Management of Opioids in People Living with Pain:

Do we or don't we use Urine Screening

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Speaker Disclosure

- John Fraser: none
- Peter MacDougall
  - Nova Scotia Prescription Monitoring Program
  - Valeant
  - Pfizer
  - Purdue Canada
  - Eli Lilly Canada
  - Nova Scotia Department of Health

Universal Precautions

- Identify patients at risk
  - careful substance use history (personal and family)
  - screening tools
- Collateral information
  - Prescription Monitoring Program
- Treatment agreement
- Collaboration
  - pharmacist
- Adequate trial of non-opioid therapy before opioids
- Use long acting opioids
- Avoid higher risk opioids in high risk patients
  - oxycodone, hydromorphone
- Appropriate dispensing (daily/weekly if needed)
- Monitor aberrant behaviours
- Urine drug testing
- Pill counts/patch returns

Gourlay et al, 2005, Pain Med; Kahan et al, 2006, Can Fam Physician

Urine Toxicology in CNCP

- 67 studies reviewed, patients on opioid for CNCP
  - Most studies retrospective
- 5 studies, n=15,442, average exposure time 22 months
  - 20.4% no opioid or non-prescribed opioid in urine
- 5 studies, n=1,965, average exposure time 36 months
  - 14.5% illicit drugs in urine

Fishbain et al, 2008, Pain Med

Inappropriate drug use in CNCP

- Retrospective analysis
- CNCP patients prescribed opioids
- All urine test results over 3 year period
- 938,586 samples

Couto et al, 2009, Popul Health Manag

Inappropriate drug use in CNCP

- 75% unlikely taking opioids as prescribed
- 38% no prescribed opioid
- 29% other non-prescribed opioid
- 27% higher opioid level than expected
- 11% illicit drugs

Couto et al, 2009, Popul Health Manag

UDT
frequency of abnormal results

- Retrospective analysis
- Patients receiving opioids for CNCP at pain management program
- n=470
- Random UDT by gas chromatography-mass spectrometry
- Outcomes
  - frequency of expected and unexpected results

Michna et al, 2007, Clin J Pain

UDT
frequency of abnormal results

- 45% UDT had unexpected results
  - 10.2% no prescribed opioid
  - 14.5% non-prescribed opioid
  - 20.2 % illicit substance
- Young age (<45) predictive of unexpected results (p<.001)
- Other variables not predictive of unexpected results
  - sex
  - opioid formulation (SR vs IR)
  - number of opioids prescribed
  - pain site
  - morphine equivalent dose

Michna et al, 2007, Clin J Pain

UDT with Opioid Therapy for CNCP in Primary Care

- Written survey, n=248
  - 70% family physicians
  - 29% internists
- Outcomes
  - Opioids prescribed
  - Pain diagnoses treated
  - Opioid prescribing concerns
  - Treatment of patients with substance abuse history
  - Office-based protocols

Bhamb et al, 2006, Curr Med Res Opin

UDT with Opioid Therapy for CNCP in Primary Care

Approaches to prescribing opioids for CNCP (n=248)

UDT before starting opioids	7%
Random UDT while on opioid therapy	15%
System to track patients on opioid therapy	56%
Agreement among staff about opioid Rx	65%
Policy for after hours opioid replacement	76%

Bhamb et al, 2006, Curr Med Res Opin

UDT interpretation

- Knowledge of UDT interpretation
- Physicians attending “opioid for CNCP” conferences, n=114
- 7 question instrument
  - Six 5-option, single best answer multiple choice questions
  - One yes/no question

Reisfield et al, 2007, J Opioid Manag

UDT interpretation

- 77 (68%) utilized UDT
- None answered all questions correctly
- 30% answered more than half correctly

Reisfield et al, 2007, J Opioid Manag

UDT with Opioid Therapy for CNCP in Primary Care

- Discomfort
  - therapeutic relationship will be compromised
  - patient will feel they are not trusted
- No reason for concern
  - reverse stereotyping
    - 35 year old employed well dressed woman
    - 65 year old familiar stable man
  - no past aberrant behaviours
  - no history of substance misuse

Discomfort

- Patient acceptance is high if UDT is routine part of pain assessment
- Resistance to UDT raises red flag

No reason for concern

- Patients often conceal drug use
- Patient deception is difficult to detect
- Tracking aberrant behaviours is not sufficient to detect opioid misuse

Urine Drug Testing and CNCP

- Self-reports of drug use unreliable in patients receiving opioid Rx for CNCP
- 9% to 44% CNCP patients in treatment conceal substance use

Jage, 2005, Eur J Pain

Detecting Patient Deception

- 6 studies reviewed
- Physicians visited by standardized patients (actors) taught to mimic a patient with a specific illness
  - depression, headache, back pain, osteoarthritis, abdominal pain
- n=790
- Standardized patients identified 10% of the time
- Real patients erroneously identified as standardized patients
- Deception is difficult to detect

Jung et al, 2007, Pain Med

Urine Toxicology and Aberrant Behaviours

- retrospective chart review
- CNCP patients on opioid Rx
- n=122, 3 years
- Urine toxicology results compared with five aberrant behaviours
  - Lost prescriptions
  - Unsanctioned dose increase
  - Visits without appointments
  - Multiple drug intolerance
  - Frequent telephone calls

Katz et al, 2003, Anesth Analg

Urine Toxicology and Aberrant Behaviours

	Aberrant behaviours		
	yes	no	total
+ve urine	10 (8%)	26 (21%)	36 (29%)
-ve urine	17 (14%)	69 (57%)	86 (71%)
total	27 (22%)	95 (78%)	122

Katz et al, 2003, Anesth Analg

Urine Toxicology and Aberrant Behaviours

- 53 (43%) patients identified with problem
  - 70% identified by urine
  - 51% identified by aberrant behaviour
- monitoring aberrant behaviour alone would miss half of problems

Katz et al, 2003, Anesth Analg

Urine Toxicology Monitoring

- Purpose
  - confirm adherence
  - detect non-prescribed and illicit drugs
- Use as routine part of assessment and monitoring
  - initial assessment
  - prior to initiation of opioid
  - randomly when stable
  - change of medication
  - deteriorating function
  - aberrant behaviours

Tenore, 2010, J Addict Dis; Gilbert et al, 2010, Pain Physician

Urine Toxicology Monitoring

- Non-punitive response
  - Presence of non-prescribed opioid or illicit substance may represent concurrent disorder (addiction) which needs treatment
  - Withdrawal of opioid management may result in exacerbation of both pain problem and addiction problem

Katz et al, 2002, Clin J Pain; Heit et al, 2004, J Pain Symptom Manage

Urine Drug Testing - Immunoassay

- Laboratory or point-of-care (dipstick)
- Rapid, practical, inexpensive
- Labeled antigen competes with drug to bind with antibody. The amount of labeled antigen-antibody is inversely proportional to the drug present
  - “no line” is positive
- Detects drug classes
  - opioid test uses anti-morphine antibody
  - benzodiazepine test uses anti-diazepam antibody

Pergolizzi et al, 2010, Pain Practice; Tenore, 2010, J Addict Dis

immunoassay

- Opioids: low sensitivity for semi-synthetic and synthetic
  - Semisynthetic: oxycodone ≤12%
    hydromorphone ≤ 60%
  - Synthetic: fentanyl, methadone, meperidine ≤ 3%
- Amphetamines: cross reactivity common
- Benzodiazepines: low sensitivity to clonazepam
- Cocaine: high specificity
- THC: generally high specificity, some cross reactivity
  - passive exposure will not test +ve

Cone et al, 2009, Postgrad Med; Tenore, 2010, J Addict Dis

Immunoassay Cutoff Values

- Immunoassays are calibrated at established cut-off concentrations
- Cut-off values are not synonymous with assay detection limits
  - Established at higher than the detection limit
  - But low enough to detect drug use within a reasonable time
- Specimens giving responses greater that the cut-off/threshold values are considered positive
  - These values were established to help eliminate false-positive levels *ie.* poppy seeds causing positive opiate levels
- Values below the cut-off are considered negative
  - This can lead to false-negative results
- Established for the workplace only, the role of these cut-offs in substance abuse programs remains controversial because of the potential for negative results

Dr. Nasser – CDHA Labs

Cutoff Values – Nova Scotia

Amphetamine	300-1000 ng/ml
Benzodiazepine	150-300 ng/ml
Opiate	20-2000 ng/ml
THC	50-150 ng/ml
Barbiturates	200-300 ng/ml
TCA	300-1000 ng/ml
PCP	25 ng/ml
Cocaine	150-300 ng/ml
Methamphetamines	300-1000 ng/ml
Oxycodone	100 ng/ml
Methadone	100-300 ng/ml

Urine Drug Testing
Gas Chromatography – Mass Spectrometry

- Specimens separated into component molecules (gas chromatography) and unique structural features identified and measured (mass spectrometry)
- High sensitivity (99%) and specificity (99%)
- Detects specific drugs
- More expensive
- May be used to confirm an unexpected result from immunoassay

Pergolizzi et al, 2010, Pain Practice; Cone et al, 2009, Postgrad Med

Gas Chromatography–Mass Spectroscopy (GC-MS)

- GC-MS is considered the criterion standard for confirmatory testing
- Considered the most accurate, sensitive and reliable method of testing
- Can detect small quantities of a substance and confirm the presence of a specific drug
  - Morphine in an opiate screen
- Disadvantages:
  - Time consuming: can be up to 8 hours
  - Requires high level of expertise to perform
  - Costly
  - Therefore only performed after a positive result is obtained by immunoassay
  - However, can fail to identify a positive specimen:
    - eg hydromorphone or fentanyl if the column is designed to detect only certain substances eg morphine or codeine

Immunoassay vs Chromatography

- Comparison of POC immunoassay UDT (index) to chromatography/mass spectrometry (reference)
- Consecutive patients in pain management program, n=1000
- Index results compared to reference in all cases
- Outcomes
  - sensitivity, specificity, false positive rates, false negative rates, index test efficiency

Manchikanti et al, 2011, Pain Physician

Immunoassay vs Chromatography

	sensitivity	false-ve	specificity	false+ve	efficiency
morphine, codeine, HM	92.2%	7.8%	93.1%	6.9%	92.5%
oxycodone	75.4%	24.6%	92.3%	7.7%	90.0%
methadone	96.1%	3.9%	98.8%	1.2%	98.7%
THC	90.9%	9.1%	98.0%	2.0%	97.8%
cocaine	25.0%	75%	100%	0%	99.4%
methamph	40.0%	60%	98.8%	1.2%	98.5%
amphet	47.0%	53.0%	99.1%	0.9%	98.2%

Manchikanti et al, 2011, Pain Physician

Immunoassay vs Chromatography

- 32.9% immunoassay tests required chromatography confirmation
  - prescribed opioid not present
  - non-prescribed opioid present
  - illicit substance present
- High specificity
- High agreement with chromatography
- Variable sensitivity suggests need for careful interpretation of results
- Office based POC immunoassay UDT appropriate, convenient, and cost-effective

Manchikanti et al, 2011, Pain Physician

Capital Health

- EMIT
  - Enzyme multiplied immunoassay test
- ‘Forensic vs. Clinical’
- Forensic includes community services
  - EMIT and gas chromatography
  - Not available to clinicians

Across the Province

CDHA	EMIT +/- GC/MS
GASHA/CBDHA	Innovacon multi-drug
SSDHA/Colchester	Profile V-Medtox
PCHA/Southwest/Cumberland/AVH	Triage drugs of abuse plus TCA

Before interpreting UDT

- What substances are being measured
- What are the detection times
- What substances cause false +ve results
- What substances cause false –ve results
- How do you know if a urine has been tampered with
- What laboratory errors might result in inaccurate results

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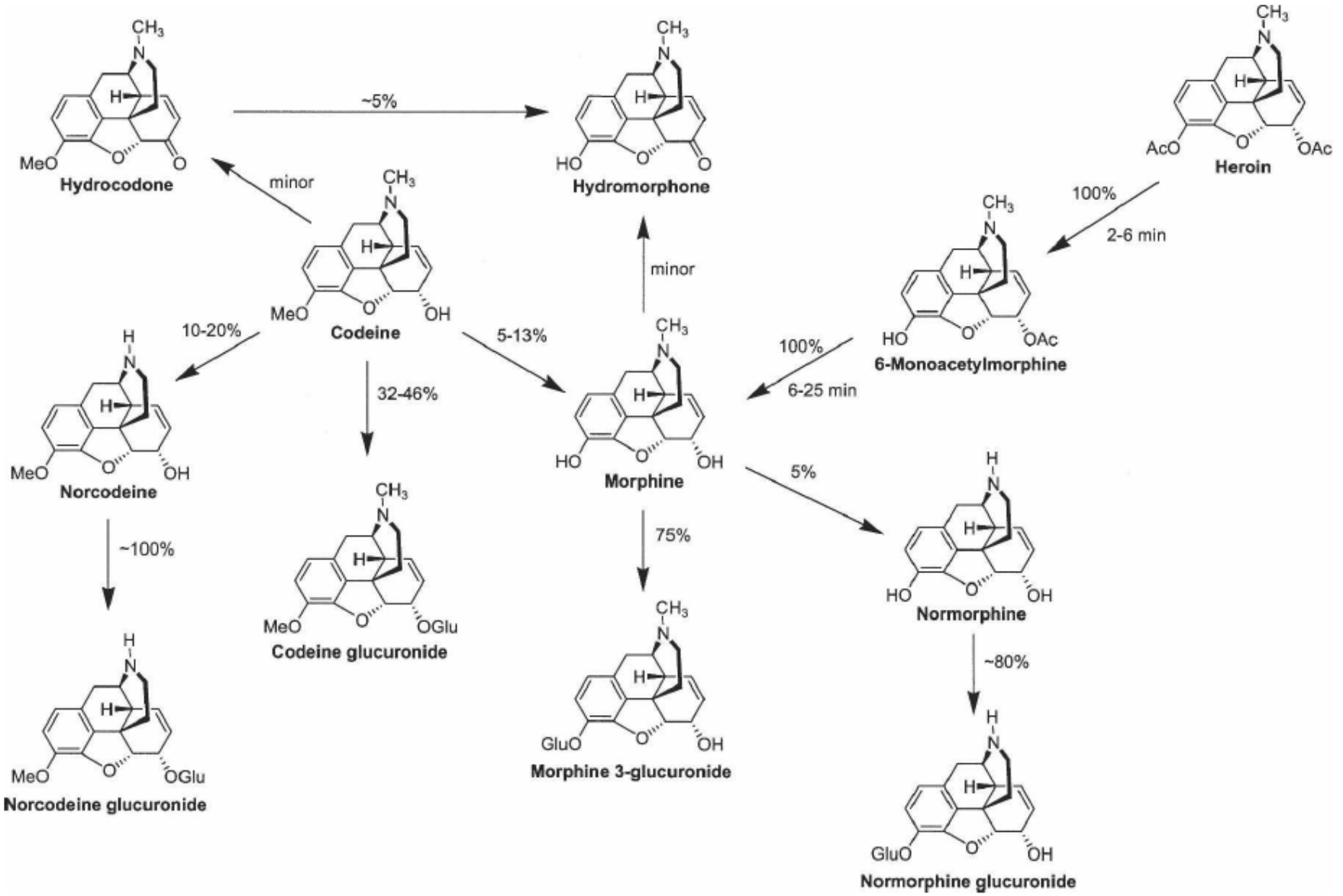
Hydrocodone
~5%
Hydromorphone
minor
Codeine
minor
Heroin
100%
2-6 min
6-Monoacetylmorphine
10-20%
5-13%
100%
6-25 min
Norcodeine
32-46%
Morphine
5%
~100%
75%
Codeine glucuronide
Normorphine
~80%
Norcodeine glucuronide
Morphine 3-glucuronide
Normorphine glucuronide

Opioid Metabolites

TABLE 4. **Major Opioid Metabolites**

Opioid	Inactive metabolites	Active metabolites identical to pharmaceutical opioids	Active metabolites that are not pharmaceutical opioids
Morphine[28,43,53-55]	Normorphine	Hydromorphone[a]	Morphone-3-G glucuronide Morphone-6-G glucuronide
Hydromorphone[17]	Minor metabolites	None	Hydromorphone-3-glucuronide
Hydrocodone[56]	Norhydrocodone	Hydromorphone	None
Codeine[57,58]	Norcodeine	Hydrocodone[a] Morphine	None
Oxycodone[11]	None	Oxymorphone	Noroxycodone
Oxymorphone[18]	Oxymorphone-3-glucuronide	None	6-Hydroxy-oxymorphone
Fentanyl[10]	Norfentanyl	None	None
Tramadol[16]	Nortramadol	None	*O*-desmethyltramadol
Methadone[59]	2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine 2-Ethyl-5-methyl-3,3-diphenylpyrroline	None	None
Heroin[60]	Normorphine	Morphine	6-Monoacetylmorphine

[a] Only very low levels are seen in the urine: less than 11% for hydrocodone after codeine administration and less than 2.5% for hydromorphone after morphine administration.[53,54,58]

Opioids that metabolize to other prescribed opioids

- Codeine: morphine, hydrocodone
- Heroin: morphine (codeine contaminant)
- Morphine: hydromorphone

- Buprenorphine, fentanyl, hydromorphone, meperidine, methadone, oxycodone do not metabolize to other prescribed opioids

Reisfield et al, 2009, Bioanalysis
Pergolizzi et al, 2010, Pain Pract; Manchikanti et al, 2010, Pain Phys

Benzodiazepines that metabolize to other prescribed benzodiazepines

- Chlordiazepoxide: oxazepam
- Clorazepate: oxazepam
- Diazepam: temazepam, oxazepam
- Temazepam: oxazepam

- Alprazolam, clonazepam, flurazepam, lorazepam, midazolam, triazolam and flunitrazepam (“date rape” drug) do not metabolize to other prescribed benzo’s

Reisfield et al, 2009, Bioanalysis

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UDT – detection times

Drug	Detection time
amphetamines	**2 days**
barbiturates	**Short acting 1 day** **Long acting 2 – 3 weeks**
benzodiazepines	**Therapeutic dose 3 days** **Extended use 4-6 weeks**
cocaine	**2 to 4 days**
opioids	**2 to 3 days**
cannabinoids	**Light smoker (1 joint) 2-3 days** **Moderate smoker (4/week) 5 days** **Daily smoker 10 days** **Chronic smoker 4 weeks**

Heit et al, 2004, J Pain Symptom Manage

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False Positive Urine Toxicology

- **THC**: ketoprofen, naproxen, ibuprofen, sustiva, pantoprazole, promethazine, riboflavin, marinol, sativex, hemp seed oil
- **Opioid**: poppy seeds, chlorpromazine, rifampin, dextromethorphan, quinine, fluoroquinolones
- **Methadone:** quetiapine, methotrimeprazine
- **Benzodiazepines:** sertraline, oxaprozin, flurbiprofen, indomethacin, ketoprofen

Reisfield et al, 2009, Bioanalysis

Trescot et al, 2008, Pain Physician; Tenore, 2010, J Addict Dis

False Positive Urine Toxicology

- **Amphetamine**: vicks vapor nasal inhaler, ephedrine, pseudoephedrine, tyramine, ciprofloxacin, mefanamic acid, labetalol, methylphenidate, trazodone, desipramine, bupropion, propranolol, phenylephrine, mexilitine, selegiline, amantadine, ranitidine, metronidazole, phenothiazines, some diet pills
- **Cocaine:** salicylates, fluconazole

Reisfield et al, 2009, Bioanalysis

Trescot et al, 2008, Pain Physician; Tenore, 2010, J Addict Dis

Before interpreting UDT

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False Negative Urine Toxicology

- Opioids
  - semi-synthetic

    hydromorphone, oxycodone
  - synthetic

    fentanyl, methadone, meperidine
- Benzodiazepines
  - clonazepam, lorazepam

Trescot et al, 2008, Pain Physician; Tenore, 2010, J Addict Dis

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UDT tampering

Techniques

- Dilution
- Ingestion of diuretics, sodium bicarbonate, salicylates
- Adulteration: drain cleaner, bleach, soap, ammonia, lemon juice, hydrogen peroxide
- Urine substitution

Safeguards

- temperature 32º – 38º (90º - 100º) temperature strip
- pH 4.5 to 8
- Specific gravity 1.002 – 1.020
- Urine creatinine < 2–3 mmol/liter nonphysiologic

Manchikanti, 2010, Pain Physician; Moeller, 2008, Mayo Clin Proc

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Laboratory Errors

- Specimen incorrectly labeled
- Result posted to the wrong patient's record
- Incorrect test ordered ("drug screen")
- Incorrect container containing compound that causes sample instability
- Compound present that interferes with testing process

Reisfield et al, 2009, Bioanalysis

Part 2 - Cases

T.K. Mymed

- 46 yo male long standing back pain
- Came to your practice 1 year ago
- Meds:
  - Morphine LA 60 mg bid
  - Morphine SA 10 mg, 4 tabs per day
  - Dispensed monthly
- As a routine part of your practice you check a urine screen

T.K. Mymed

- What are you looking for?
- What do you do if it is negative for morphine?
- What if it is positive for hydromorphone?

Prescribed opioid not present

- Concentration of measured drug below cutoff (false –ve)
- Synthetic/semisynthetic opioid not detected
- Patient binging (pseudoaddiction, addiction, chemical coping)
- Patient taking less medication than prescribed

  (side effects, symptom abatement, fear of addiction, hoarding)
- Rapid metabolism (metabolic, pharmacologic induction)
- Patient not taking drug (diversion)
- Adulterated urine
- Laboratory error

Heit et al, 2004, J Pain Symptom Manage; Reisfield, 2009, Bioanalysis

Prescribed opioid not present

Response

- Repeat with chromatography/mass spectrometry, specify opioid to be tested
- Obtain regular UDT
- Ask about patient's medication use
- Ask about diversion
- Review treatment agreement
- Shorten opioid dispensing interval
- Monitor with pill counts

Christo et al, 2011, Pain Physician

S. T. Reet

- 46 yo male long standing back pain
- Came to your practice 1 year ago
- Meds:
  - Hydromorphone LA 12 mg bid
  - Hydromorphone 4 mg, 4 tabs per day
  - Dispensed monthly
- Another patient tells you that S.T. is selling his meds.

S. T. Reet

- What do you order?
- Can a urine test be useful? How?
- What if it is negative for hydromorphone?
- What if it is positive for morphine?

Non-prescribed opioid present

- Metabolite of prescribed opioid
  - Morphine metabolite of codeine
  - Hydromorphone metabolite of morphine
- Cross reaction (false positive)
- Taking opioid from another source (pseudoaddiction, addiction, chemical coping, acute pain)
  - double doctoring
  - buying from street
- Laboratory error

Non-prescribed opioid present

Response

- Repeat with chromatography/mass spectrometry
- Repeat UDT regularly
- Ask about substances that cross react
- Ask about opioids from other sources
- Obtain print out from Prescription Monitoring
- Review pain management
- Assess for opioid addiction
- Review treatment agreement
- Consider shortening opioid dispensing interval
- Increase frequency of visits

Christo et al, 2011, Pain Physician

S. Ommore

- 46 yo male long standing back pain
- Came to your practice 1 year ago
- Meds:
  - Hydromorphone LA 12 mg bid
  - Hydromorphone 4 mg, 4 tabs per day
  - Dispensed monthly
- On routine urine screening, amphetamine is detected.

S. Ommore

- How do you interpret the findings?
- How do you handle the patient conversation?

Illicit substances present

- Cross reaction (false positive)
  - Amphetamines
  - THC
  - Cocaine
- Patient using illicit substances
- Laboratory error

Illicit substances present

Response

- Repeat with chromatography/mass spectrometry
- Repeat UDT regularly
- Ask about substances that cross react
- Assess for addiction and refer for addiction treatment as appropriate
- Review treatment agreement
- Shorten opioid dispensing interval
- Increase frequency of visits

Christo et al, 2011, Pain Physician