Drug Testing to Support Pain Management Clinics

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Outline

- Provide an overview of “pain management”, and discuss concerns relative to use and availability of opioid drugs
- Describe the role of drug testing to support pain management clinicians, and patients
- Discuss approaches to drug testing
- Review considerations for interpretation of test results
  - Unexpected negative results
  - Unexpected positive results
  - Drug adherence versus dose and dosing 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 U.S. 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 U.S. >$100 billion/yr

Pain management in medicine

Pain management is a medical specialty (American Board of Pain Medicine)

Treatment approach is multi-disciplinary

Commonly used medications include opioids, benzodiazepines, antidepressants, anticonvulsants, THC, and muscle relaxants

Drugs in "Top 200" U.S. scripts (2009)

- Opioid analgesics
  - Hydrocodone (#1, 3, 66)
  - Oxycodone (#33, 57, 126, 160, 175)
  - Tramadol (#47, 138)
  - Codeine (#73)
  - Propoxyphene (#79, 163)
  - Buprenorphine (#189)
- Non-opioid analgesics
  - Ibuprofen (#27, 171)
  - Naproxen (#135, 195)
- Benzodiazepines
  - Alprazolam (#39, 58, 83, 122)
  - Clonazepam (#46)
  - Lorazepam (#86, 144)
  - Diazepam (#111)
- Other medications
  - Gabapentin (#70, 186)
  - Pregabalin (#71)
  - Carisoprodol (#112)
  - Antidepressants (#11, 95, 116, 134)

Rank #s from www.pharmacytimes.com

Pain relievers are misused

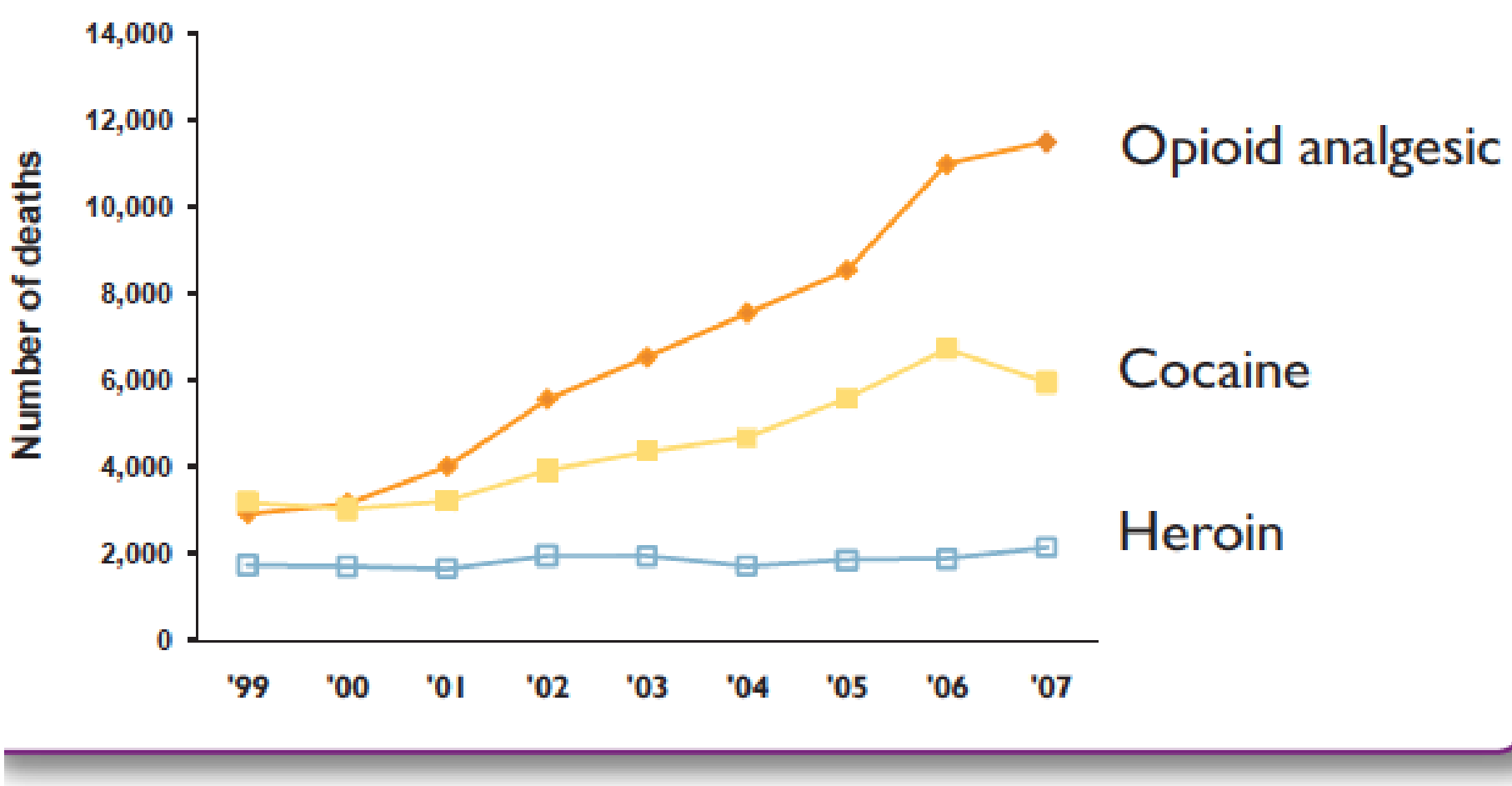
- Pain relievers are the #1 new illicit drug in the U.S.
  National Survey on Drug Use in Health (NSDUH), 2009
- 13% of 12th graders reported nonmedical use of hydrocodone or oxycodone *NSDUH, 2009*
- 60% of people who use pain relievers for nonmedical reasons obtain the drug from a friend or relative *SAMHSA, 2006*

Motive for drug diversion may be $

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

Unintentional U.S. 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”*

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

Opioid drug sponsors/manufacturers of select formulations (primarily ER) will be required to provide educational programs and materials, for both prescribers and patients, as part of “new safety information” requirements – discussions currently ongoing

Drugs selected for REMS include fentanyl, morphine, buprenorphine, methadone, oxycodone, oxymorphone, and hydromorphone

Objectives of drug testing

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

2. Discourage drug misuse

Drug testing is a tool, intended to supplement self-reporting, as well as behavioral and clinical monitoring

Drug testing approaches

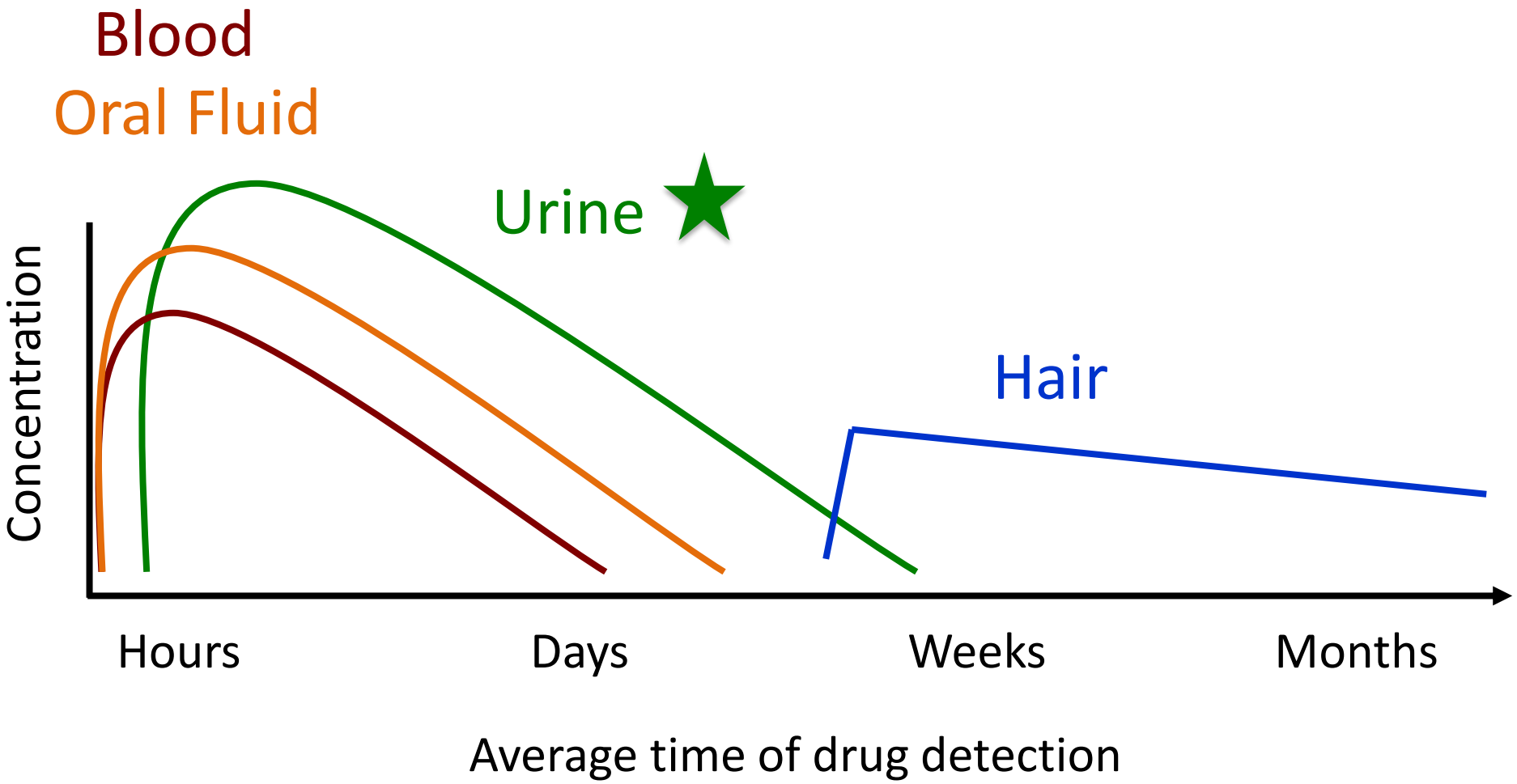
Pre-therapeutic comprehensive testing:

selected illicit and prescription drugs

Periodic testing (during therapy):

random testing, to detect selected illicit and prescription drugs, every 1-12 months, tailored to patient scenario

Specimen selection



Caplan, YA, Cone, EJ, (2009), Laboratory Testing in Pain Management: Approaches & Issues, www.samhsa.gov.

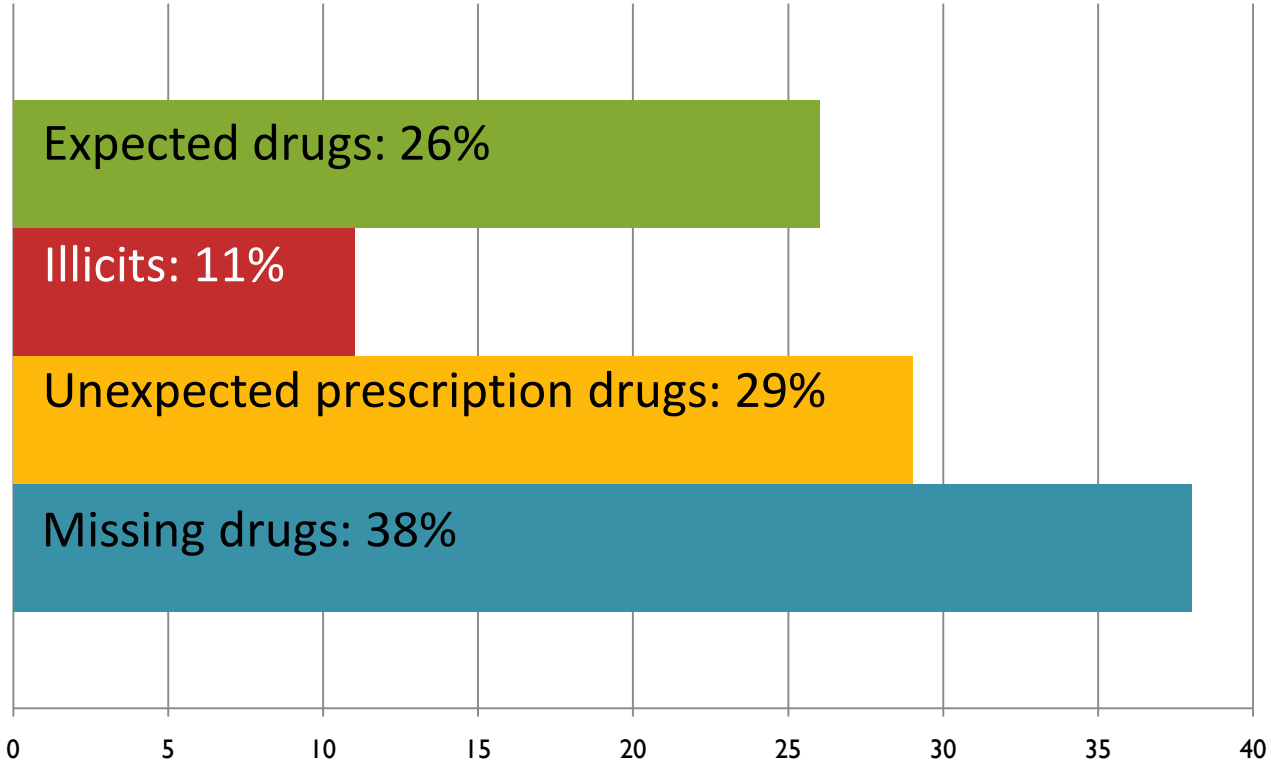
Actual pharmacokinetics (PK) varies

- Absorption and Distribution
  - Formulation
  - Route of administration
- Metabolism
  - First pass
  - Phase I enzymes (e.g. cytochrome P450 isozymes)
  - Phase II enzymes (e.g. UDP-glucuronosyltransferase)
  - Drug/drug or food/drug interactions
  - Hepatic function
- Elimination
  - Renal function

Consider specific prescribed medications, patient clinical status, genetics, history, etc.

Urine drug testing (UDT) results

AmeriTox (938,586 results); Couto et al, *Population Health Management* 12(4), 185-90 (2009)



Another example of UDT results

- Retrospective study of 470 pain clinic 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. 22%)
– Missing opioid	10% (vs. 38%)
– Unexpected opioid	15% (vs. 29%)
– Illicit substances	20% (vs. 11%)

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

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

- Objective(s) of testing?
- Define testing needs
  - Time to result
  - Specimen(s)
  - Specific drug(s) of interest
  - Qualitative or quantitative
  - Sensitivity
  - Specificity

Lab definitions (cont.)

- Sensitivity: the minimum concentration that is reliably detected. May be defined by the limit of quantification (LOQ) of an assay or the "cutoff," which is the concentration used to distinguish between a positive and a negative result. Cutoff concentration is defined by the assay manufacturer, or by the laboratory.

Example cutoffs: SAMHSA vs ARUP (ng/mL)

Drug Class	Forensic Screen	Medical Screen	Drug	Forensic Confirm	Medical Confirm
Amps	500	300	Amphetamine, Methamphetamine, MDMA, MEA, MDA	250	200
THC	50	20	THC-COOH	15	4
Cocaine	300	150	Benzoylecgonine	100	50
Opiates*	2000	300	Morphine	2000	5
			Codeine	2000	5
PCP	25	25	PCP	25	10

* New for 2010, guidelines mandate screening for 6-monoacetylmorphine at 10 ng/mL

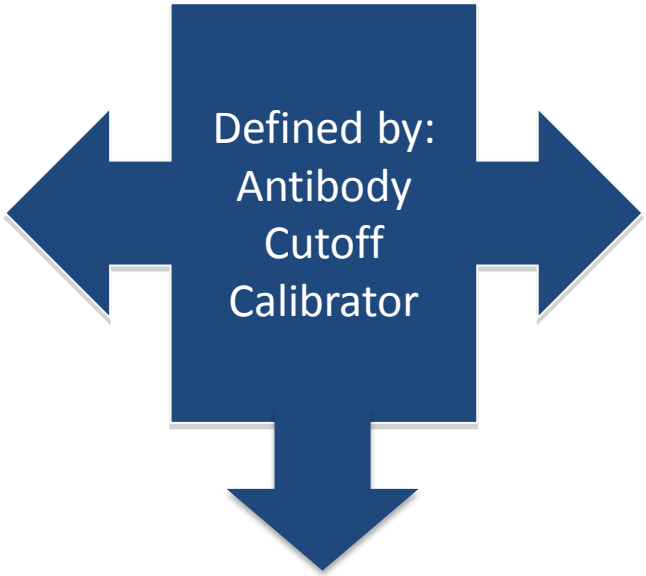
Lab definitions (cont.)

- Specificity: accuracy. Ability of a test to detect and distinguish between individual drugs/compounds. Poor specificity could lead to false positive or false negative results. Consult the cross-reactivity profile (~affinity of the antibody) for immunoassays.

Specificity and immunoassay results

SPECIFICITY

Poor = FALSE negative



Good (but wrong drug) = FALSE positive

TRUE negative/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* 2010;13:E1-22
Tenore *J of Addictive Diseases* 2010; 29:436-48

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* 2011;14:123-43
Tenore *J of Addictive Diseases* 2010; 29:436-48

Most likely approach

- Random urine
- Multi-drug qualitative screen
  - POCT common
    - Rapid turnaround time
    - Ease/convenience of use
    - Some tests have been granted “waived” status under CLIA
    - Detects most drugs of interest for monitoring in pain management settings
  - Discuss results with patient, *real-time*
- Targeted testing for drugs of interest, or when confirmation testing is indicated

When to “confirm” a result

2nd immunoassay

Chromatography

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

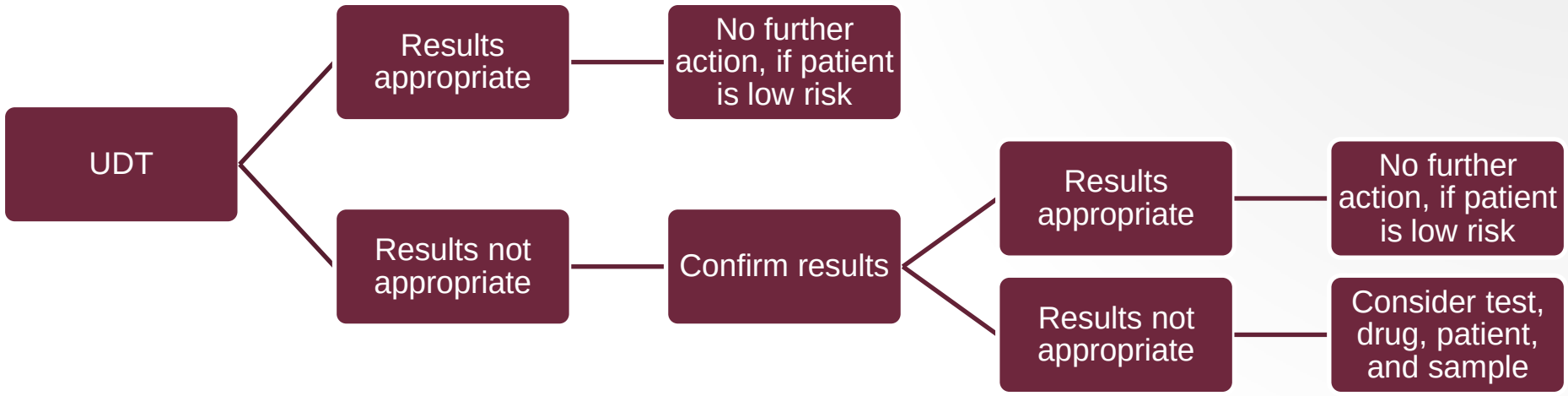
1. Screen does not detect drugs of interest
2. Screen results are inconsistent with clinical expectations
3. Quantitative results are necessary for interpretation

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

Possible UDT algorithm



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

Interpretation consideration:

Unexpected negative results

Reasons for a negative result

Drug was not taken

Drug was taken incorrectly (less than prescribed or less frequently than prescribed)

Drug was not absorbed

Accelerated metabolism/elimination

Drug delivery was variable

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

Reasons for a negative result

Drug was not taken

Drug was taken incorrectly (less than prescribed or less frequently than prescribed)

Drug was not absorbed

Accelerated metabolism/elimination

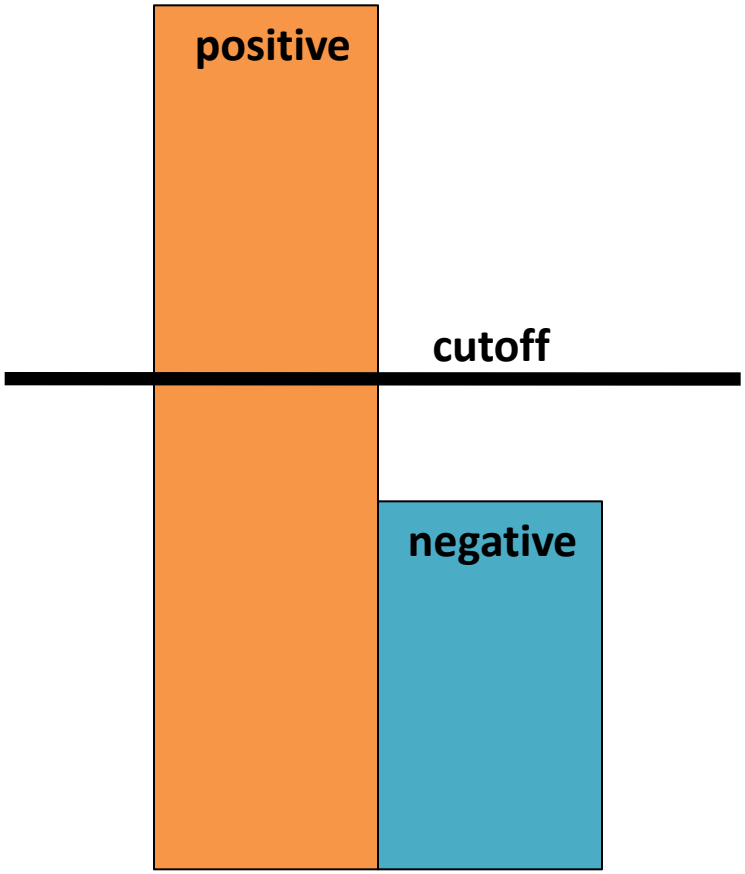
Drug delivery was variable

Specimen was collected too late after use

Specimen was dilute, or adulterated

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

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Drug was not absorbed

Accelerated metabolism/elimination

Drug delivery was variable

Specimen was collected too late after use

Specimen was dilute, or adulterated

Clinic or lab mixup

Test performed is not designed to detect drug

“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

Summary Point 1:

Failure to detect an expected drug should stimulate investigation of the test, the drug, the patient, and the sample

Interpretation consideration:

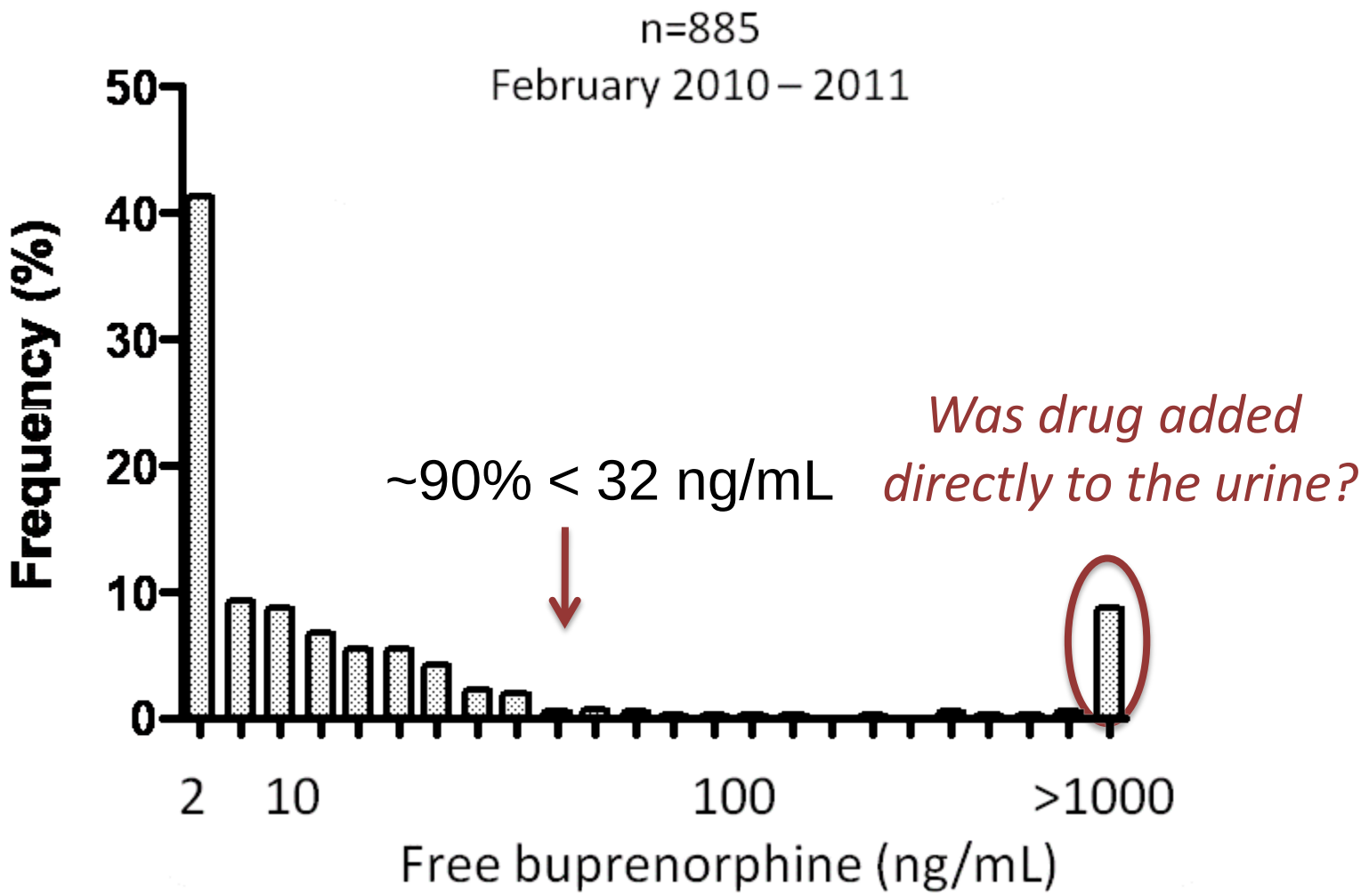
Unexpected positive results

Reasons for a positive result

Appropriate drug was taken

Appropriate drug was added directly to the urine

Distribution of free buprenorphine



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):

$$\frac{500{,}000\ \text{ng}}{100\ \text{mL}} = 5{,}000\ \text{ng/mL naloxone}$$

Patient results suggest adulteration

	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

Reasons for a positive result

Appropriate drug was taken

Appropriate drug was added directly to the urine

Inappropriate use of unprescribed drug

Past prescription and time since drug discontinuation insufficient for elimination

Prescription obtained from another clinic

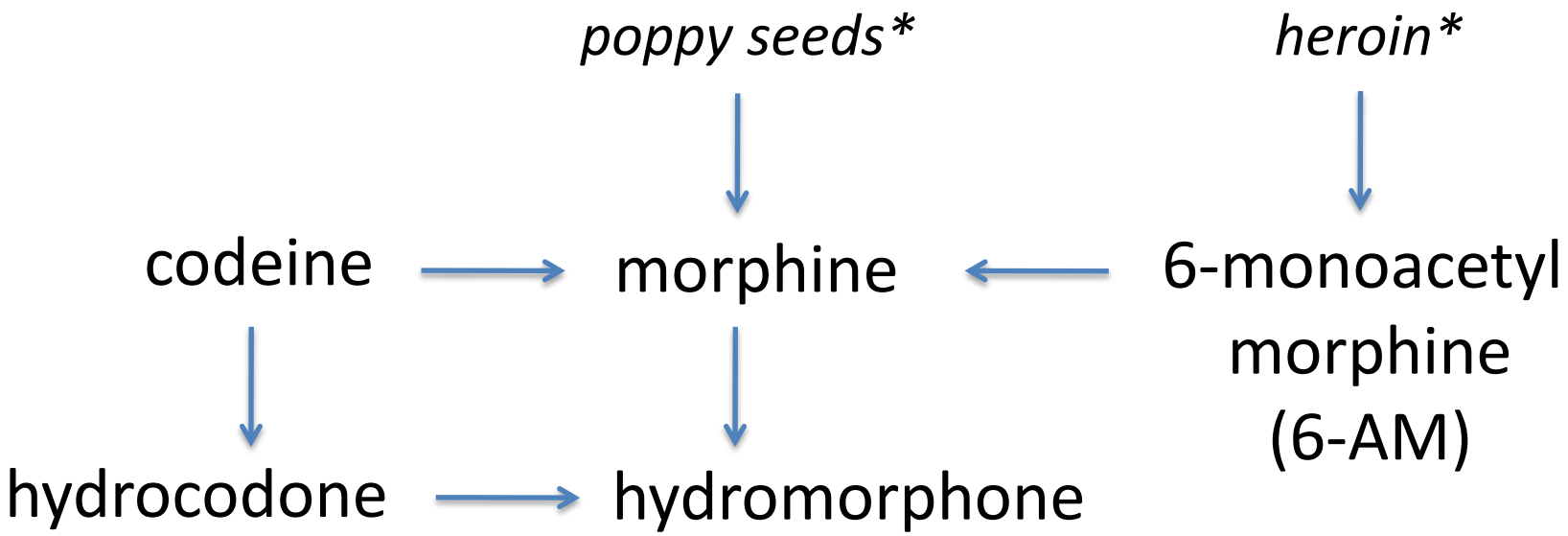
Incorrect prescription was filled

Clinic or lab mixup

Test performed has poor specificity (false positive)

Drug detected is a metabolite of prescribed drug

Simplified opioid metabolism



** Not specifically detected by most assays*

Interpreting concentrations

Patient results

2033 ng/mL Morphine

15 ng/mL Hydromorphone

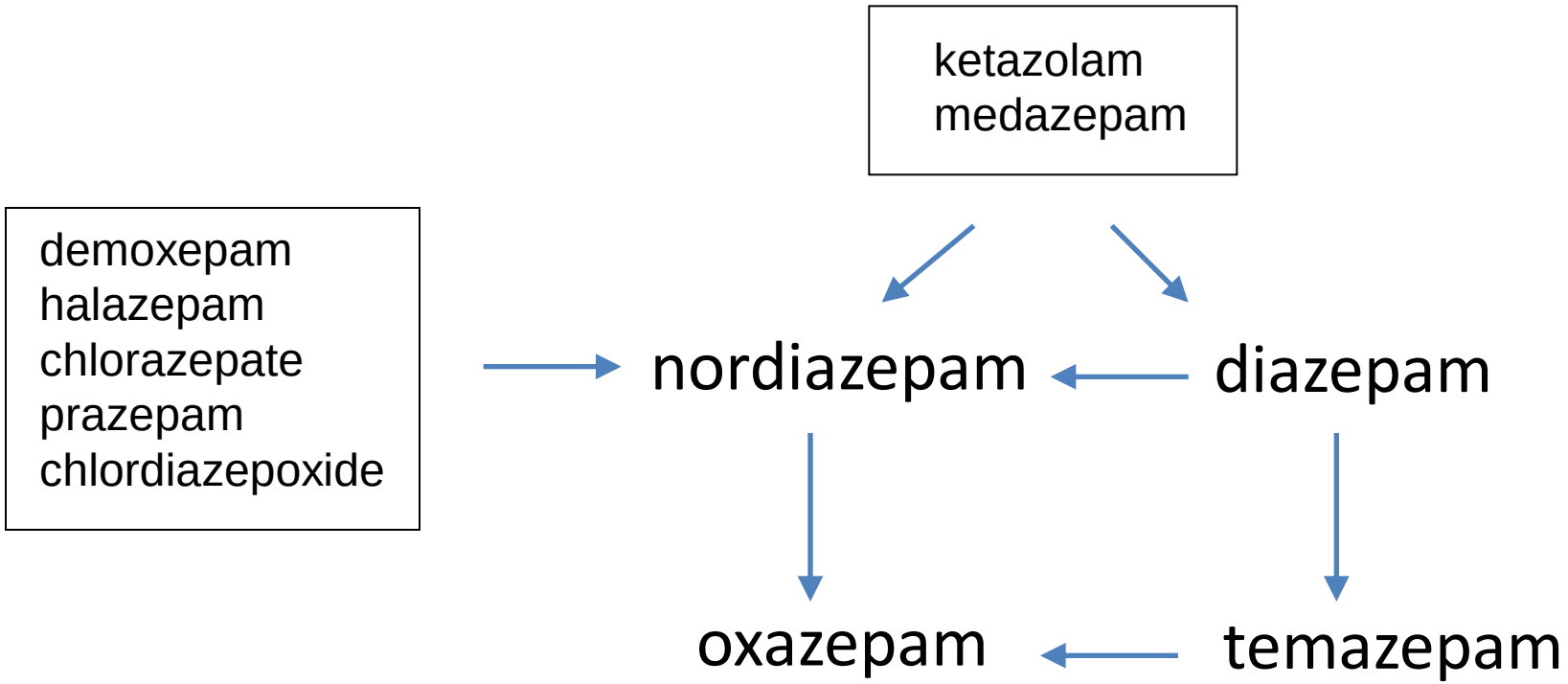
Metabolic ratios

Hydromorphone:Morphine

- Morphine is metabolized to hydromorphone (minor pathway); usually <3%
- Thresholds for independent use of hydromorphone are not well established, but >1:1 is very suggestive

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

Simplified benzodiazepine metabolism



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Past prescription and time since drug discontinuation insufficient for elimination

Prescription obtained from another clinic

Incorrect prescription was filled

Clinic or lab mixup

Test performed has poor specificity (false positive)

Drug detected is a metabolite of prescribed drug

Drug detected represents a process impurity

Interpreting concentrations (cont.)

Patient results

2033 ng/mL Morphine

15 ng/mL Hydromorphone

5 ng/mL Codeine

Process Impurity?

- 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

Summary Point 2:

Detection of an unexpected drug should stimulate investigation of the test, the drug, the patient, and the sample

Interpretation consideration:

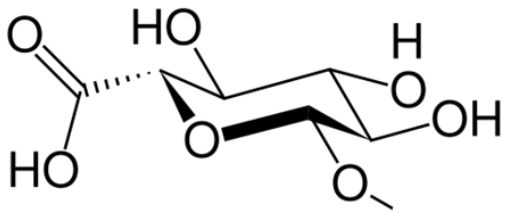
Drug adherence versus dose and dosing adherence

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

Free vs Total: laboratory tests differ

- Free drug concentrations reflect the concentrations observed of non-glucuronidated compound
- Total drug concentrations in urine reflect the concentrations observed after cleaving glucuronide conjugates through hydrolysis
  - Enzymatic
  - Chemical



- Patient variation in proportion of metabolites is known
- Changes in proportion of metabolites occurs over time
- Glucuronide metabolites may not be stable *in vitro*
- Efficiency of hydrolysis reactions varies

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

Timed blood testing may help

- Fentanyl pharmacokinetic highlights
  - Absorption varies with application site, body temperature, etc
  - Drug delivery rate varies with product
  - Time to peak (Cmax), 24-72 hrs after administration
  - Half-life, 13-22 hrs
  - CYP3A4 substrate

	Expected Cmax (ng/mL)	SD (%)
25 μg/h	0.85	0.26 (30)
50 μg/h	1.72	0.53 (31)
75 μg/h	2.32	0.86 (37)
100 μg/h	3.36	1.28 (38)

- Blood is the preferred specimen for dose assessments and pharmacokinetic studies

http://www.rxlist.com/duragesic-drug.htm

Summary Point 3:

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

Conclusions

- UDT offers many useful opportunities to identify and evaluate patient 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
- Testing alternative specimens may be appropriate

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