Urine Testing for Opioids

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The Role of Urine Drug Monitoring and Other Biofluid Assays in Pain Management

26 June 2008

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WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 60 mg, 80 mg and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or a total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Acknowledgements

Edward J. Cone, PhD

Theodore F. Shults, MS, JD

Parts of this presentation are based, in part, on a CME monograph authored by:

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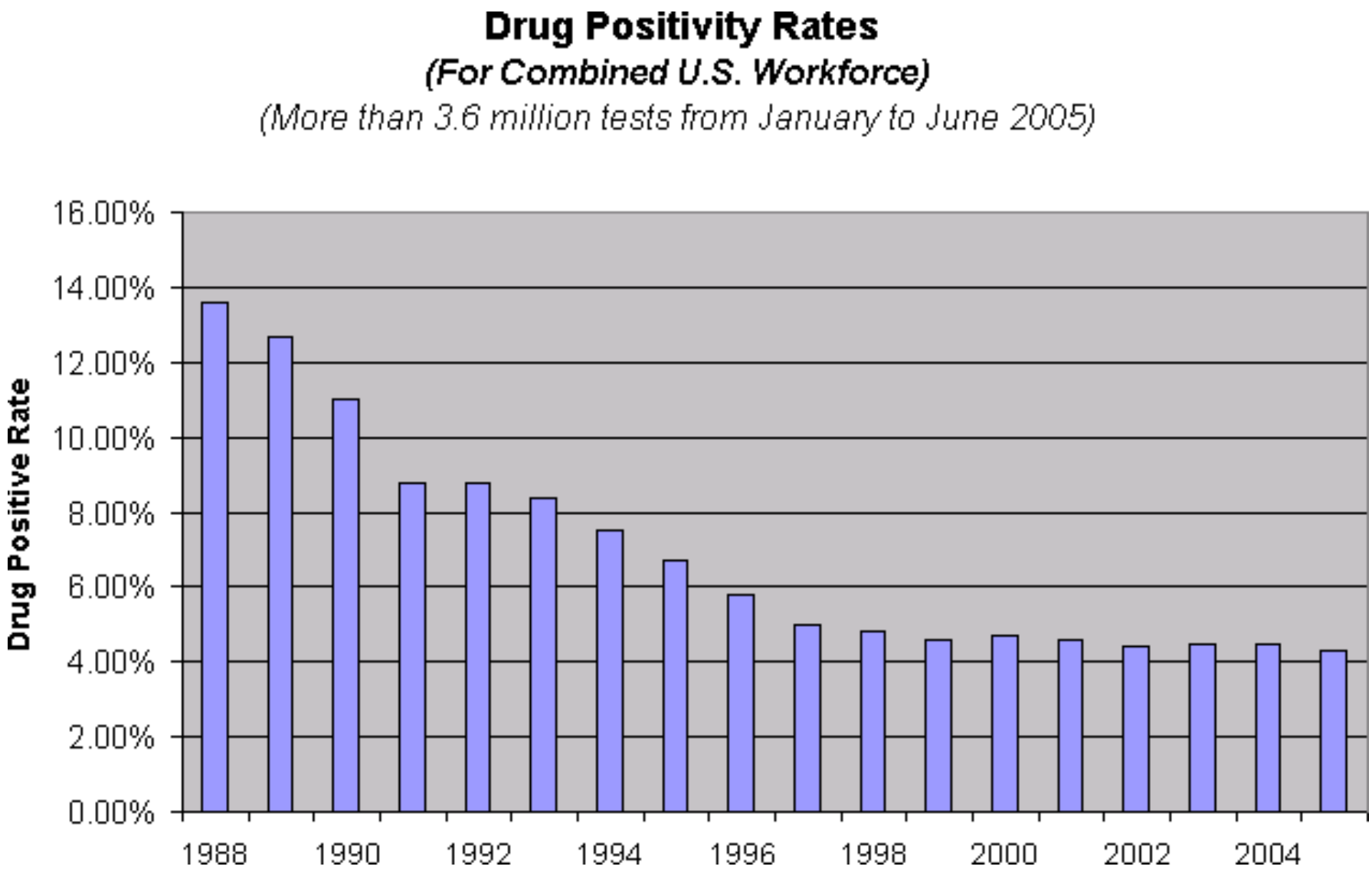
Monograph available at:
http://www.familydocs.org/assets/Professional_Development/CME/UDT.pdf



http://www.questdiagnostics.com/employersolutions/DTI_11_2005/dti_2.html

Background

- Using the term urine drug “screening” to apply to all urine drug testing is a misnomer.
- All Urine Drug Tests (UDT) are not equal.
  - No “standard” UDT is suitable for all purposes & settings.
  - To optimize clinical utility, clinicians should:
    - Indicate any substance(s) suspected or expected,
    - Communicate with testing laboratory,
    - Understand what they are ordering, and
    - Use accepted specimen collection & handling procedures.

Hammett-Stabler C, et al. *Clinica Chimica Acta*. 2002;315:125-35.
Galloway JH, et al. *J Clin Pathol*. 1999;52:713-8.

Background

- Controversies exist regarding clinical value of typical UDT devices/methods.
  - Most were designed for deterrent-based testing to discourage the use of illicit substances.
- When used with appropriate understanding, UDTs can, however, improve ability to
  - Manage controlled-substance therapy,
  - Diagnose substance use disorders (SUDs),
  - Monitor substance use disorder therapy, and
  - Advocate for patients with pain or SUDs.

Hammett-Stabler C, et al. *Clinica Chimica Acta*. 2002;315:125-35.

Federally Regulated Urine Drug Testing

- Most established use of UDTs
- "Federal Five"
  - marijuana metabolite (Δ-9-carboxy-THC)
  - cocaine (benzoylecgonine)
  - opiates (morphine, codeine, 6-AM)
  - phencyclidine (PCP)
  - amphetamine/methamphetamine
- Mandated cutoff concentrations set for deterrence, not for adherence monitoring
- Requirements of federally-regulated testing not always applicable to clinical practice

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002. Gourlay DL, et al. *Urine Drug Testing in Clinical Practice: Dispelling the Myths & Designing Strategies* [monograph]. 2004.

Nonregulated Urine Drug Testing

- Inform laboratory of purpose of test
  - Forensic
    - Pre-employment
    - Child custody
    - Driver's license renewal
    - Criminal justice system
    - Insurance / Workers' Compensation
  - Clinical
    - Monitoring adherence
    - Abuse of illicit substances
    - Diversion

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002. Simpson D, et al. *Ann Clin Biochem*. 1997;34:460-510. Wolff K, et al. *Addiction*. 1999;94:1279-98.

Urine Drug Testing in Clinical Practice

- Why to test
  - Evaluate patients
  - Support assessment & diagnosis
  - Monitor adherence
  - Identify use of undisclosed substances
  - Patient advocacy
  - Uncover diversion

Gourlay DL, et al. *Urine Drug Testing in Clinical Practice: Dispelling the Myths & Designing Strategies* [monograph]. 2004.

Urine Drug Testing in Clinical Practice

- *Consideration* of whom to test
  - People presenting for evaluation and treatment
  - Any person for whom you are considering prescribing controlled substances
  - Any person for whom you are prescribing controlled substances

Gourlay DL, et al. *Urine Drug Testing in Clinical Practice: Dispelling the Myths & Designing Strategies* [monograph]. 2004.

Urine Drug Testing in Clinical Practice

- *Consideration* of whom to test
  - Persons who are resistant to full evaluation
  - Persons for whom prior records have not be obtained
  - Persons who request a specific drug
  - Persons who display aberrant behavior
  - Persons in recovery

Gourlay DL, et al. *Urine Drug Testing in Clinical Practice: Dispelling the Myths & Designing Strategies* [monograph]. 2004.

Urine Drug Testing in Clinical Practice

- When to test
  - Considering controlled substances treatment
  - Making major treatment changes
  - Support decision to refer
  - As a component of treatment agreements
  - Any aberrant drug-related behavior observed
  - Third-party reports about aberrant drug-related behaviors (family, friends, insurers, law enforcement, etc)

Gourlay DL, et al. *Urine Drug Testing in Clinical Practice: Dispelling the Myths & Designing Strategies* [monograph]. 2004.

Specimen Collection in Clinical Practice

- Random collection preferred
  - Adulterants, substituted specimens
- Chain-of-custody forms
- Unobserved donation is usually acceptable
- Collection facility
  - No basin – wash hands after delivering specimen
  - Pigmented toilet water
- Routinely check
  - Temperature = 90°F-100°F
  - Creatinine >20 mg/dL
  - pH 4.5-8.0
  - Color

Cook JD, et al. *J Anal Toxicol*. 2000;24:579-88. Galloway JH, et al. *J Clin Pathol*. 1999;52:713-8. Gourlay DL, et al. *Urine Drug Testing in Clinical Practice: Dispelling the Myths & Designing Strategies* [monograph]. 2004.

Urine Drug Testing Process

- **Immunoassay** screening
  - Laboratory-based or point-of-care (POC)
  - Classify substances or class as present or absent
  - Presumptive positives

- **Confirmatory** & quantitative
  - Laboratory-based, specific drug identification
  - Gas Chromatography/Mass Spectroscopy (GC/MS) is the standard

- Use a reputable laboratory
  - DHHS or CAP certified

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002.
Braithwaite RA, et *Ann Clin Biochem*. 1995;32:123-53. al.

DHHS=Department of Health & Human Services
CAP=College of American Pathologists

Urine Drug Testing Process: Immunoassays

- Proprietary antibody screens
  - Examples: EMIT® II, KIMS®, CEDIA®, DRI®, AxSYM®
- Know which screen is being used
  - Sensitivity & specificity vary
  - Read the package insert for the test
- Information is continually updated by
  - Manufacturer
  - Laboratory

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002.

“Opiate” Screens

Most semisynthetic & synthetic opioids not reliably detected by commonly used screens

Natural (from opium)	Semisynthetic (opium-derived)	Synthetic (man-made)
▪ codeine	▪ hydrocodone	▪ meperidine
▪ morphine	▪ oxycodone	▪ fentanyl
▪ thebaine	▪ hydromorphone	▪ sufentanil
	▪ oxymorphone	▪ propoxyphene
	▪ buprenorphine	▪ methadone

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002.

“Opiate” Immunoassay Screens

- Originally designed to detect heroin use, not adherence to therapeutic opioid regimen
- Heroin metabolized → 6-AM (6-MAM) → morphine
  - Morphine in urine is not proof of heroin use
    - Codeine metabolized → morphine
    - Morphine use or misuse
    - Morphine from poppy seeds addressed by cutoff change from 300 to 2000 ng/mL
  - 6-AM by GC/MS is *absolute proof* of heroin use
- Street heroin often contaminated with codeine, as codeine is a naturally-occurring opioid alkaloid

6-AM = 6-acetylmorphine 6-MAM = 6-monoacetylmorphine

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002.
Vandevenne M, et al. *Acta Clinica Belgica*. 2000;55:323-33.

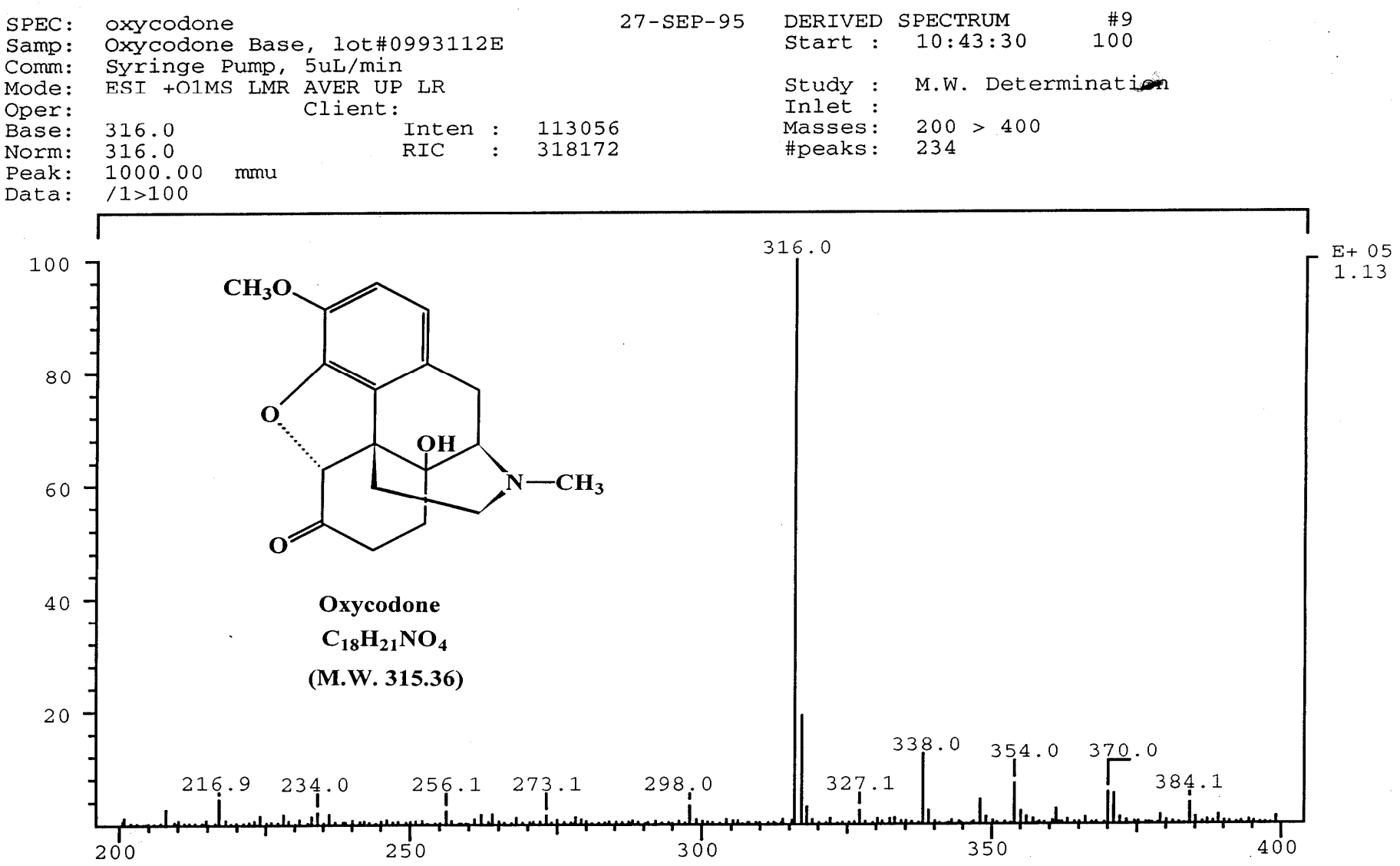
Urine Drug Testing Process: Confirmatory

- Identifies specific drug &/or metabolite(s)
  - GC/MS is standard
  - Variation still exists
    - Different methods for performing assays
    - Variation in factors affecting assays
    - Potential for carryover from another specimen
    - Cutoff levels
- Clinically used to
  - Confirm presence of given drug &/or metabolite(s)
  - Identify drugs not included in immunoassay (oxycodone, hydromorphone hydrocodone, fentanyl, etc)

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002.

Finnigan MAT LCQ MS

GC/MS of Oxycodone



Drug-Class-Specific Windows of Detection in Urine

Drug	Days	**Federal immunoassay cutoff** (ng/mL)
▪ Amphetamine (misuse)	≤5	1000
▪ Cannabinoids, 1 cigarette – Chronic smoker	2-4 ≤30	50
▪ Benzoylecgonine after street doses of cocaine	≤7	300
▪ Opiates (morphine, codeine)	1-2	2000
▪ Phencyclidine – Chronic user	8 ≤30	25

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002. Vandevenne M, et al. *Acta Clinica Belgica*. 2000;55:323-33. Wolff K, et al. *Addiction*. 1999;94:1279-98.

Interpretation of UDT Results

- Immunoassays report each sample as positive or negative for particular drug/class
  - Based on predetermined cutoffs
- Confirmed positives cannot be used to determine:
  - exactly when exposure occurred,
  - route(s) of administration,
  - frequency of use,
  - dose(s), because:
    - No reliable correlation between urine drug concentration & dose,
    - Many factors affect the excretion of drugs & metabolites,
    - Detection windows can vary among substances, persons, & methods.

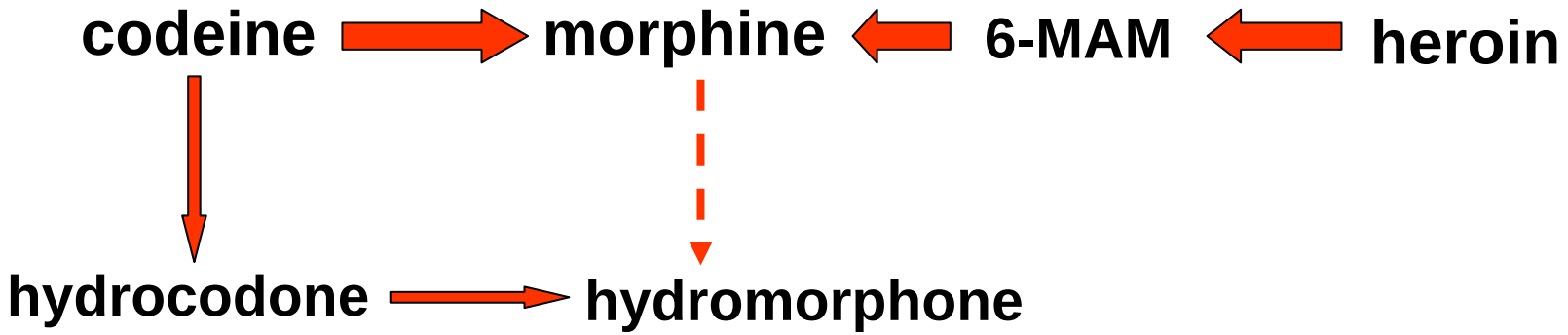
Wolff K, et al. *Addiction*. 1999;94:1279-98. Casavant MJ. *Pediatr Clin N Am.* 2002;49:317-27. Vandevenne M, et al. *Acta Clinica Belgica*. 2000;55:323-33.

Interpretation of UDT Results

Behavior / Test Result	**Took drug**	**Did not take drug**
Positive	True positive	False positive
Negative	False negative	True negative

Wolff K, et al. *Addiction*. 1999;94:1279-1298.

Metabolism* of Opioids



oxycodone → **oxymorphone**

*Pathways illustrated are not comprehensive or necessarily the dominant pathways in all patients, but may help to explain the presence of apparently unprescribed drugs

Gourlay DL, et al. *Urine Drug Testing in Clinical Practice: Dispelling the Myths & Designing Strategies* [monograph]. 2004.

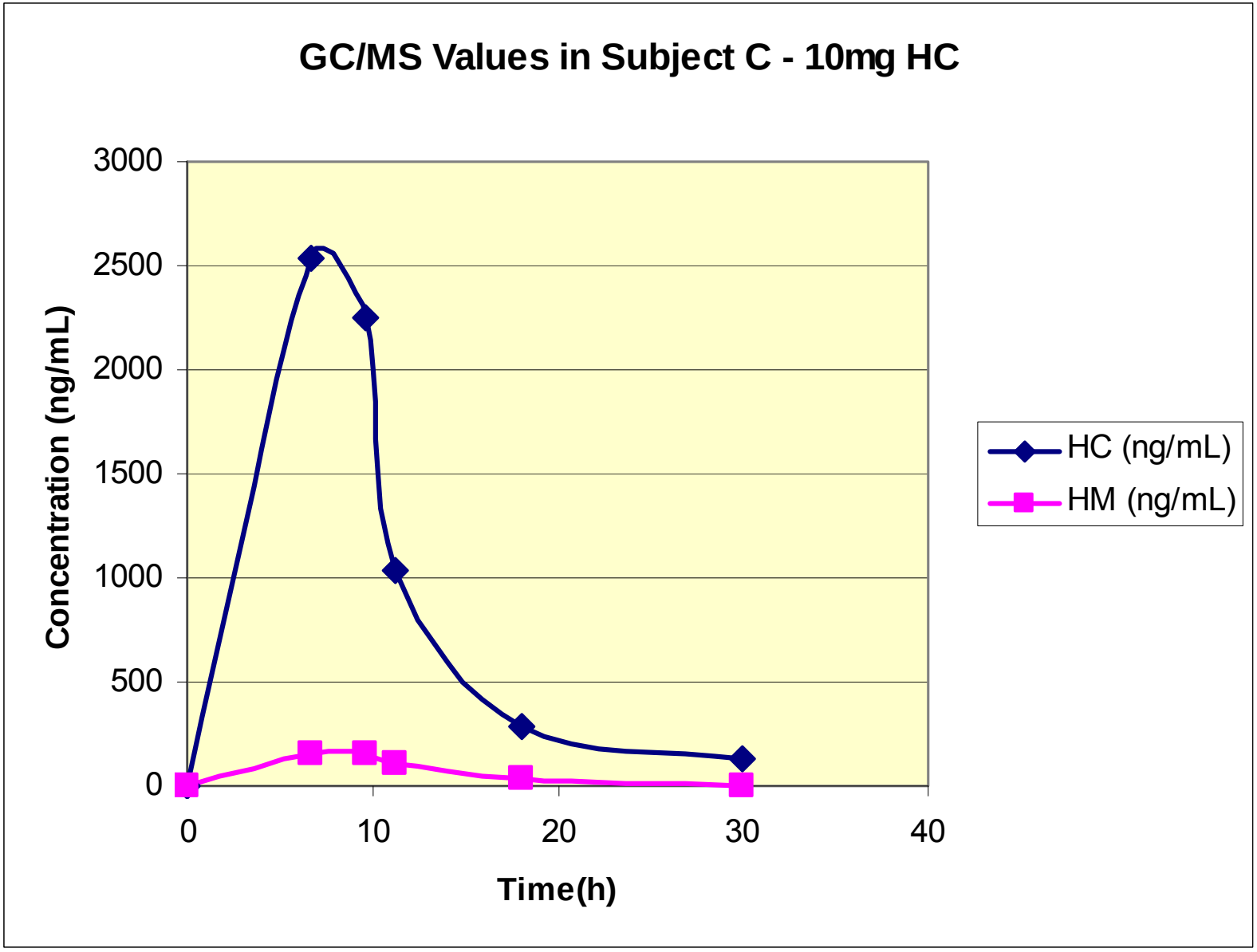
Common Error of Interpretation
One Type of False Negative

- Patient taking one of the following per prescription:
  - fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, tramadol
- Urine screen calibrated to federal testing standards reports “opiates” as “**none detected**”
- Therefore, lab does not perform GC/MS
- Patient accused of non-adherence and discharged from practice
- Solution
  - Understand limitations of screening method
  - Order GC/MS

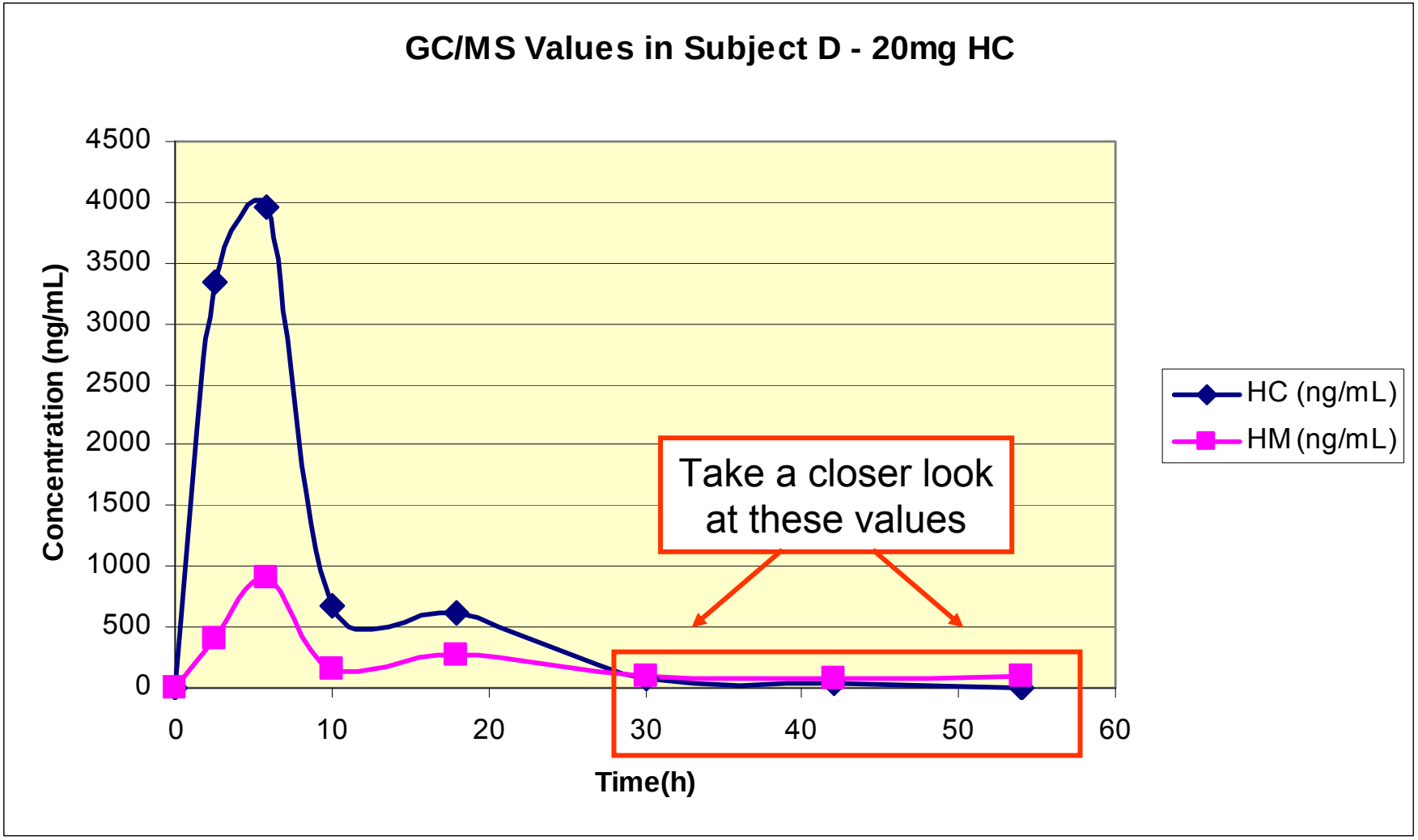
Von Seggern RL, et al. *Headache.* 2004;44:44-7.

Common Error of Interpretation
One Type of False Positive

- Patient taking hydrocodone per prescription
- Urine screen calibrated to detect various opioids reported as "**positive**"
- Confirmatory GC/MS reveals:
  - hydrocodone
  - hydromorphone
- Patient accused of not adhering to treatment plan & discharged
- Solution: understand metabolism



Smith ML, Hughes RO, Levine B, Dickerson S, Darwin WD, Cone EJ.Forensic Drug Testing for Opiates. VI. Urine Testing for Hydromorphone, Hydrocodone, Oxymorphone, and Oxycodone with Commercial Opiate Immunoassays and Gas Chromatography-Mass Spectroscopy. J Analytical Tox 19:18-26, 1995.



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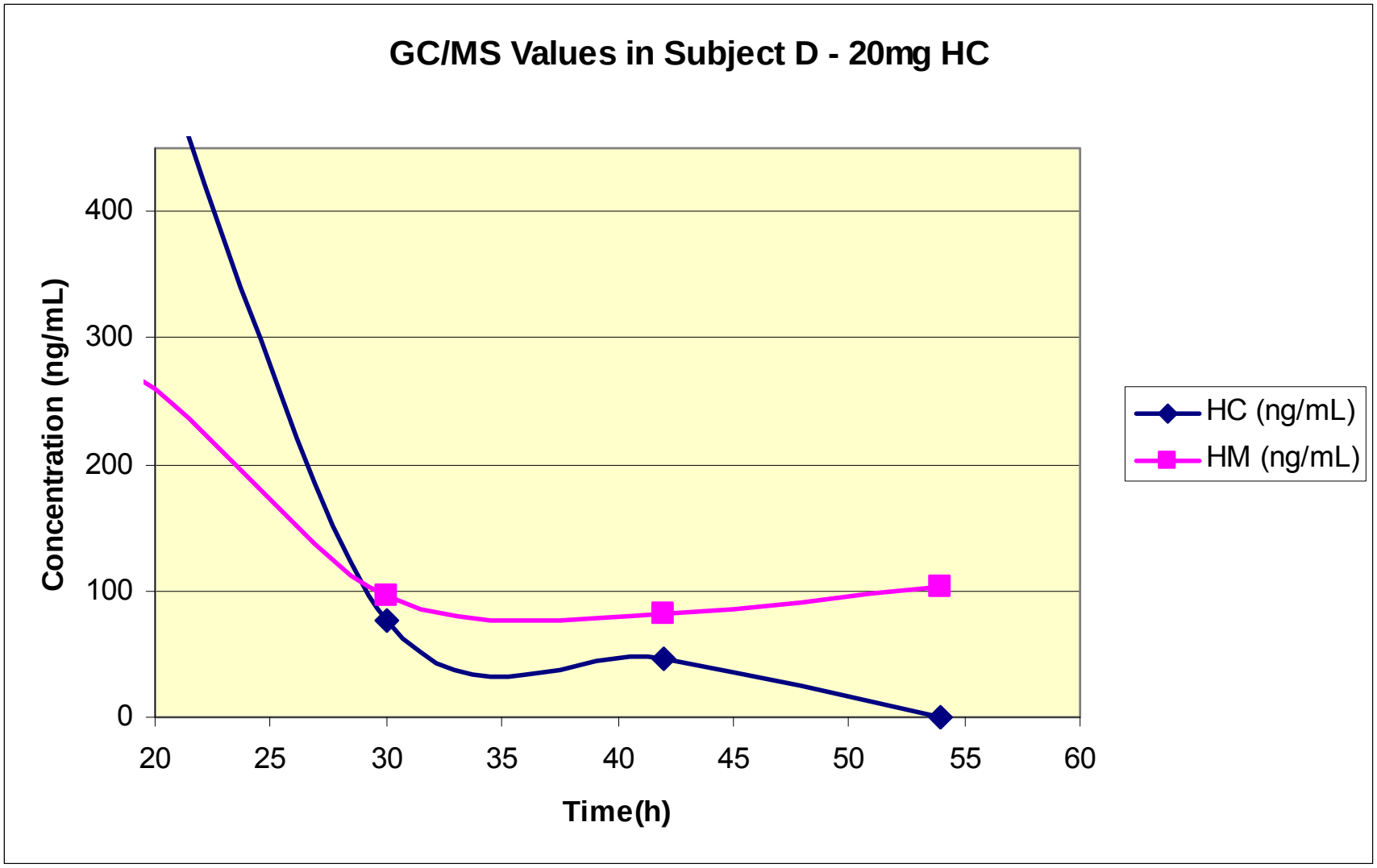

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Explanations for Positive Opioid Results

- Codeine metabolized to morphine
  - Prescribed codeine may explain both drugs in urine
  - Prescribed codeine does not usually explain morphine only
    - Codeine alone possible in patients who lack CYP2D6 activity
  - Prescribed morphine does **not** account for codeine
  - Prescribed codeine may explain codeine with trace of hydrocodone

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002. Braithwaite RA, et al. *Ann Clin Biochem*. 1995;32:123-53. Wolff K, et al. *Addiction*. 1999;94:1279-98. Oyler JM, et al. *J Anal Toxicol.* 2000;24:530-5.

Other False Positive Results

- Technician or clerical error
  - Chain-of-custody breach
  - Recording error in lab
- Cross-reaction with other compounds in urine
  - May be structurally unrelated; e.g., quinolone antibiotics can cause positive opiate screen results
  - GC/MS not influenced by cross-reacting compounds

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002. Baden LR, et al. *JAMA*. 2001;286:3115-9. Zacher JL, et al. *Ann Pharmacother*. 2004;38:1525-8.

Explanations for "None Detected"

- May mean any of following:
  - Person
    - Does not take the drug
    - Has not recently taken drug
    - Excretes drug/metabolite faster than normal
  - UDT used not sufficiently sensitive to detect drug at concentration present
    - Ask for "no threshold" testing by lab
  - Clerical error

- In adherence testing, may raise concerns about misuse/diversion

Wolff K, et al. *Addiction.* 1999;94:1279-98. Gourlay DL, et al. *Urine Drug Testing in Clinical Practice: Dispelling the Myths & Designing Strategies* [monograph]. 2004.

Other False Negative Results

- Technical or clerical error
  - Chain-of-custody breach
  - Recording error in lab
- Tampering with urine sample
  - Adulteration
  - Substitution
    - Suspect if sample characteristics are inconsistent with normal human urine

Shults TF. *Medical Review Officer Handbook*. 8th ed. 2002.
Wolff K, et al. *Addiction.* 1999;94:1279-98.

Summary: Interpretation of UDT Results

Requires that you know

- Who donated specimen
- How specimen is collected / handled
- What was prescribed
- Detection windows
- Alternative medical explanations
- Metabolism of drugs
- Scams
- Laws, regulations, & guidelines

Conclusion

- UDT can be valuable tool in clinical practice
- Interpretation requires information and care
  - Your laboratory director or certifying scientist can be very helpful
  - Consider medical review officer consult