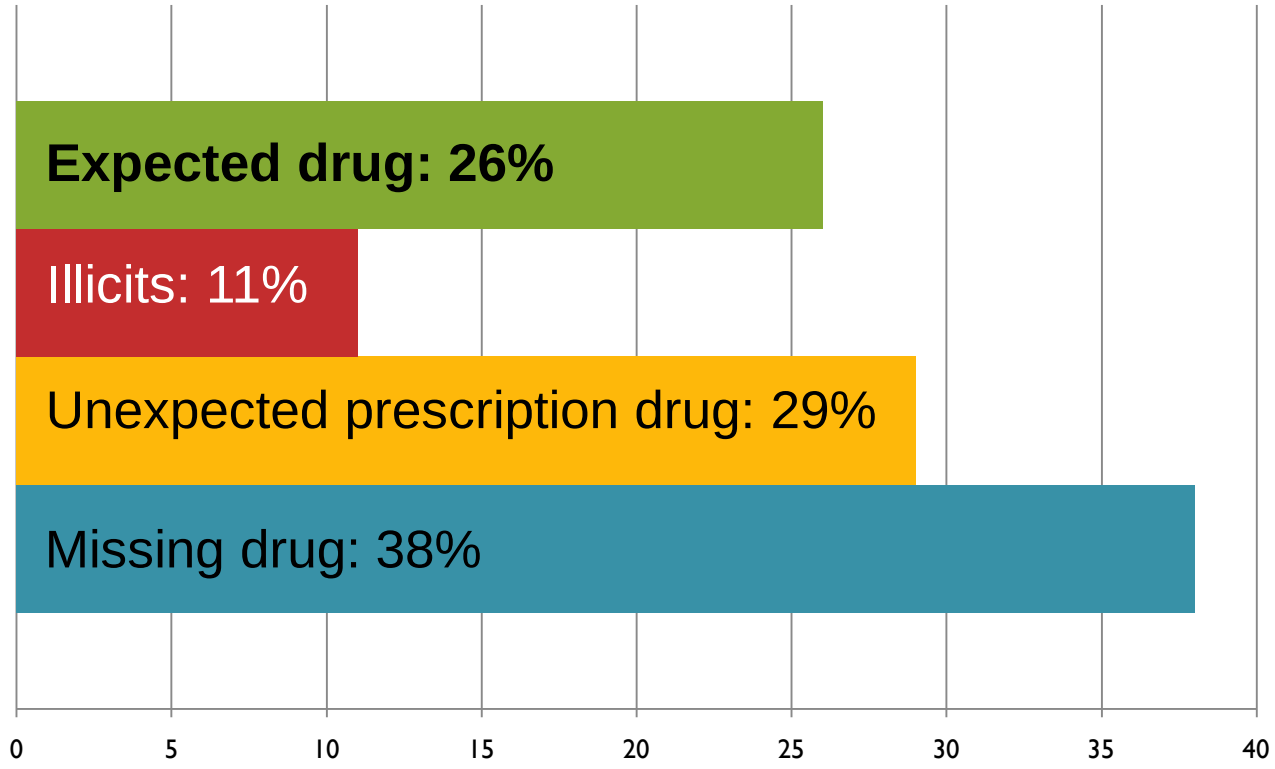
Preserve access to therapy

Christo*, Pain Physician* 14:123-43, 2011

How do patients perform???

Urine drug testing (UDT) results

Reference lab study, representing 938,586 results



Couto et al, *Population Health Management* 12(4), 185-90, 2009

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%)

Michna et al, *Clin J Pain* 23:173-9, 2007

Sources of variation in UDT

- Pharmacokinetic variability of drugs, drug formulations, and patients
- Limitations of urine
- Testing methods involved
- Inappropriate interpretation of results

✓ Drug
✓ Patient
✓ Sample
✓ Test

“Take-home” message #1

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

- oLittle standardization exists among laboratory tests today
- oDrugs used in pain management have complicated pharmacokinetics, interactions, and some are not “pure”
- oPatients are often “high risk”
- oConsequences of false positive or false negative results are severe, for all involved

Lab definitions

- 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 and immunoassay results

SPECIFICITY

Poor =
FALSE negative
result

Defined by:
Antibody, Cutoff, and Calibrator

Good (for wrong drug) = FALSE positive result

TRUE result,
negative or positive

Substances with poor cross-reactivity

Drug class	Compounds not detected
• Marijuana	• Spice, K2
• Amphetamines	• Methylphenidate
• Benzodiazepines	• Clonazepam, Zolpidem
• Methadone	• EDDP
• Opiates	• Oxycodone, Fentanyl, Tramadol, Buprenorphine

Possible FALSE negative

Manchikanti et al, *Pain Physician 1*3:E1-22, 2010
Tenore, *J of Addictive Diseases* 29:436-48, 2010

Substances with good cross-reactivity

Drug class	Compounds detected
• Cannabinoids	• NSAIDs, Pantoprazole
• Opioids	• Chlorpromazine, Fluoroquinolones
• Benzodiazepine	• Oxaprozin, Sertraline
• Methadone	• Propoxyphene, Seroquel
• PCP	• Dextromethorphan, Meperidine
• Amphetamines	• Vicks, Desipramine, Trazodone

Possible FALSE positive

Christoi et al, *Pain Physician* 14:123-43, 2011
Tenore, *J of Addictive Diseases* 29:436-48, 2010

Detection limits reflect

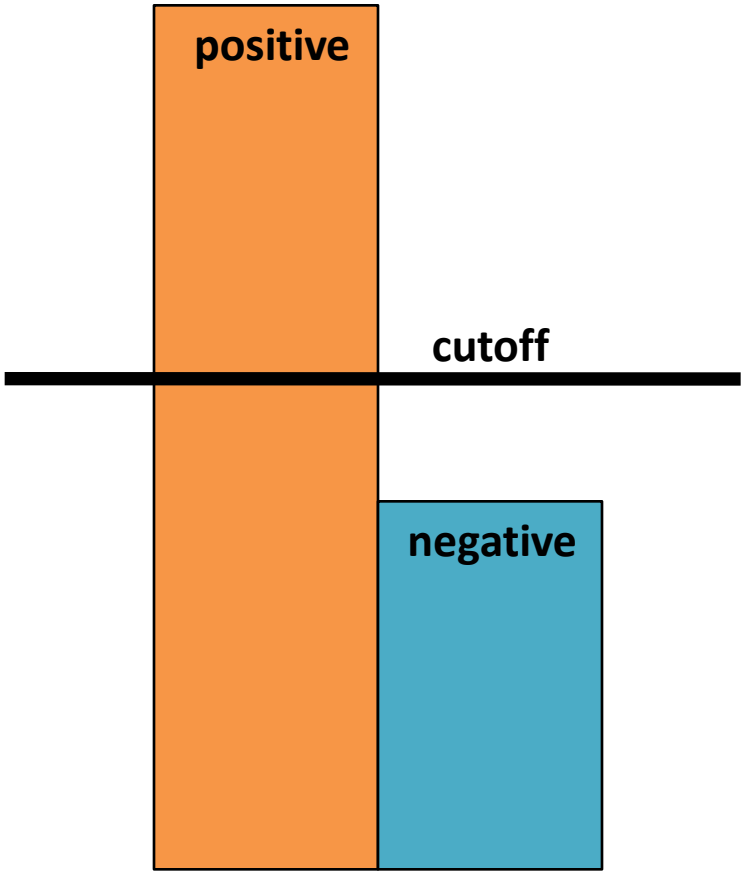
Assay method and cutoff

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

$$\frac{\text{Drug x 100}}{\text{Creatinine}} = \text{ng drug/mg creatinine}$$

Substitution may not be detected

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

VP Villena, *JAT* 34:39-44, 2010

UDT in Pain Management

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

POCT in pain patients

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

Manchikanti et al, *Pain Physician*;14:175-87 & 259-70, 2011

When to “confirm” a result

2nd immunoassay

Chromatography

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

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

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

Drug (ng/mL)	Abbott FPIA	Dade Behring (Syva) EMIT II	Roche CEDIA DAU	BIOSITE Triage
Morphine	300	300	300	300
Hydrocodone	100	300	364	300
Oxycodone	1000	5,388	10,000	20,000

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)

✓ Drug
✓ Patient
✓ Sample
✓ Test

Interpreting concentrations

Patient results

2033 ng/mL Morphine

15 ng/mL Hydromorphone

Patient Rx

MS Contin® (morphine sulfate)

- Morphine is metabolized to hydromorphone (minor pathway, <3% expected)
- Thresholds for independent use of hydromorphone are not well established

Cone et al *JAT* 32(4):319-23, 2008

Interpreting concentrations (cont.)

Patient results

2033 ng/mL Morphine

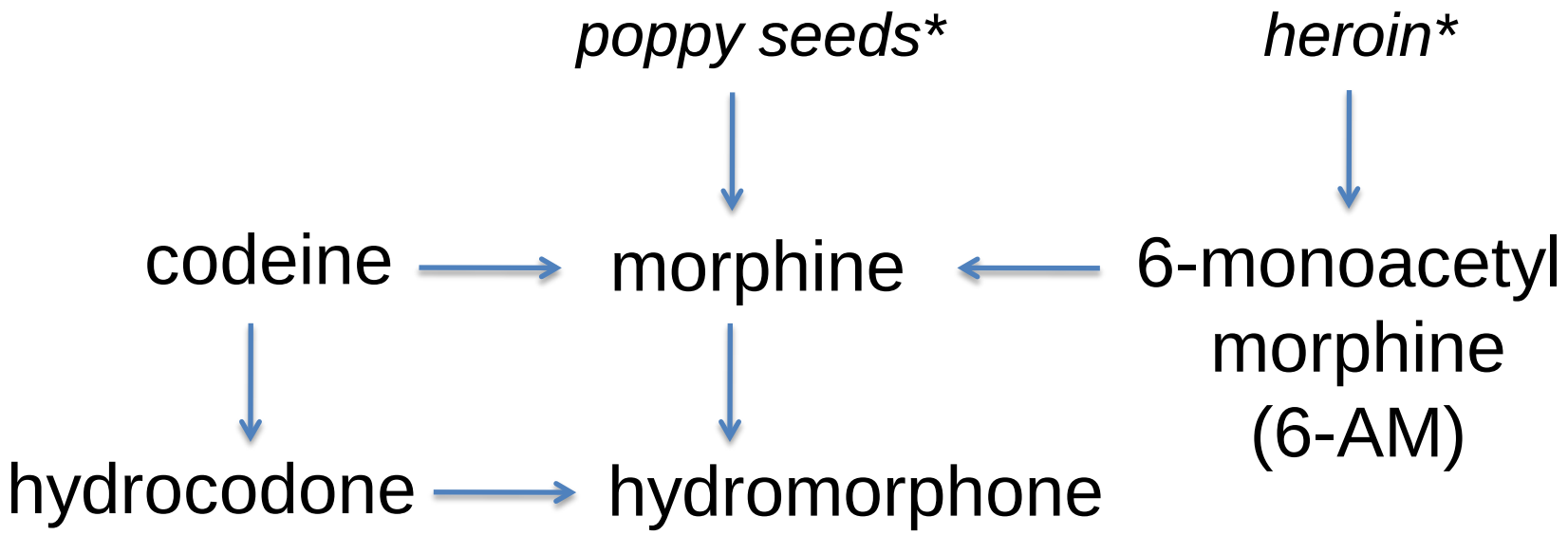
15 ng/mL Hydromorphone

8 ng/mL Codeine

Patient Rx

MS Contin® (morphine sulfate)

Simplified opioid metabolism



** Not specifically detected by most assays*

Interpreting concentrations (cont.)

Patient results

2033 ng/mL Morphine

15 ng/mL Hydromorphone

8 ng/mL Codeine

Patient Rx

MS Contin® (morphine sulfate)

Codeine is not a metabolite of morphine or hydromorphone

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

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

Opioid process impurities

Active pharmaceutical compound	Process impurities	Allowable pharmaceutical impurity limit (%)
Codeine	Morphine	0.15
Hydrocodone	Codeine	0.15
Hydromorphine	Morphine Hydrocodone	0.15 0.1
Morphine	Codeine	0.5
Oxycodone	Hydrocodone	1.0
Oxymorphone	Hydromorphone Oxycodone	0.15 0.5

MRO Alert XXI, No. 3, 2010

Interpretation:

Detecting adulteration intended to *mimic* adherence to prescribed medications

Results suggesting drug was added to urine

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

NOTES:

Glucuronides were < 20 ng/mL

Expected ratio of BUP:Naloxone for Suboxone® = 4

Average ratio of BUP:Naloxone for these patients: 4.4

McMillin et al., *JAT*, 2011*, in press*

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

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

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

Morphine Metabolite	Chemical (acid)	Enzyme (*P. vulgata, 2 hrs*)	Enzyme (*H. pomatia, 16 hrs*)
Morphine-3-glucuronide	100 ± 4	94 ± 2	50 ± 13
Morphine-6-glucuronide	98 ± 5	12 ± 1	0 ± 0
Patient urine	100 ± 0	64 ± 19	35 ± 20

Wang et al, *JAT* 30:570-5, 2006

Urine concentrations with Duragesic®

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

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

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