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Urine Drug Testing for Chronic Pain Therapy:

How to Interpret the Results

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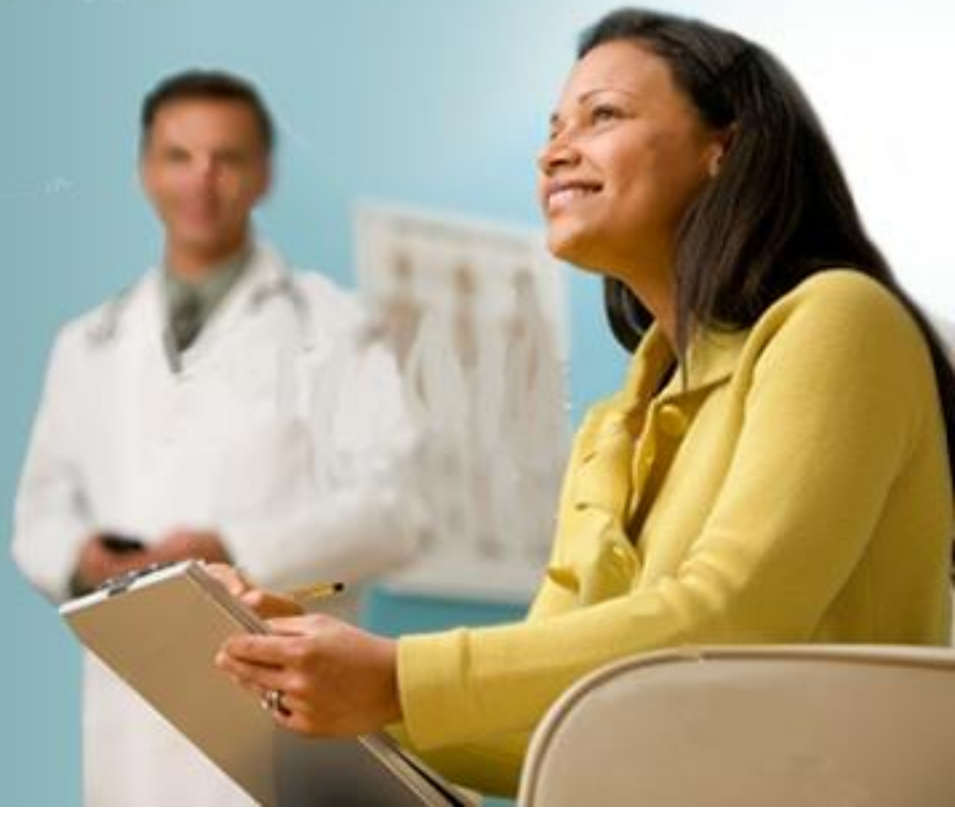
New Mexico Health Resources
Annual Health Provider Retreat



Objectives

- Identify the clinical issues related to opioid prescribing for chronic pain indications
- Define the clinical needs and expectations of urine drug testing in pain management
- Address preanalytical and analytical issues of drug testing for pain management
- Interpret drug testing results
- Provide effective clinical consultation on drug test results

Drug Utilization Is On The Rise

- 2009: approximately 4.5 million drug related visits to the ED
  - Increase of 80% from 2004
  - Non-medical use of pharmaceuticals second only to marijuana in drug abuse
- Opioid analgesics were involved in more than 40% of drug poisoning deaths in 2008.*

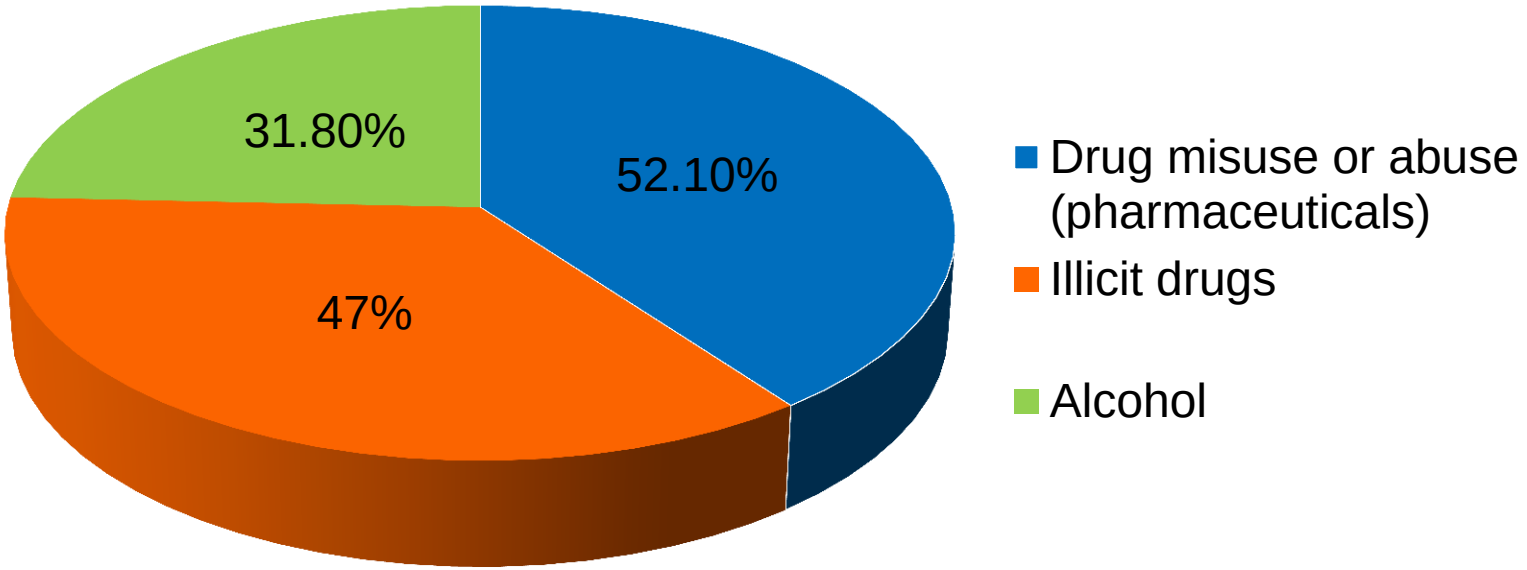
http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/PDF/DAWN2k9ED.pdf

*Drug Poisoning Deaths in the United States, 1980-2008, NCHS Data Brief Number 81, December 2011

"Drug Abuse Warning Network" DAWN nonmedical use of pharmaceuticals:

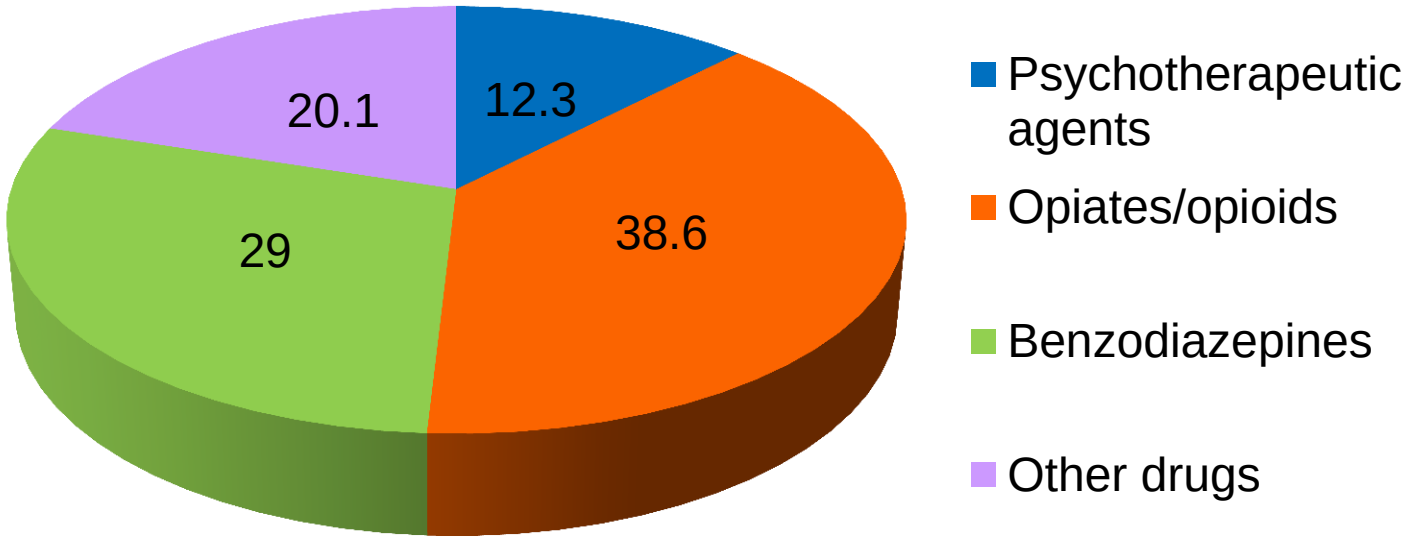
- Taking more than the prescribed dose of a prescription pharmaceutical
- Or more than the recommended dose of an over-the-counter pharmaceutical or supplement
- Taking a pharmaceutical prescribed for another individual
- Deliberate poisoning with a pharmaceutical by another person
- Documented misuse or abuse of a prescription drug, an over-the-counter pharmaceutical, or a dietary supplement

DAWN (2009)
DRUG RELATED ED VISITS



NONMEDICAL USE OF PHARMACEUTICALS DAWN 2009

% of ED visits involving non-medical use of pharmaceuticals



URINE DRUG TESTING AND NONCOMPLIANCE

- Retrospective study 470 pain clinic patients
- Urine drug testing (UDT) by GC-MS
- All UDT results were reviewed/verified vs. patient charts for appropriateness of test results
  - Appropriate opioid 55%
  - Missing opioid 10.2%
  - Additional opioid 14.5%
  - Illicit substance 20.2%

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

PAIN CLINIC URINE DRUG TEST DATA

- >900,000 urines from chronic opioid patients
- Screened by immunoassays; if positive, confirmed by LC-MS/MS
- 11% had illicit drugs
- 29% had non-prescribed drug(s)
- 38% had no prescribed drug

Couto et al. (Population Health Management 2009;12:185-190)

CLINICAL GUIDELINES

Responsible Opioid Prescribing, Federal State Medical Boards

Monitoring of therapy

- Assess patient periodically, or with changing circumstances:
  - Progress to therapeutic goal
  - Adherence to prescribed therapies
  - Presence of adverse events: substance abuse, psychological issues
- Tools include:
  - Pill counts
  - Urine drug tests
  - Family or caretaker interview
  - Prescription monitoring program data

ROLE OF THE URINE DRUG TEST IN CHRONIC OPIOID THERAPY

- Supplements self-reporting and behavioral monitoring
- Identifies problems otherwise undetected:
  - Use of undisclosed medications
  - Non-use of prescribed medications
  - Undisclosed use of alcohol and illicit drugs

Objective means to document aberrant drug behavior

- Checks for “Compliance” to prescribed medication

JOURNAL OF OPIOID MANAGEMENT 3:6 NOV/DEC 2007
REISFILED, WEBB, BERTHOLF AND WILSON

#1) In a patient prescribed Tylenol #3 (codeine and acetaminophen), one would reasonably expect the following to be detected in the urine:

A. Codeine
B. Oxycodone
C. Morphine
D. All of the above

REISFIELD, ET AL

#2) In a patient prescribed MS Contin (morphine), one would reasonably expect the following to be detected in the urine:

A. Morphine
B. Oxycodone
C. Hydromorphone

REISFIELD, ET AL

#3) A patient on OxyContin (oxycodone) is administered a urine drug test. He stated that he ate a poppy seed Danish for breakfast. What substance might reasonably be detected in the urine?

A. Oxycodone
B. Codeine
C. Morphine
D. All of the above

REISFIELD, ET AL

#4) A patient on chronic Dilaudid (hydromorphone) therapy tests negative for opioids on a urine drug screen. He claims to be using the medication as prescribed. The most appropriate next step would be:

A. Subject this urine to a different kind of test
B. Re-administer a urine drug screen at the next visit
C. Taper and discontinue opioid therapy
D. Refer the patient to a detoxification/rehabilitation center
E. Notify law enforcement

#5) In a patient using heroin, one would be likely to detect which of the following in the urine:

A. Heroin
B. Hydromorphone
C. Morphine
D. All of the above

URINE DRUG TEST: PHYSICIANS' INTERPRETIVE SKILL

Reisfield, J Opioid Management 2007

- 5 question multiple-choice survey
- 150 physicians at opioid education meeting;

68% used drug tests, 76% prescribed opioids

- 19% Board-certified in pain management
- 6% addiction medicine/psychiatry

- Of those who ordered drug tests, none had 5 correct answers, only 30% scored more than half correctly

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DRUG TESTING AND PAIN MANAGEMENT ANALYTICAL CONSIDERATIONS

Drug Test and Pain Management: Analytical Considerations

- Specimen types
- Test menu/drug list
- Screening/confirmation assays
  - In terms of sensitivity and specificity
  - In affecting test result interpretation
  - In determining the usefulness of the test

Drug Test and Pain Management: Analytical Considerations

- Specimen Types
  - Urine
    - Most frequently used matrix: extensive experience in analysis and interpretation
    - Collection issues
    - Adulteration
  - Oral fluid
    - Gaining in popularity but limited by volume collected

What Medications / Drugs To Test For?

- Typical opiods for non-cancer chronic pain
  - Morphine, oxycodone, hydrocodone, hydromorphone, dihydrocodeine, methadone, fentanyl, buprenorphine, propoxyphene, others
- Typical illicit drugs
  - Amphetamines, benzodiazepines, cannabinoids, cocaine, others

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Screening Challenges / Synthetic Opioids

Buprenorphine
Buprenex
Subutex
Suboxone
Butran

Hydrocodone
Hycodan
Vicodin

Oxymorphone
Opana

Tramadol
Ultram

Tapentadol
Nucynta

Oxycodone
OxyContin
Percodan
Oxceta

Hydromorphone
Dilaudid

Methadone
Dolophine

Fentanyl
Duragesic

Issues With Immunoassay-based Drug Test

1. Most immunoassays are ‘class’ assays: amphetamines, benzodiazepines, opiates. Specific identification of drug not possible

   - The following combinations will give the same positive ‘opiates’ result:

     Morphine
     Morphine + hydrocodone + hydromorphone
     Morphine + hydromorphone

   - Specific identification requires confirmation testing (mass spec)

Issues with Immunoassay-based Drug Test

2. Assay immunospecificity and sensitivity

3. Assay cutoffs for therapeutic vs. toxic concentrations

Opiate Immunoassay

Two Types:

- ‘Standard’ opiate immunoassay
- ‘Specific’ opioid immunoassay

Opiate Immunoassay

‘Standard’ Opiate immunoassays

- Targets morphine. Lesser reactivity with hydromorphone, hydrocodone, dihydrocodeine, oxycodone
  False negative possible after pain control doses

- Low or minimal reactivity with non-opiate opiods: methadone, buprenorphine, fentanyl, tramadol, meperidine (separate assays)

- True positive: poppy seeds (300ng/ml vs 2000 ng/ml)

- False positives: ofloxacin, levofloxacin; rifampin in KIMS

Table 26-2 Cross-reactivity (%) of Several Opiates Immunoassays at 300 ng/ml Cutoff*

Opiate	Abbott Architect	Biosite Triage	Microgenic CEDIA **	Roche Cobas	Siemens EMIT
6-Acetylmorphine	107	75	81	78	69
Codeine	200	100	125	134	88-294
Dihydrocodeine	46	NA	50	59	103
Hydrocodone	46	60	48	28	121
Hydromorphone	21	60	57	21	60
Morphine	100	100	100	100	100
Oxycodone	2.9	1.5	3.1	<0.4	20
Oxymorphone	0.8	0.8	1.9	NA	3.2

Cross (%) reactivities calculated from data in reagent kit package inserts
NA Data Not Available in package insert

Opiate Immunoassay

"Specific" opioid immunoassays

- Oxycodone, methadone, buprenorphine
- Minor non-specificity can still give false positives if no confirmation is done

Assay Cutoffs vs. Positivity Rates

Compound	Cutoffs, ng/ml MS/MS	EIA	MS/MS Pos (%)	EIA Pos (%)	%'Missed Sample'
Cocaine Metab	25	300	297 (4.1)	171 (2.3)	42.4
Hydromorphone	50	(300)*	2709 (33)	831 (10)	69.3
Hydrocodone	50	(300)*	3005 (37)	2304 (28)	23.3
Oxycodone	50	100	2129 (27)	2028 (25)	4.7

•Opiates cutoff of 300 ng/ml

Modified from Mikel et al. Ther Drug Monit 2009;31:746

Interpretation of Drug Test Results

Interpretation of Unexpected Negative Result

- Non-compliance
- Alternative interpretations:
  - Assay does not detect that opioid
  - Adulterated, dilute or substituted urine
  - Genetic polymorphism in opioid metabolism and transport: CYP, UGT, P-glycoprotein
  - Altered pharmacokinetics

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"White Coat Compliance"

Urine Excretion Kinetics of Oxycodone

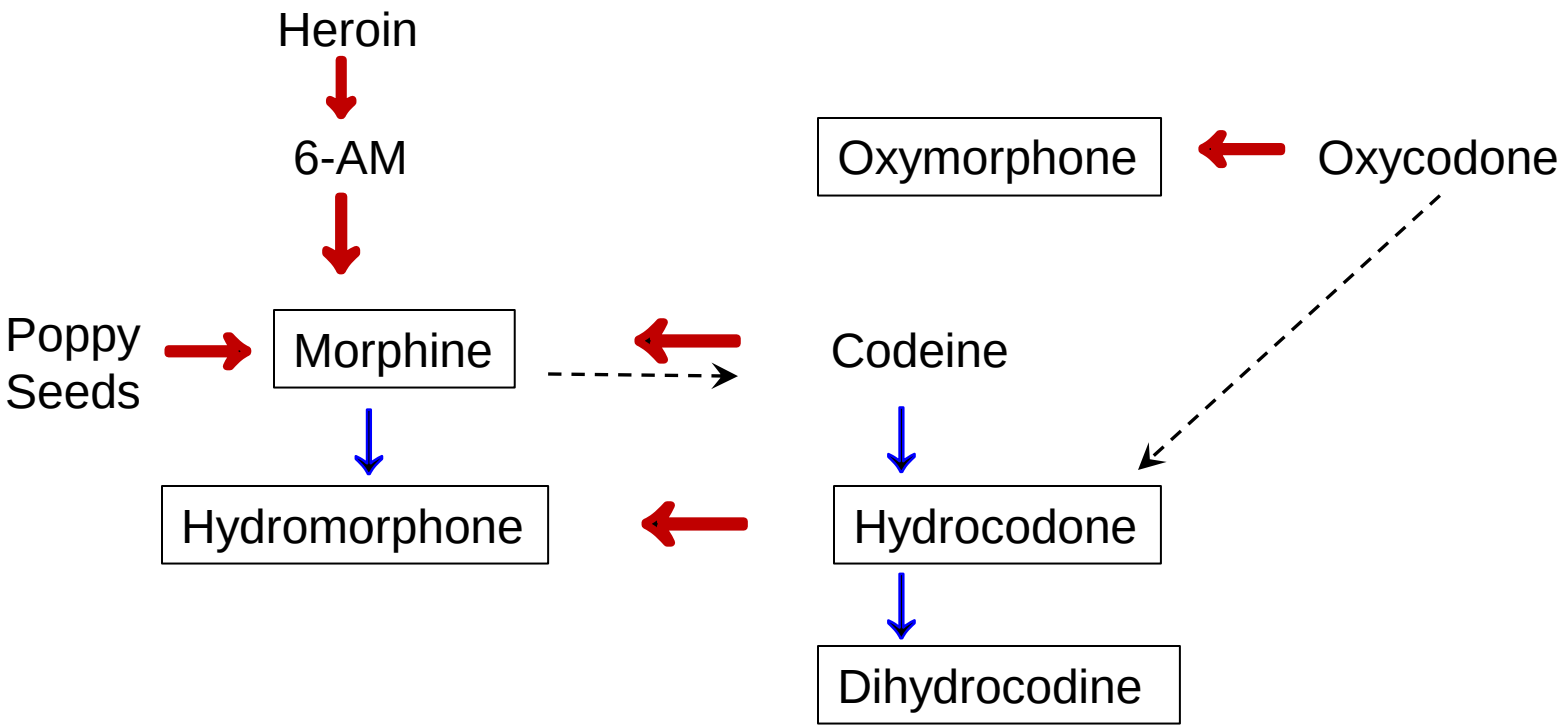
Oxycodone 20mg dose		
Time (h)	Oxymorphone ng/ml	Oxycodone ng/ml
0	0	0
2.8	4714	9958
6.6	4393	5925
8.8	2457	2447
12/24	1006	679
24/36	524	283
36/48	425	21
48/60	132	0
60/72	60	0
72/84	38	0
84/96	34	0
96/108	0	0

Smith JAT 1995;19:18

Interpretation of Unexpected Positive Result

- Use of non-prescribed or illicit drug
- Alternative interpretations:
  - Opioid metabolic pathways
    - Metabolites which are also prescribed medications
    - Late in terminal elimination phase: parent absent, metabolite present (oxymorphone and oxycodone; hydromorphone and hydrocodone)
  - Pharmaceutical impurities

Opiates Metabolic Pathways



Metabolite as well as prescribed medication

Major Pathway **Minor Pathway** **Manufacturing Impurity**

High Sensitivity Mass Spectrometry Assays

Mostly LC-MS/MS

- Advantages
  - Specific identification of parents/metabolites
  - High analytical sensitivity enhances detection of low concentration analytes
- Disadvantage
  - Costly technological challenge
  - Complicates interpretation of positive results

CLINICAL CASES

Case 1

A 42 year old male with chronic low back pain returns to the clinic for a follow-up visit. The patient has a known right L5-S1 disc extrusion osteophyte complex and is being prescribed oxycodone 10 mg twice per day, acetaminophen 500 mg 1-2 tablets daily, nabumetone 750 mg twice per day and diazepam 5 mg twice per day.

The results of the in-house **urine immunoassay drug screen** are as follows:

Opiates	**DETECTED**
Cocaine	**DETECTED**
Amphetamines	NONE DETECTED
Phenothiazine	NONE DETECTED
Benzodiazepines	**DETECTED**
Barbiturates	NONE DETECTED
Methadone	NONE DETECTED
Cannabinoids	NONE DETECTED
Phencyclidine	NONE DETECTED

Case 1-1

The results from the initial immunoassay drug screen:

A. Are consistent with a positive opiate result because the patient is taking oxycodone

B. Demonstrate a false positive cocaine result due to the nabumetone

C. Are consistent with a patient taking diazepam

D. Require no further follow-up testing

Case 1-1

- **C. Is correct. The patient is taking diazepam and that drug cross reacts with the benzodiazepine class assay**
- **A.** Is incorrect. Not all opiates class assays can produce a positive result following pain-control doses of oxycodone. Detection of oxycodone following lower doses of oxycodone is particularly uncertain
- **B.** Is incorrect. The cocaine (metabolite) immunoassay is very robust assay and nabumetone does not cross react to produce a positive result
- **D.** Is incorrect. This patient will need follow-up testing to understand what drug has produced the positive opiates class result.

Case 1

- Confirmatory testing by either GC/MS (cocaine metabolite) or LC/MS/MS (expanded opiates) revealed the following:

Test	Results
Codeine	Negative
Hydrocodone	**3400 ng/ml**
Oxycodone	**560 ng/ml**
Morphine	Negative
Hydromorphone	Negative
Oxymorphone	Negative

- **Cocaine**, Confirmation by GC/MS
- Cocaine metabolite, Benzoylecgonine **52000 ng/ml**

Case 1-2

Interpretation of the results of the drug testing are as follows:

A. The results are consistent with hydrocodone as a primary metabolite of oxycodone

B. Hydrocodone and oxycodone have the same cross-reactivity with the opiates class assay

C. It is highly unusual for only benzoylecgonine and not cocaine to be present in the urine

D. Patient taking oxycodone regularly as prescribed (such as 10-20 mg twice per day) usually have oxymorphone present in their urine.

Case 1-2

- **D. is correct. In patients taking oxycodone regularly (ie, 10-20 mg 2 to 3 times a day, the metabolite oxymorphone should be present in the urine**

- **A.** is incorrect. Oxymorphone is the primary metabolite of oxycodone
- **B.** is in incorrect. Hydrocodone is more likely to cross-react with the opiates class assay compared to oxycodone.
- **C.** Is incorrect. The usual finding in urines of cocaine users is benzolyecgonine only, with little of nondetectable amount of cocaine because cocaine is rapidly hydrolyzed, enzymatically and chemically, to benzoylecgonine. Moreover, all immunoassays used clinically for detection of cocaine use detect benzoylecgonine, not cocaine.

Case 1-3

Based on the results from the confirmation testing:

A. The clinician should consider referring the patient for assessment for an addictive disorder

B. The clinician should continue to provide prescriptions without intervention

C. The clinician should feel confident that the oxycodone is being taking daily at the prescribed amount

D. The pathologist should review the opiate screen for false positive cross-reactivity

Case 1-3

- **A. Is correct. If the patient is taking cocaine, the clinician should be concerned about addictive behaviors**

- **B.** Is incorrect. Illicit drug use is considered a contract breaking event if the clinician is using an “agreement for long-term opioids use”
- **C.** Is incorrect. There is only a small amount of oxycodone present and no oxymorphone present
- **D.** Is incorrect. There are no results in this drug screen which suggest that the opiates screen produced a false positive result

Case 1-4

The opiates class assay:

A. Will detect the synthetic drugs such as fentanyl

B. Will not produce a positive result from someone who has eaten a poppy seed enriched bagel

C. Cannot detect semi-synthetics such as hydrocodone

D. Was designed with morphine as the primary target analyte

Case 1-4

- D. **Is correct. The opiates assay is designed to detect the naturally occurring opiates such as morphine and codeine.**

- A. Is incorrect. Synthetic opioids are not detected by the opiates class assay
- B. Is incorrect. Heavily laden poppy seed bagels may produce a positive result
- C. Is incorrect. Some semi synthetic opioids such as hydrocodone may be detected, but this is assay dependent