URINE DRUG TESTING

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DISCLOSURES

- President of the World Institute of Pain

OBJECTIVES

Identify	Identify risk management strategies for chronic opioid therapy
Define	Define the purpose of urine toxicology
Review	Review variables affecting results of urine drug testing
List	List clinical applications of urine drug testing

CHRONIC OPIOID THERAPY

- Pain is subjective
- Must rely on self-report
- Addicted individual will not provide reliable information if it will result in discontinuation of their drug of choice
- Self-report of drug use in pain population is unreliable (Katz 2002)

CHRONIC OPIOID THERAPY

Must rely on subjective and objective report

Objective observations are:

- Pill counts
- Prescription monitoring programs
- Aberrant behaviors
- Urine drug testing (UDT)

ABERRANT BEHAVIORS

- Self-escalation
- Lost or stolen controlled medications
- Treatment non-compliance
- Behavioral monitoring alone is inadequate
- Aberrant UDT
  - Illicit substances
  - Non-prescribed controlled substances
  - Absence of prescribed controlled substance(s)

INCIDENCE OF ABERRANT UDT

▪ Cook RF,	1995	50%
▪ Fishbain DA,	1999	46.5%
▪ Hariharin J,	2007	38%
▪ Ives TJ,	2006	32%
▪ Berndt S,	1993	32%
▪ Katz NP,	2003	29%
▪ Michna E,	2007	45%
▪ West R ,	2010	9-33%
▪ Manchikanti L,	2006	16%

Texas Medical Board (TMB) rule 170.3(a)(1)(B)(v)

Known Risk Factors:

- Personal/family history of substance abuse or ETOH
- Age <45
- Nicotine dependency
- Impulse control problems
  - ADD, OCD, Bipolar, Schizophrenia, Personality Disorders
- Hypervigilance states
  - PTSD, Preadolescent sexual abuse
- Somatoform disorders
- Organic mental syndrome
- Pain after a motor vehicle accident
- Pain involving more than three regions of the body
  - Webster 2005, Manchikanti 2006

RISK ASSESSMENT TOOLS

- ORT (Opioid Risk Tool)
- PMQ (Pain Medication Questionnaire)
- DIRE (Diagnosis, Intractability, Risk, Efficacy Score)
- SOAPP-R (revised Screener and Opioid Assessment for Patients with Pain)
- Formal psychological assessment
- Risk divided into high, moderate, and low

SCREENER AND OPIOID ASSESSMENT FOR PATIENTS WITH PAIN REVISED

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)

The following are some questions given to patients who are on or being considered for medication for their pain. Please answer each question as honestly as possible. There are no right or wrong answers.

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
1. How often do you have mood swings?	○	○	○	○	○
2. How often have you felt a need for higher doses of medication to treat your pain?	○	○	○	○	○
3. How often have you felt impatient with your doctors?	○	○	○	○	○
4. How often have you felt that things are just too overwhelming that you can't handle them?	○	○	○	○	○
5. How often is there tension in the home?	○	○	○	○	○
6. How often have you counted pain pills to see how many are remaining?	○	○	○	○	○
7. How often have you been concerned that people will judge you for taking pain medication?	○	○	○	○	○
8. How often do you feel bored?	○	○	○	○	○
9. How often have you taken more pain medication than you were supposed to?	○	○	○	○	○
10. How often have you worried about being left alone?	○	○	○	○	○
11. How often have you felt a craving for medication?	○	○	○	○	○
12. How often have others expressed concern over your use of medication?	○	○	○	○	○
13. How often have any of your close friends had a problem with alcohol or drugs?	○	○	○	○	○
14. How often have others told you that you had a bad temper?	○	○	○	○	○
15. How often have you felt consumed by the need to get pain medication?	○	○	○	○	○
16. How often have you run out of pain medication early?	○	○	○	○	○
17. How often have others kept you from getting what you deserve?	○	○	○	○	○
18. How often, in your lifetime, have you had legal problems or been arrested?	○	○	○	○	○
19. How often have you attended an AA or NA meeting?	○	○	○	○	○
20. How often have you been in an argument that was so out of control that someone got hurt?	○	○	○	○	○
21. How often have you been sexually abused?	○	○	○	○	○
22. How often have others suggested that you have a drug or alcohol problem?	○	○	○	○	○
23. How often have you had to borrow pain medications from your family or friends?	○	○	○	○	○
24. How often have you been treated for an alcohol or drug problem?	○	○	○	○	○

- Low risk: SOAPP-R score < 10
- Moderate risk: SOAPP-R score 10-21
- High risk: SOAPP-R score > 21

Table 4. *UDT recommendations based on risk stratification. Modified from Official Disability Guidelines for UDT (25) and Sundwall et al (26).*

Risk	Number of Urine Drug Tests per Year
Low	1 or 2
Moderate	3 or 4
High	4 or every month, office visit, or every drug refill

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VARIABLES AFFECTING RESULTS OF URINE TESTING

- Cutoff Selection
- Pharmacokinetics, pharmacodynamics, and pharmacogenetics
- Laboratory technology used in urine drug test
- Subversion and adulteration of the urine specimen

CUTOFF SELECTION

- Key word: cutoff threshold
  - Any sample having a drug concentration equal to or above a specified level is considered a "positive result"
  - May vary from screening to confirmation test
  - A lower cutoff results in a longer detection time which in turn increases sensitivity at the expense of specificity which it decreases

Drug	Screening cut-off concentrations ng/mL urine	Confirmation cut-off concentrations ng/mL (non-regulated)	Confirmation cut-off concentrations ng/mL (federally regulated)	Urine detection time
Opioids				
Morphine	300	50	2,000	3-4 days
Codeine	300	50	2,000; 300	1-3 days
Hydrocodone	300	50	2,000	1-2 days
Oxycodone	100	50	2,000	1-3 days
Methadone	300	100	2,000	2-4 days
Benzodiazepines	200	20-50	NA	Up to 30 days
Cocaine	300	50	150	1-3 days
Marijuana	50	15	15	1-3 days for casual use; up to 30 days for chronic use
Amphetamine	1,000	100	500	2-4 days
Methamphetamine	1,000	100	500	2-4 days
Heroin*	10	10	NA	1-3 days
Phencyclidine	25	10	25	2-7 days for casual use; up to 30 days for chronic use

*6-MAM, the specific metabolite is detected only for 6 hours.

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PHARMACOKINETICS, PHARMACODYNAMICS, AND PHARMACOGENETICS

Absorption

- Varies depending on route of administration

Distribution

- Transporters across different membranes influence the rate of drug absorption, excretion, or arrival at the site of action
  - Also exhibit **genetic polymorphism**
  - Ultimately affects the efficacy of opioids

PHARMACOKINETICS, PHARMACODYNAMICS, AND PHARMACOGENETICS

- Metabolism
  - Very important secondary to genetic polymorphism
  - Patients essentially categorized into several metabolizer groups
    - Poor metabolizer (SE's at standard doses)
    - Intermediate metabolizer (Too much medication at standard doses)
    - Extensive/Rapid or "normal" metabolizer
    - Ultra-rapid metabolizer (Med removed from system too quickly to provide symptom relief)
  - Which enzymes?
    - Cytochrome P450 (CYP)
      - CYP1A2, **CYP2B6**, CYP2C19, **CYP2D6**, **CYP3A4**
    - UGT: UDP-glucuronosyltransferases
    - Demethylation
    - Glucoronidation

Table 2. *Frequently used opioids and their metabolic routes.*

Drug	CYP1A2	CYP2B6	CYP2C19	CYP2D6	CYP3A	UGT	Demethylation	Glucuronidation	Reference
Codeine				++++		+			(172,173)
Hydrocodone				+++	+		+++		(173)
Hydromorphone					+++			+++++	(166)
Meperidine							+		(179)
Methadone							+++++		(174)
R-methadone		+++++	+	+	+				(175)
S-methadone		+++++	+		+				(176)
Oxycodone				+++	++		+++++		(176)
Tramadol		+	+	+++	+		++		(177,178)

CYP indicates cytochrome P450; UGT, UDP-glucuronosyltransferases.

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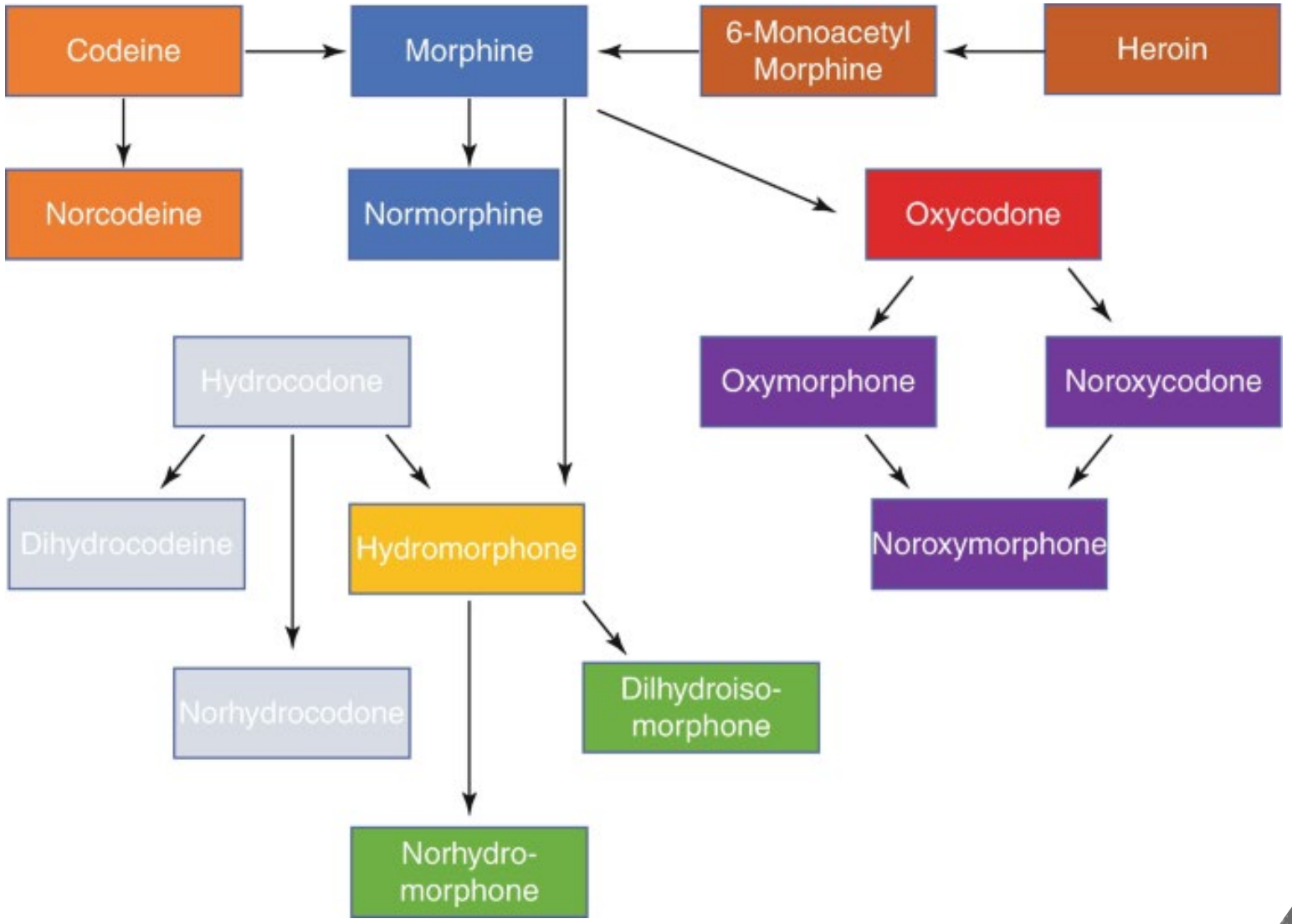
Codeine
Morphine
6-Monoacetyl Morphine
Heroin
Norcodeine
Normorphine
Oxycodone
Hydrocodone
Oxymorphone
Noroxycodone
Dihydrocodeine
Hydromorphone
Noroxymorphone
Norhydrocodone
Dilhydroiso-morphone
Norhydro-morphone

PHARMACOKINETICS, PHARMACODYNAMICS, AND PHARMACOGENETICS

- Importance
  - Could affect whether an inactive prodrug is converted to an active drug

Table 2. The Metabolism of Codeine, Hydrocodone, and Oxycodone into their Active Metabolites

Prodrug	*Active Metabolite*
Codeine	Morphine
Hydrocodone (Vicodin)	Hydromorphone (Dilaudid)
Oxycodone (Percodan)	Oxymorphone

Anesth Prog 45:154–156 1999

  - Individual genotype plays an important role in determining the rate of metabolism and the efficacy of a **specific dose** for particular opioids, resulting that the dose of a drug might not correlate with the extent of pain relief or urine concentration
  - Genetic testing is available, but usually not covered by insurance. However, it is covered by Medicare.

DRUG RETENTION TIMES

Table 1
Drug Retention Times

Drug	Retention Time
Amphetamines	48 hours
Barbiturates	Short-acting (e.g., secobarbital) 24 hours
	Long-acting (e.g., phenobarbital) 2–3 weeks
Benzodiazepines	3 days if therapeutic dose ingested
	Up to 4–6 weeks after extended use (or abuse quantities)
Cocaine metabolite (cocaine parent)	2–4 days (few hours)
Methadone	Approximately 3 days
Opiates	2-3 days (morphine/codeine)
	6-acetyl morphine (metabolite of heroin) <12 hours
	opioids (semisynthetic/synthetic) 2–3 days[a]
Propoxyphene	6–48 hours
Cannabinoids	Light smoker (1 joint) 2–3 days
	Moderate smoker (4 times/week) 5 days
	Heavy smoker (smokes daily) 10 days
	Retention time for chronic smokers may be 20 days–28 days
Phencyclidine (including ketamine)	Approximately 8 days
	Up to 30 days in chronic users (mean value = 14 days)

URINE DRUG TESTING

URINE DRUG TESTING IN TEXAS

- Texas Medical Board (TMB) rule 170.3(a) (1)(B)(v) requires an assessment of a patient's potential for substance abuse.
- Baseline UDT, combined with a psychological evaluation, perhaps including validated psychometric screening tools, provides a valuable risk assessment basis with which the clinician can assess the patient's candidacy for COT and comply with the TMB rule.

TECHNOLOGY OF UDT

- Methods of testing
  - Screening: Immunoassay (EIA)
    - Sensitive, but not specific
      - Can produce false-negatives by missing compounds such as oxycodone, fentanyl, tramadol and methadone
      - Can produce false-positives secondary to cross reactivity with other substances
  - Confirmatory: gas chromatography and mass spectrometry (GC/MS) or liquid chromatography and mass spectrometry (LC/MS)
    - Must know the common metabolites of the tested compound to interpret the results properly

TECHNOLOGY OF UDT

TABLE 2.
Pros and Cons of Urine Testing Techniques

Use	Technique	Pros	Cons
Screening	Immunoassay (EMIT)	• Sensitive • Inexpensive • Requires a small sample of urine • Conducted at the point of care • Can handle a high volume of cases • Rapid turnaround • Can be performed by minimally trained staff	• Qualitative analysis only • Subject to cross-reactivity • Cannot determine exposure, time, dose, frequency of use • Sensitivity and specificity vary by manufacturer and devices/ equipment • Does not reliably detect semisynthetic/synthetic opioids
Confirmatory test	GC/MS	• Quantitative • Highly specific & sensitive • Few false results; when present, due to human error	• Relatively expensive; insurance may not cover • Limited by laboratory services/ quality

EMIT, enzyme multiplies immunoassay technique; GC/MS, gas chromatography/mass spectrometry. Data from: Center for Substance Abuse Treatment, 1993; Katz & Fanciullo, 2002; Substance Abuse and Mental Health Services Administration, 2005, 2007

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DRUG CROSS REACTANTS

Table 3. *Drug cross-reactants.*

Drug Cross-Reactants	
Drug	Cross-Reactant
Cannabinoids	NSAIDs, Marinol, Protonix
Opioids	Poppy seeds, chlorpromazine, rifampin, dextromethorphan quinine
Amphetamines	Ephedrine, methylphenidate, trazodone, bupropion, desipramine, amantadine, ranitidine, phenylpropanolamine, Vicks Vapor Spray
PCP	Chlorpromazine, thioridazine, meperidine, dextromethorphan, diphenhydramine, doxylamine
Benzodiazepine	Oxaprozin (Daypro), some herbal agents
ETOH	Asthma inhalers (sometimes)
Methadone	propoxyphene, Seroquel

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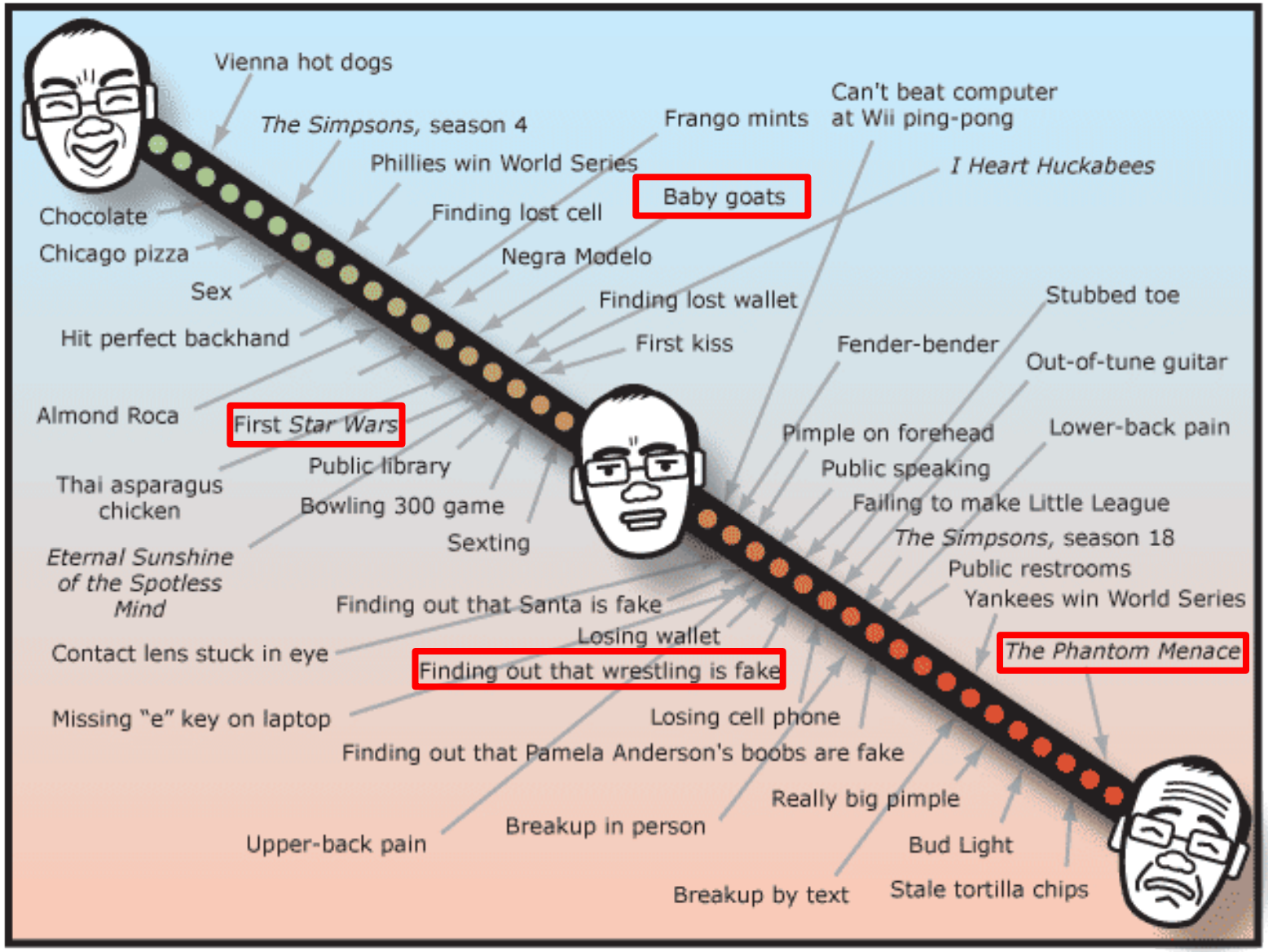
THE PLEASURE–PAIN INDEX



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ADULTERATION/SUBVERSION IN UDT

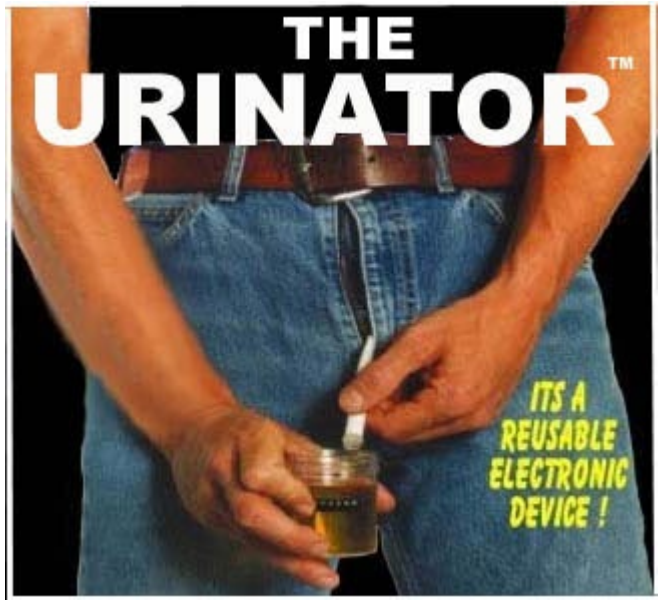
- Urine temperature
  - Urine collected within 4 minutes should have a temperature of 90-100°F and a pH value of 4.5-8.0.
- Urine dilution
  - Creatine concentration should be greater than 20
    - Anything less indicates a specimen that has been diluted by adulteration, by consumption of excessive fluids, or possibly by cachexia or renal dysfunction.
  - Specific gravity should be between 1.002 and 1.030
  - Methods:
    - Adding tap water to the urine
    - Ingesting large amounts of water
    - Taking diuretics

ADULTERATION/SUBVE
UDT

- Urine Detoxification

ADULTERATION/SUBVERSION IN UDT

- Urine Substitution



REASONS TO TEST PATIENTS FOR APPROPRIATE USE OF OPIATES

Protecting	Protecting the patient
Protecting	Protecting the practitioner
Protecting	Protecting the pain therapy plan
Protecting	Protecting the community
Protecting	Protecting society
Promoting	Promoting cost-effectiveness
Protecting	Protecting resources
Practicing	Practicing safe and effective medicine
Practicing and fulfilling	Practicing and fulfilling ethics in medical practice
Preserving	Preserving access to therapy.

CLINICAL APPLICATION OF UDT

UDT should be a component of your informed consent and opioid agreement

An office policy regarding UDT needs to be in place

Strongly recommend that a baseline UDT be conducted before initiating COT

Frequency of UDT depends of the individual's risk assessment

Random UDT preferred over scheduled UDT

CLINICAL APPLICATION OF UDT

- Easiest strategy to prevent urine tampering is to refer the patient to an independent laboratory for urine collection and testing
- Typically, patients should not be given their prescription until they return from the laboratory with a note indicating that they provided an adequate urine sample
- If testing in office, the practitioner may want to consider the following:
  - The sink's water flow should be turned off or disconnected
  - The toilet should have a coloring agent added to it
  - The patient should completely disrobe in the exam room and put on a gown

INTERPRETATION OF THE RESULTS

UDT positive for prescribed drugs and negative for other licit or illicit drugs

- Routine monitoring once or twice a year

UDT negative for prescribed opioid

- Secondary to
  - Non-compliance secondary to irregular intake of opioids
  - Diversion
  - False-negative results
- Action:
  - Repeat the test with qualitative and quantitative testing for specific drugs
  - Counsel patient
  - Compliance monitoring: frequent pill counts, fewer pills prescribed, possible termination

INTERPRETATION OF THE RESULTS

- UDT positive for non-prescribed opioid or benzodiazepines
  - Secondary to:
    - False positive
    - Patient acquired opioids/benzos from other sources or doctor shopping
  - Action
    - Review recent past history of patient
    - Repeat qualitative and quantitative UDT
    - Check your states prescription monitoring program or pharmacy records
    - Educate patient and reiterate opioid agreement

- UDT positive for illicit drugs
  - Approximately 10% of patients in chronic pain management settings use illicit drugs
  - Whether infrequently used or is an addict, these patients are at increased risk for opioid misuse, abuse and diversion
  - Action:
    - Inform and advise patient that continues drug use is incompatible with opioid therapy
    - Reiterate opioid agreement
    - Inform patient that continues use illicit drug use prohibits opioid therapy
    - Repeat UDT with confirmation test regularly (at least 4 times/year)
    - Failure to comply = termination

INTERPRETATION OF THE RESULTS

- UDT specimen tampered with, i.e. low urine creatinine or temperature
  - Rule out all explanations although most are usually incriminating
  - Repeat UDT with supervised collection
  - Educate patient
  - Check your states prescription monitoring program or pharmacy records

DELTA-9 AND DELTA-8 THC

Delta-9 vs. Delta-8 THC

Delta-8 and Delta-9 are both cannabinoids, but they have key differences.

Characteristic	Delta-9 THC	Delta-8 THC
Potency	More potent and produces stronger psychoactive effects.	About half as potent, resulting in a milder, less intense high.
Effects	More pronounced euphoria, relaxation, and altered perception.	Often described as a clearer high with a lower risk of anxiety or paranoia.
Availability	Primarily extracted from marijuana, a federally illegal plant.	Usually synthesized from hemp-derived CBD because it is present in much smaller natural quantities.
Legal status	Federally illegal, except for hemp-derived products under 0.3%.	Federally legal if hemp-derived, though many states have their own restrictions or bans.

LEGAL LANDSCAPE IN TEXAS

- **Current Legal Status of Delta-9 THC** Delta-9 THC is legal in Texas, but its use is highly restricted and regulated. It is primarily accessible through the Texas Compassionate Use Program (TCUP), which allows for the medical use of low-THC cannabis.
- **Texas Compassionate Use Program (TCUP)** The Texas Compassionate Use Program permits the use of Delta-9 THC for patients with specific qualifying medical conditions. These conditions include epilepsy, multiple sclerosis, terminal cancer, and other debilitating conditions. Under TCUP, the THC content is capped at 1%, and patients must have a prescription from a registered medical cannabis doctor. The program ensures that Delta-9 THC is provided safely and legally to those who need it for medical purposes.

CONCLUSION

UDT is not as easy as it seems

Need to perform a risk assessment prior to initiating chronic opioid therapy which should include UDT

Establish a protocol for UDT and adhere to it

Pain management can continue despite abnormal UDT results

Document, document, document!

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