

**A Combined Lecture...**  
**Methodone: Friend or Foe**  
*and*  
**Prescribing Opioids to Patients with a Previous or Current History of  
Substance Abuse, employing Urine Screens**

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<p><i>For supportive Pain Documents and to contact Dr.Fudin, please visit</i> <b><i>www.NOVAPAIN.net</i></b></p>
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**LEARNING OBJECTIVES:**


Upon completion of this overview, the attendee should be able to:

**Methodone**

1. Describe the goals of therapy when opioid analgesics are employed.
2. Compare the opioid/opiate analgesics in terms of their pharmacology, chemistry, therapeutics, and advantages/disadvantages.
3. Describe the unique pharmacokinetics and special dosing considerations and precautions of methadone.
4. Describe the clinically relevant methadone drug interactions.

**Substance Abuse**

1. Understand the concept of BALANCE among clinicians who treat pain, clinicians who treat addiction, those who regulate, and enforce legislation.
2. Compare and Contrast Addiction, Pseudo-addiction, Tolerance, Physical Dependence.
3. Understand the role and necessary content of an opioid agreement.
4. Understand the appropriate proactive and reactive prescribing strategies based on perceived patient risk.
5. Understand the medicinal chemistry of opioids and apply this understanding to drug selection and urine tox screens.
6. Interpret positive and negative results of urine tox screens



**Combined Lecture...  
Methadone: Friend or Foe  
and  
Prescribing Opioids to Patients with a Previous or  
Current History of Substance Abuse:  
A FOCUS on UDS**

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## Overview of Topics

### METHADONE

- Goals of Therapy
- Methadone
- Special dosing considerations and precautions
- Unique pharmacokinetics
- Drug interactions

### SUBSTANCE ABUSE & UDS

- **Brief Overview of "Addiction" Lingo**
- **Need for monitoring, Urine drug screen**
- **Medicinal Chemistry, Analytical Chemistry**
- **Opiate serum predictability, place in therapy**

# Analgesic Choices

## *Executive Summary*

- Extended Release Products:
  - Fentanyl (Duragesic®)
  - Morphine-ER (Kadian®, MS Contin®, Oramorph SR® others)
  - Oxymorphone (Opana®)
  - Oxycodone-ER (Oxycontin®)
- Synthetic “Atypicals”
  - Methadone (Dolophine®, Methadose®)
  - Tramadol (Ultram®)
- Poor Choices for Chronic Pain
  - Propoxyphene (Darvon®, Darvocet®)
  - Meperidine (Demerol®)
  - Other short acting combination products

## MedWatch Alert:

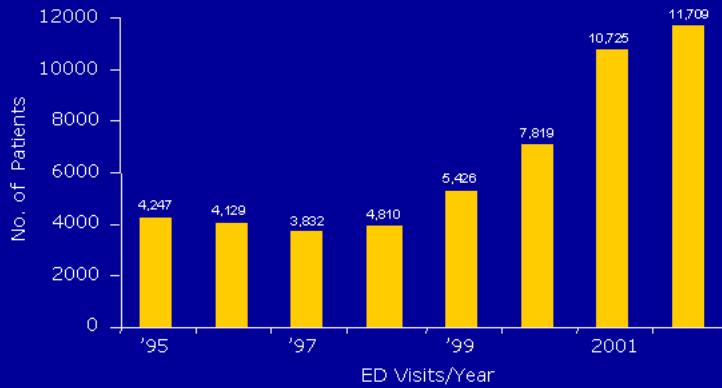
FDA Public Health Advisory  
November 2006

“Methadone Use for Pain Control May Result in  
Death and Life-Threatening Changes in  
Breathing and Heart Beat.”

What prompted this warning?

Methadone Public Health Advisory, Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat. Available from:  
<http://www.fda.gov/cder/drug/advisory/methadone.htm>. Accessed February 28, 2007.

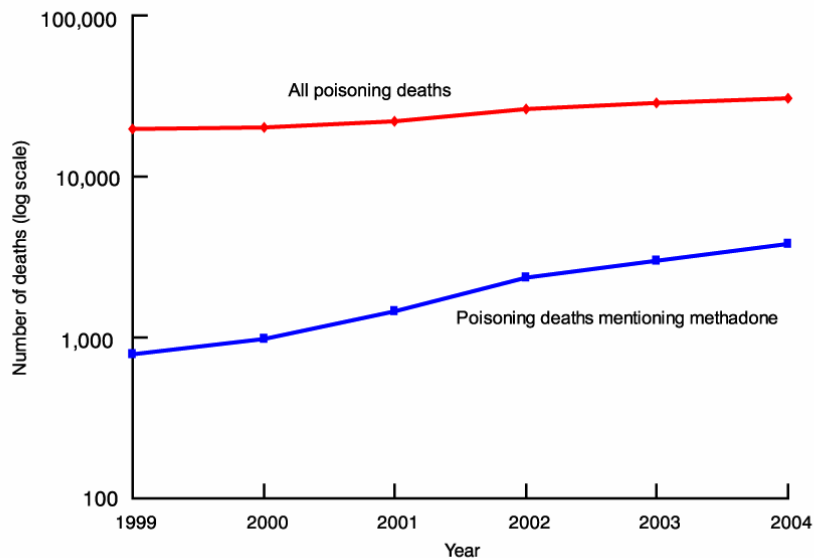
## Methadone-Related ED Visits: Trend



- The number of methadone-related emergency room visits in the country has jumped in recent years

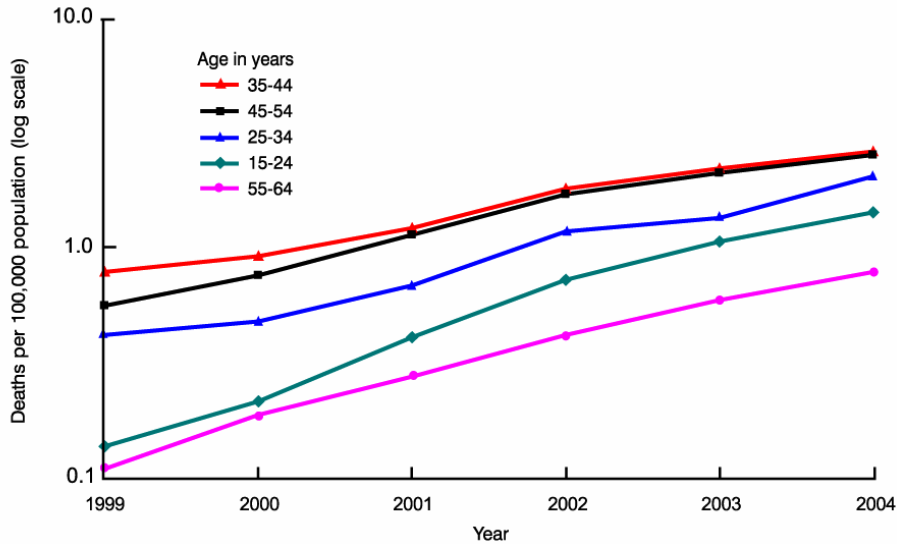
US Dept. of Health & Human Services/SAMHSA/OAS: Emergency Department Trends From the Drug Abuse Warning Network, 1995-2002, Table 2.8.0, Pub. D-24, July 2003.

**Figure 1. Poisoning and methadone-related poisoning deaths: 1999-2004**



SOURCE: National Center for Health Statistics, data from the National Vital Statistics System.

**Figure 2. Age-specific methadone-related death rates: 1999-2004**



NOTE: Methadone-related deaths were selected regardless of underlying cause of death.  
SOURCE: National Center for Health Statistics, data from the National Vital Statistics System.

## Metabolic Pathway from Drug Elimination

DRUG	Opioid Class	Major Metabolic Pathway
Morphine	Phenanthrene (w/ -OH)	Glucuronidation
Hydromorphone	Phenanthrene	Glucuronidation
Codeine	Phenanthrene (w/ -OH)	Demethylation, glucuronidation
Levorphanol	Phenanthrene	Glucuronidation
Oxycodone	Phenanthrene	Demethylation, glucuronidation, keto-reduction
Oxymorphone	Phenanthrene	Glucuronidation
Meperidine	Phenylpiperidine	Oxidation, hydrolysis, demethylation, glucuronidation
Fentanyl	Phenylpiperidine	Oxidation, hydrolysis, minor 3A4
Alfentanil	Phenylpiperidine	Oxidation
Sufentanil	Phenylpiperidine	Dealkylation, demethylation
Methadone	Diphenylheptane	Demethylation, 3A4 substrate (significant)

Volles DF, McGory R. Pharmacokinetic considerations, 15:5:Jan 1999.

## Opioid Analgesic P-Kinetics

Agent	Time to Peak (hr)	Half-life (hr)	Analgesic Onset (min)	Analgesic Duration (hr)
Morphine (IM)	0.5-1	2	10-20	3-5
Hydromorphone (IM)	0.5-1	2-3	10-20	3-5
Levorphanol (IM)	0.5-1	12-16	10-20	5-8
Hydrocodone (PO)	1	4	30-60	4-6
Codeine (IM)	0.5-1	3	10-20	4-6
Oxycodone (PO)	0.5-1	2-3	30-60	4-6
Meperidine (IM)	0.5-1	3-4	10-20	2-5
Fentanyl (IM)	10-20	3-4	7-15	1-2
Methadone (IM)	0.5-1	15-30	10-20	>8 (chronic)
Propoxyphene (PO)	2-2.5	6-12	30-60	4-6

Combined data from: Reisine T, Paternak G 1995 and Pasero C, Portenoy RK, McCaffery M. 1999

## Important Opioid Metabolism Considerations

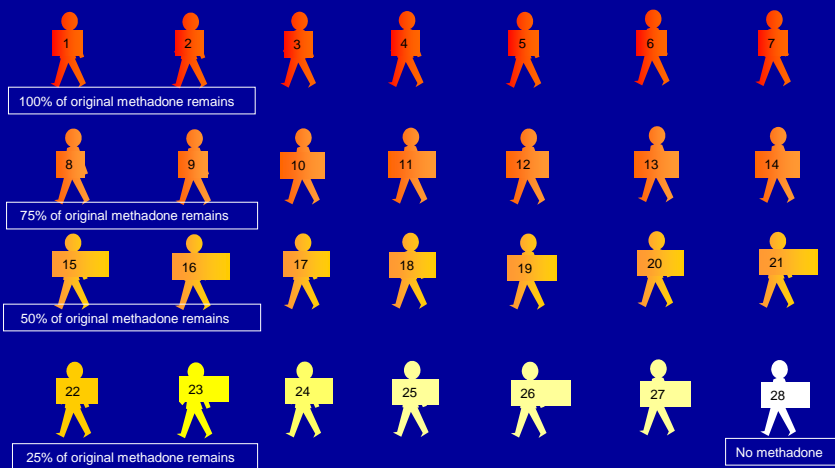
- Morphine (compare to oxycodone)
  - morphine-3-glucuronide (M3G)
    - no analgesic activity
  - morphine-6-glucuronide (M6G)
    - active metabolite eliminated by kidneys
- Meperidine
  - metabolized to nor-meperidine
  - nor-meperidine is renally cleared
    - ergo, Rx accumulation ⇒ CNS excitability ⇒ seizure activity
- Methadone
  - Substrate for 3A4, consider reduced serum levels in presence of 3A4 inducers such as anti-retrovirals (nivirapine), rifampin, others

## Points to Consider About Equianalgesic Methadone Conversions

- A number of equianalgesic tables underestimate the potency of methadone.
- Conversion ratios in many equianalgesic dosing tables do not apply to repeated doses of opioids.<sup>1</sup>
- The morphine-to-methadone conversion ratio increases as the previous dose of morphine increases.<sup>2</sup>
- Conversion ratios may not be bi-directional (i.e. the morphine-to-methadone conversion ratio may not be the same as the methadone-to-morphine ratio; a single ratio may not be applicable to all patients).<sup>3</sup>
- The use of high but ineffective doses of previous opioid may result in overestimation of the equivalent dose of methadone.

1. Management of Cancer pain, Clinical Practice Guidelines, AHCP (1994); Cancer pain: a monograph on the management of cancer pain, Health & Welfare Canada (1984); Twycross (1990); Levy (1985).
2. The oral morphine to oral methadone conversion ratio may be unexpectedly much higher in patients who previously received very high doses of morphine.
3. Bruera E, Neumann CM. Role of methadone in the management of pain in cancer patients. Oncology (Huntingt) 1999;13:1275-82; discussion 1285-8, 1291

After Discontinuing Methadone  
serum levels remain x 28 days  
morphine to methadone  $\neq$  methadone to morphine



# Methadone Conversion Study

- Ripamonti, et al 1998
  - Cross-sectional
  - Morphine to methadone
  - 38 patients

- Dose Ranges

Morphine (mg)	Morphine to Methadone Ratio
30-90	3.70 to 1
91-300	7.75 to 1
301 and higher	12.25 to 1

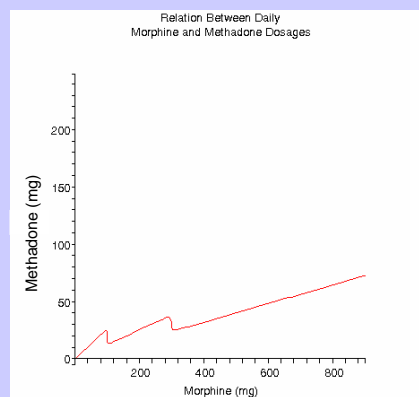
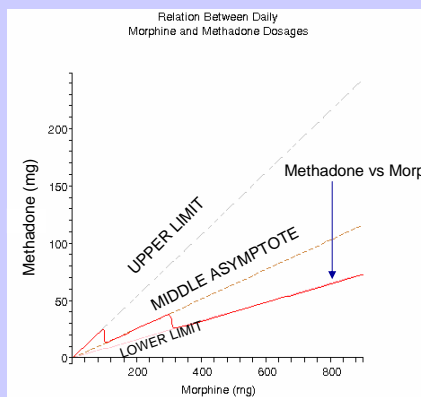
J Clin Oncol 1998;16:3216-3221

## “Fudin Factor” A Methadone Conversion Formula

Most exact to data from Ripamonti, et al 1998; less flowing and unlikely in real life

$$\text{Methadone (mg)} = \frac{X}{21} \left\{ 5.7 - 3 \sin \left( \frac{90}{\left( \frac{100}{X} \right)^{100} + 1} \right) - \sin \left( \frac{90}{\left( \frac{310}{X} \right)^{100} + 1} \right) \right\}$$

Let X= Morphine (mg)



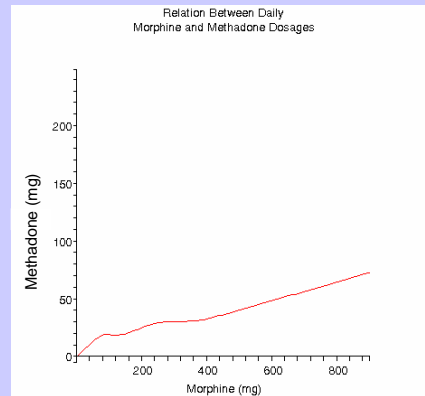
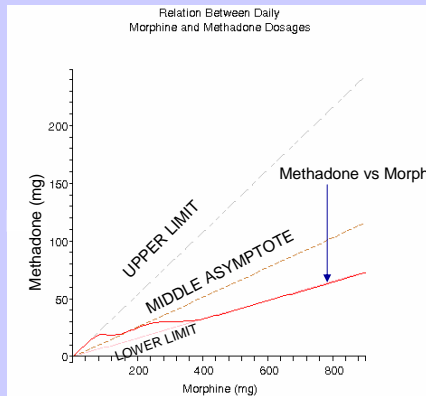
Formula derived by Jason Fudin (Engineering Student, McGill University) in collaboration with Dr. Jeffrey Fudin

**“Fudin Factor”**  
**A Methadone Conversion Formula**

Less exact to data from Ripamonti, et al 1998; more flowing and more likely in real life

$$\text{Methadone (mg)} = \frac{X}{21} \left\{ 5.7 - 3 \sin \left( \frac{90}{\left( \frac{110}{X} \right)^5 + 1} \right) - \sin \left( \frac{90}{\left( \frac{320}{X} \right)^7 + 1} \right) \right\}$$

Let X= Morphine (mg)



Formula derived by Jason Fudin (Engineering Student, McGill University) in collaboration with Dr. Jeffrey Fudin

## Potentially Clinically Relevant Methadone-Drug Interactions

- Agents That May **DECREASE** Serum Methadone Concentrations
  - Antiepileptics: carbamazepine, Phenobarbital, phenytoin
  - Antipsychotics: risperidone
  - Antiretrovirals: nevirapine, ritonavir
  - Antitubercular: rifampin
- Agents That May **INCREASE** Serum Methadone Concentrations
  - Antidepressants: SSRIs (venlafaxine is least likely), amitriptyline
  - Antifungals: fluconazole, Ketoconazole
- Agents That May Significant Increase Adverse Effects of Methadone
  - Benzodiazepines
  - St. John’s Wort

## Special Population Precautions When Dosing Methadone

- Patients 65 years old and older have decreased clearance of methadone.<sup>1</sup>
- Two prospective studies on methadone excluded patients with kidney and liver disease.<sup>2,3</sup>

1. Plummer JL, Gourlay GK, Cherry DA, Cousins MJ. Estimation of methadone clearance: application in the management of cancer pain. *Pain* 1988;33:313-22.
2. Ripamonti C, Groff L, Brunelli C, Polastri D, Stravakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol* 1998;16:3216-21.
3. Mercadante S, Casuccio A, Fulfaro F et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. *J Clin Oncol*. 2001;19:2,898-904.

## Summary

- Extended activity opioids have less side effects than short-acting products and foster extended periods of pain relief.
- Dosing and product selection must be patient-specific for each unique patient. No single medication is perfect for every patient.
- Methadone is not an extended release formulation.
- Only experienced clinicians should initiate and titrate methadone.
- Improper dosing of methadone (or any other opioid) could cause severe respiratory depression and death.

## Methadone has higher Potency in Some Patients. Why?

- Decreased Cross-tolerance
- d-isomer has NMDA receptor antagonism
- Opioid tolerance increases NMDA receptor activity; mediated by morphine-3-glucuronide (M-3-G)
- Conversion to methadone allows elimination of M-3-G, thereby decreasing opioid requirements.

Journal of Palliative Medicine 2002;5:127-138.

## The Concept of Balance in Chronic Pain Management

### Use of Opioids in an Ambulatory Clinic Setting:

#### *Proactive Strategies to Reduce Aberrant Behavior and Minimize Practitioner Liability*

#### SUBSTANCE ABUSE & UDS

- ✓ **Brief Overview of “Addiction” Lingo**
- ✓ **Need for monitoring, Urine drug screen**
- ✓ **Medicinal Chemistry, Analytical Chemistry**
- ✓ **Opiate serum predictability, place in therapy**

## Defining the Issues

- Misunderstandings about addiction, tolerance, dependence
- Difficulties in assessing patient's risk
- Absence of articulated strategies to manage patients at risk

(Passik, 2000; Passik 1998)

## Street Value Perspective

- 120 Percocet 5/325 (brand name)  
– \$2400.00
- 120 Lortab 5/500 (any brand)  
– \$2000.00
- 60 Oxycontin 80mg  
– \$4800
- 120 Actiq Lollipop 200mcg  
– \$3240.00
- Knowing when your patient is diverting drug...  
– PRICELESS!

## The Terminology of Abuse

- **Physical Dependence**
  - Abstinence syndrome induced by administration of an antagonist or by dose reduction
  - Usually unimportant if abstinence is avoided
  - Assumed to exist after few days' dosing but actually highly variable
  - Does not independently cause addiction
- **Addiction**
  - Disease with pharmacologic, genetic, psychosocial elements
  - Fundamental features: loss of control, compulsive use, use despite harm
  - Diagnosed by observation of aberrant drug-related behavior

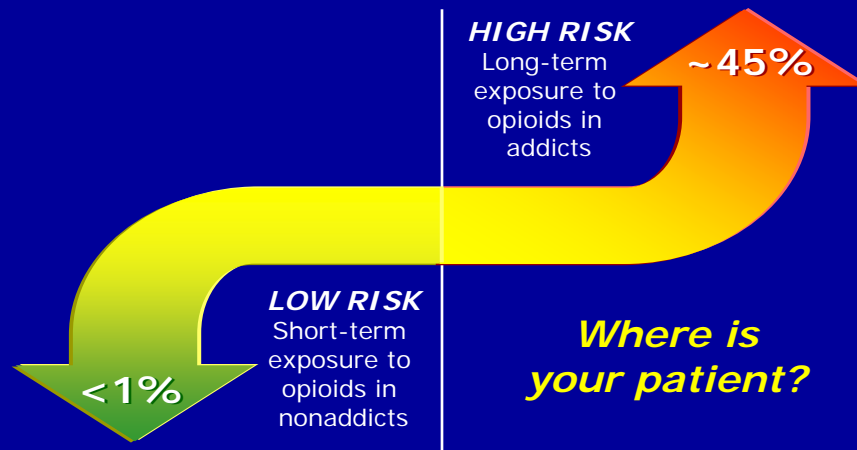
(AAPM/APS, 1996; NIDA, 2001; Passik et al, 2000; Portenoy, 1996)

## The Terminology of Abuse

- **Tolerance**
  - Diminished drug effect from drug exposure
  - Varied types: associative vs. pharmacological
  - Tolerance to analgesia is seldom a problem in the clinical setting:
    - Tolerance rarely "drives" dose escalation
    - Tolerance does not cause addiction
- **Pseudoaddiction**
  - Aberrant drug-related behaviors driven by uncontrolled pain
  - Reduced by improved pain control
  - Complexities
    - How aberrant can behavior be before it is inconsistent with pseudoaddiction?
    - Can addiction and pseudoaddiction coexist?

(Passik et al, 1998; Passik et al; Portenoy RK, 1996)

## Risk of Addiction or Aberrant Behavior With Opioids



Porter, 1980; Dunbar, 1996; Passik, 1998

## Diagnosing and Monitoring Aberrant Behaviors

### Two-Step Monitoring Approach

- Step 1: **Are there aberrant drug-related behaviors?**
- Step 2: **If yes, are these behaviors best explained by the existence of an addiction disorder?**

### Differential Diagnosis

- **Addiction/pseudoaddiction**
- **Other psychiatric disorders (e.g., borderline personality disorder)**
- **Mild encephalopathy**
- **Family disturbances**
- **Criminal intent**

(Passik et al, 1998; Passik et al, 1998)

## Risk Assessment for Addiction

### Low Addiction Risk

- Acute pain
- Cancer pain
- Patients without abuse background or psychopathology

### Chronic Noncancer Pain

- Probability of addiction is small
  - surveys that include patients with abuse or psychopathology show mixed results
- Predictors of addiction may include
  - history of substance abuse
  - Age
  - personality factors
  - family dynamics and social factors

(Passik et al, 1998; Passik et al, 1998)

## Drug-Related Behavior Predictive of Addiction

### Probably More Predictive

- Selling prescription drugs
- Prescription forgery
- Stealing or “borrowing” drug from another person
- Injecting oral formulation
- Obtaining prescription drugs from non-medical source
- Multiple episodes of prescription “loss”
- Concurrent abuse of related illicit drugs
- Multiple dose escalations despite warnings
- Repeated episodes of gross impairment or dishevelment

### Probably Less Predictive

- Aggressive complaining
- Drug hoarding when symptoms milder
- Requesting specific drugs
- Acquisition of drugs from other medical sources
- Unsanctioned dose escalation once or twice
- Unapproved use of the drug to treat another symptom
- Reporting psychic effects not intended by the clinician
- Occasional impairment

(Passik et al, 1998)

## Addressing Aberrant Drug-Related Behavior

- **General Management Principles**
  - know laws and regulations
  - structure therapy to match perceived risk
- **Proactive Strategies**
  - communicate goals of therapy
  - provide written guidelines (treatment agreement)
  - assess often
- **Reactive Strategies**
  - require frequent visits and small quantities of drug
  - use of urine toxicologies
  - long-acting drugs with no rescue doses
  - relate to addiction-medicine community (sponsor, program, addiction-medicine specialist, psychotherapist)

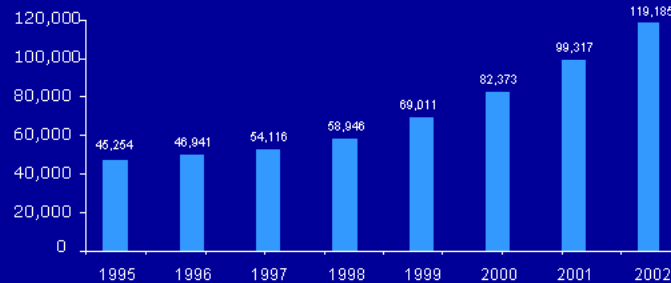
(Mironer et al, 2000; Portenoy et al, 1997; Passik et al, 2000)

## Opioid Agreements

- One provider writes Rx
- One pharmacy dispenses medication
- No dose escalation w/o input of practitioner
- No early refills
- Limited or no access to prn meds for chronic pain
- Consent to random urine and/or serum screens
- Appropriate behavior to all professional staff
- Consequences will follow if contract is broken:
  - 1 warning (depending on behavior)
  - (+) for cannabinoids or heroin vs hydromorphone
  - Change of medication (no opioid or alternative opioid)

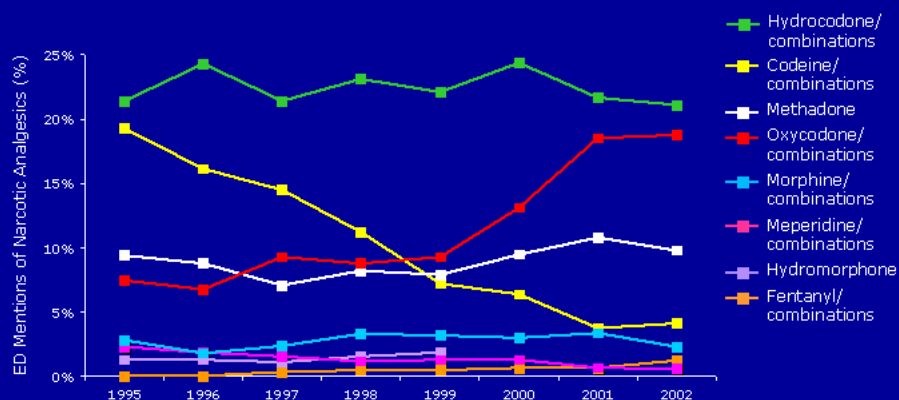
## Drug Abuse Warning Network (DAWN): Drug Diversion and Increasing Abuse

- Pain management practice may be at risk for attracting substance abusers, doctor shoppers, prescription forgers, and patient-dealers
- DAWN mentions of narcotic analgesics have doubled in the past 5 years:<sup>1</sup>



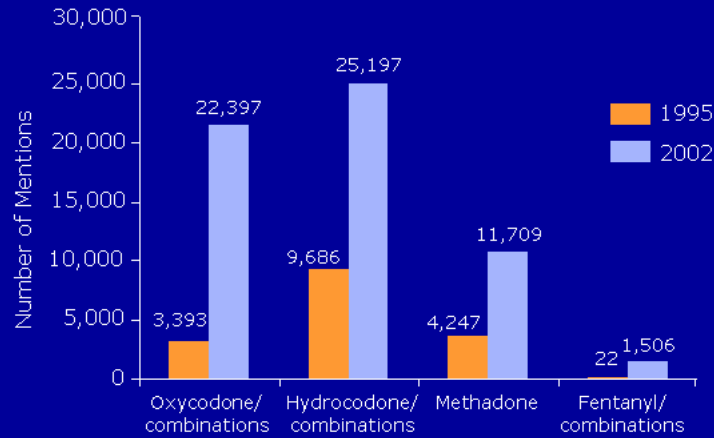
1. US Dept. of Health & Human Services/SAMHSA/OAS: Emergency Department Trends From the Drug Abuse Warning Network, 1995-2002, Table 2.8.0, Pub. D-24, July 2003.

## Percentage by Drug of Emergency Department Mentions of Narcotic Analgesics/Combinations in DAWN, by Year



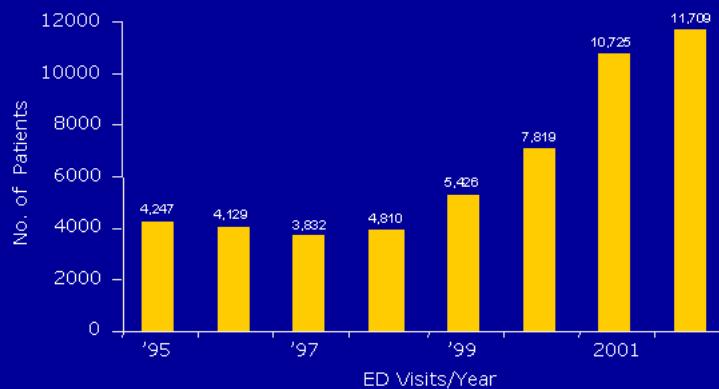
Source: Values derived from *Emergency Department Trends From the Drug Abuse Warning Network, Final Estimates 1995-2002*, DAWN Series D-24, DHHS Pub. No. SMA 03-3780, Rockville, Md, 2003.

## DAWN Emergency Department Trends 1995-2002



US Dept. of Health & Human Services/SAMHSA/OAS: Emergency Department Trends From the Drug Abuse Warning Network, 1995-2002, Table 2.8.0, Pub. D-24, July 2003.

## Methadone-Related ED Visits: Trend



- The number of methadone-related emergency room visits in the country has jumped in recent years

US Dept. of Health & Human Services/SAMHSA/OAS: Emergency Department Trends From the Drug Abuse Warning Network, 1995-2002, Table 2.8.0, Pub. D-24, July 2003.

## Internet Search for "Clean Urine"

1. **You're Clean** Provides drug testing and detox products designed to help people prepare for and pass a urine or hair drug test. Find out about the company's guarantee.  
[www.youreclean.com](http://www.youreclean.com)
2. **pass a drug test urine** Drug testing products and information to help you pass urine and hair follicle drug test.  
[www.clearatest.com](http://www.clearatest.com)  
or hair - **ClearTest**
3. **You're Clean** Drug testing, Drug test, Pass a urine drug test, pass a hair drug test, Info for helping people pass the urine drug test & hair drug test. Protect your rights. Don't be a victim of drug testing. Use our proven drug  
[www.youreclean.com/index2facts.html](http://www.youreclean.com/index2facts.html): **drug testing solutions Pass a urine drug test & hair test**
4. **pass a drug test Be Negative pass testing Clean** pass a drug test. "BeNegative.Com" Drug Testing Solutions "Be Negative" can provide you with products to help you pass a drug test. You can pass a hair follicle drug test, blood or urine test. We carry detox products and hair cleaners at low prices.  
[www.benegative.com](http://www.benegative.com)
5. **Terminader Gold 60 Clean Detox Urine Drug Testing** terminader gold 60 clean detox urine testing drink  
[www.webspawner.com/users/Terminader](http://www.webspawner.com/users/Terminader)
6. **anti drug testing products - for urine and hair follicle drug tests** Drug testing products and information to help you pass hair follicle and urine drug tests.  
[www.clearatest.com/products](http://www.clearatest.com/products)
7. **Drug Testing Marijuana - Self Test Drug Kits** Unbiased providers of drug and alcohol self / home test kits for people who want to test themselves for marijuana and other drugs.  
[www.drugtestingmarijuana.com](http://www.drugtestingmarijuana.com)
8. **Always Test Clean** Sells capsules, drinks, and shampoos designed to remove the toxins that cause positive results on urine, hair, or blood drug tests. Find out how each product works.  
[www.alwaystestclean.com](http://www.alwaystestclean.com)
9. **Passing a drug test. Pass a drug test.** Pass a drug test. Passing a drug test. Products to help you pass a drug test. Marijuana, cocaine, drug test, Pass meth drug test. False positive amphetamine drug testing information. Passing drug testing. Ways to pass a drug test. Passing a drug test  
[www.passdrugtesting.com](http://www.passdrugtesting.com)
10. **Hair Drug Testing, Urine Drug Testing, Pass Your Drug Testing has many resources to help; drug testing, pass a drug test.** Hair Drug Testing, Urine Drug Testing hair drug testing, urine drug testing Hair Drug Testing, Urine Drug Testing.  
[www.passyourdrugtesting.com/hair-drug-testing-urine-drug-testing.htm](http://www.passyourdrugtesting.com/hair-drug-testing-urine-drug-testing.htm)
11. **passing urine drug testing, pass a drug test.** [www.PassDrugTesting.com](http://www.PassDrugTesting.com) DRUG TEST ? Pass any drug test. Pass urine drug testing. Pass saliva drug test. Pass hair drug testing. Pass blood drug testing. All products formulated for high toxin levels. We also have drug test kits.  
[www.passdrugtesting.com/urine\\_drug\\_test.html](http://www.passdrugtesting.com/urine_drug_test.html)
12. **Drug Testing Products - Marijuana Information - Home Test Kits** Drug testing kits, products and

[www.passdrugtest.com/blood\\_drug\\_test\\_information..html](http://www.passdrugtest.com/blood_drug_test_information..html)



[www.PassDrugTest.com](http://www.PassDrugTest.com)

Help to pass a drug test. Pass urine drug test. Pass blood drug test. Pass saliva drug test. Pass hair drug test. We also have do it yourself drug test kits. For drug test information and list of toxins that cause false positive see Drug Test Q&A button lower left.

Order Today Receive Shipment Tomorrow.

Toll Free 1-877-345-5555

**Carbo Cleansing Shake**

Pass Urine Drug Test.  
Pass Blood Drug Test.  
Pass Saliva Drug Test.

<http://www.csun.edu/~hbcsc096/dt/ftbc.html/node114.html>

## Where to Get Clean Urine

- Urine From A Donor
- Powdered Urine
- Making Your Own Powdered Urine
- Dog Urine

I heard from Dr. Grow that dog urine (of all things) can be substituted, and will pass the test! However, I don't know how age, gender, pH, or creatinine test would result. Someone was able to use dog urine for several months to pass the test. This subsection assumes you have a clean dog. I know my dog's urine wouldn't pass; he eats more weed than humans do. It would make more sense to use human urine, but dog urine provides a workable substitution in an emergency.

<http://www.csun.edu/~hbcsc096/dt/ftbc.html/node114.html>

## Chemical Adulterants

HOUSEHOLD PRODUCTS	
Adulterant	Drug Test Affected
Chlorine Bleach	Marijuana, Morphine, Amphetamine
Liquid Drain Cleaner	Morphine, Amphetamine
Vinegar	Amphetamine
PROMOTIONAL PRODUCTS	
Adulterant	Drug Test Affected
Pyridinium Chlorochromate (PCC)	Amphetamine, Cocaine, Morphine Marijuana, Phencyclidine
UR'n Kleen	All of the above except Amphetamine
Instant Clean and Stealth	Marijuana, Phencyclidine, Cocaine

American Clinical Laboratory, 21(1):37-39, 2002. Slide adopted from Virginia L. Ghafoor, Pharm.D. as presented at 2004 Annual ACCP Meeting, Dallas TX.

## Appropriate Interpretation of Urine Drug Screens

- TEST RESULTS
  - False negative
    - Assess patient current opioid dose
      - Amount and type of opioid
      - As needed dosing
    - Inquire about quantitative data
  - False positive
    - What opioid is patient taking?
      - Synthetic opioid
      - Metabolites present
    - Additional as needed doses vs. no BT meds

Katz N, Fanciullo GJ. Clinical Journal of Pain. July/August;18(4):s76-s82, 2002.

"Blood and urine testing for opioids." Cpmision.com. Ed. Brian Fisher MD. 6 Mar 2005. <<http://www.cpmision.com/main/Fblood.html>.

### The Clean Whiz Kit (<http://www.cleanwhiz.com/cleankit.html>)

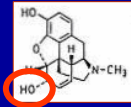
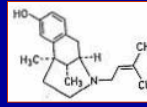
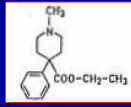
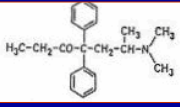


## Sample Urine Drug Screen Cutoff Levels

Screen	Cutoff (ng/mL)
Amphetamine	1000
Barbiturate	200
Benzodiazepine	200
Cocaine	300
<b>Opiates</b>	<b>2000 / 300 (Lab Dependent)</b>
Cannabinoids	50
Methadone	300
PCP (phencyclidine)	25

Example: Beckman Synchron CX5CE at Memphis VAMC.

## Chemical Classes of Opioids

	PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES
Rx EXAMPLES >	 MORPHINE morphine codeine hydrocodone* hydromorphone* levorphanol* oxycodone* oxymorphone* buprenorphine* nalbuphine butorphanol* naloxone* heroin (diacetyl-morphine)	 PENTAZOCINE <del>pentazocine</del> <del>diphenoxylate</del> <del>loperamide</del>	 MEPERIDINE <b>meperidine</b> <del>fentanyl</del> <del>sufentanil</del> <del>alfentanil</del> <del>remifentanyl</del>	 METHADONE <del>methadone</del> <del>propoxyphene</del>
X-SENSITIVITY >	PROBABLE	POSSIBLE	LOW RISK	LOW RISK

\*\*\*Opana(R) ER (oxymorphone HCl) and Opana(R) (oxymorphone HCl) Immediate Release Tablets CII

\*These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.  
 Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York, NY: McGraw-Hill Companies; 1996:521-555.  
 Willette RE. Analgesic Agents. In: Delgado JN, Remers WA, eds. *Wilson and Grisvold's Textbook of Organic Medicinal Chemistry*. 9th ed. JB Lippincott Company, Philadelphia, Pa. 1991:629-654.

## Interpreting Urine Screens: Clinical Examples (cont'd)

Patient on fentanyl transdermal System and urine screen is negative.

What does it mean?

- A. Pt is not likely to be using the patch.
- B. Pt is on too low of a dose.
- C. Something went wrong with the lab test.
- D. Most phenylpiperidines are not included in urine toxicology screens.

## OXYCODONE-1

*Calculating Patient's Ingested Dose based on Serum Levels*

- Dose proportionality and/or bioavailability has been well established for 10mg, 20mg, 40mg, 80mg, and 160mg tablets strengths for both peak plasma levels (C<sub>max</sub>) and extent of absorption (area under the curve).
- At a dose of 10mg sustained release oxycodone PO q12h, the mean maximum serum concentrations (+/- SD) for sustained release oxycodone has been reported as 15.1 +/- 4.7 ng/mL.
  - (We can expect 90% confidence levels with these numbers (Reder RF, Oshlack B, Miotto JB, Benziger DD, Kaiko RF)

## Urine versus Serum Oxycodone

- Serum GC oxycodone levels are accurate and can be predicted if we know the approximate time of last dose.
- Urine oxycodone levels MAY NOT be as RELIABLE as other opiate phenanthrenes, particularly at low doses. This is wholly dependent on laboratory test methods and availability of CONFIRMATION!

## Patient Case

- LK is a chronic back pain patient followed by a Primary Care Clinic.
- His chronic opioid therapy includes:
  - OxyContin 80mg PO q12h
  - OxyContin 20mg PO q8h
  - Oxycodone (immediate release) 10mg PO q4h.  
Pt uses #240 per month
- 07-16-04, urine screen for opiates is negative. Clinical Pharmacist is consulted.

## Laboratory interpretation

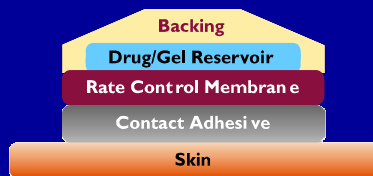
- Measured urine qualitative report yields a value of 438ng/mL and is therefore reported by Lab Service as NEGATIVE.
- F/U serum is ordered and pt is given a short timeline to report to the clinic to provide serum sample
- 07-19-04, serum oxycodone is reported as 19ng/mL

## Patient Case Conclusion

- Patient is taking no more than 30mg of immediate release oxycodone per day
- Street value of the medication balance:
  - \$10,000-12,000 per month!

## All Chronic Pain Patches Are Not Created Equal\*

Reservoir Transdermal Fentanyl Delivery System



Matrix Delivery System



\*No conclusions regarding comparative safety or efficacy can be drawn from this comparison.

## Elements of Success

Structure initial analgesic regimen based on risk

- Conduct ongoing assessment of behavior
- Educate the patient about responsible use of opioids and expected side effects
- Counsel patient on risks of driving
- Recommend appropriate laxatives for prophylaxis

(Portenoy, 1997; Passik, 1998)

## The FSMB Model Guidelines

1. Patient evaluation
2. Treatment plan
3. Informed consent and agreement for treatment
4. Periodic review
5. Consultation
6. Medical records
7. Compliance with the controlled substances laws and regulations  
(FSMB of US, 1998)

## Monitoring Recommendations

- **General considerations**
  - Patients sign an Controlled Substance agreement
  - Advised patient of risk of addiction, tolerance, etc.
  - Classify patients by potential for aberrant medication misuse
    - **High Risk**
      - Urine appropriate screens at frequent office visits
      - Use less abusable formulations
        - » Long-acting, transdermal
    - **Medium Risk**
      - Random urine opioid screens
      - Reduce frequency of visits
    - **Low risk**
      - Monitor less frequently

## Conclusions-1

- Chronic pain is common and under-treated
- Identify chronic pain patients who would most likely benefit from opioid therapy and use it responsibly
- Implement opioid treatment with a plan for ongoing monitoring
- Assess and monitor pain, side effects, and drug-related behaviors
- Prospectively choose opioid therapies commensurate with potential diversion risk
- Adjust dosage
- Manage side effects

## Conclusions-2

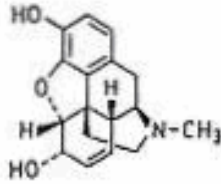
- Need to monitor patients using opioids
  - Medical, Legal
- Monitor patients appropriately for opiate use
  - Urine screen as a preliminary indicator
    - Follow-up urine drug screen with GC/MASS
  - Serum opioid levels allow dose correlation/predictability
    - More expensive, more invasive, more time consuming
    - Correlate patient specific values with known pharmacokinetic data
- React appropriately to lab results
  - Do not jump to conclusions
  - Investigate appropriately with appropriate lab tests

# Questions

[www.paindr.com](http://www.paindr.com)

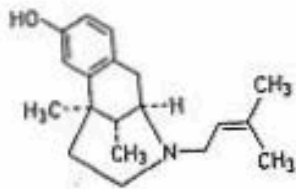
## Chemical Classes of Opioids

### PHENANTHRENES



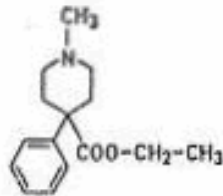
#### MORPHINE

### BENZOMORPHANS



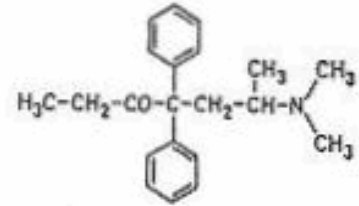
#### PENTAZOCINE

### PHENYLPYPERIDINES



#### MEPERIDINE

### DIPHENYLHEPTANES



#### METHADONE

Rx EXAMPLES >

morphine  
codeine  
hydrocodone\*  
hydromorphone\*  
levorphanol\*  
oxycodone\*  
oxymorphone\*  
buprenorphine\*  
nalbuphine  
butorphanol\*  
naloxone\*  
heroin (diacetyl-morphine)

pentazocine  
diphenoxylate  
loperamide

meperidine  
fentanyl  
sufentanil  
alfentanil  
remifentanil

methadone  
propoxyphene

X-SENSATIVITY >

PROBABLE

POSSIBLE

LOW RISK

LOW RISK

\*These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.

Courtesy of Dr. Jeffrey Fudin

#### References:

Reisine T, Pasternak G. Opioid analgesics and antagonists. In Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9<sup>th</sup> ed. New York, NY: McGraw-Hill Companies; 1996:521-555.

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**Drug Abuse Warning Network - DAWN - Publications** Drug Abuse Warning Network (DAWN) The Drug Abuse Warning Network (DAWN) is an ongoing drug abuse data collection system sponsored by SAMHSA's Office of Applied Studies. [www.samhsa.gov/oas/dawn.htm](http://www.samhsa.gov/oas/dawn.htm), <http://www.samhsa.gov/oas/dawn.htm>

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Fudin J, Levasseur DJ, Passik SD, Kirsh KL, Coleman J. Chronic pain management with opioids in patients with past or current substance abuse problems. Journal of Pharmacy Practice. 2003, 16;4:291-308.

Passik SD, Schreiber J, Kirsh KL, Portenoy RK. A chart review of the ordering and documentation of urine toxicology screens in a cancer center: do they influence patient management? J Pain Symptom Manage 2000 Jan;19(1):40-4. Oncology Symptom Control Research, Community Cancer Care Inc., Indianapolis, IN 46202, USA.

Spanbauer AC, Casseday S, Davoudzadeh D, Preston KL, Huestis MA. Detection of opiate use in a methadone maintenance treatment population with the CEDIA 6-acetylmorphine and CEDIA DAU opiate assays..IRP, NIDA, J Anal Toxicol 2001 Oct;25(7):515-9 NIH, Baltimore, Maryland 21224, USA.

## Pre/Post Test Questions for Urine Tox Screens

TOLERANCE is:

a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. To achieve the same therapeutic effect of a medication as previous, a higher dose is now needed.  
is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.  
A drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.  
None of the above.

Consider the following statements, and choose correct one:

Chronic pain may be pharmacologically and therapeutically treated identical to acute pain.

Chronic pain medications should be dosed in an “around-the-clock” fashion.

Opiate addiction is always present with chronic narcotic use, and therefore opiates should only be used as a last resort, especially morphine.

All of the above

3. A patient on sustained release oxycodone and urine screen is negative. What does it mean?

Pt is not likely to be taking the full dose.

Pt is likely to be diverting the drug.

Pt may be taking the dose prescribed.

a and b above are true

4. Patient on methadone and urine screen is positive. What does it mean?

a. This is what we would expect.

b. Pt could be selling methadone and using ONLY propoxyphene instead.

c. Pt could be selling methadone and using heroin.

None of the above

5. A patient is prescribed Oxycodone Sustained Release 10mg PO q12h. the expected serum concentration 3.2 hours after a dose is approximately...

89.3 ng/mL +/- 9.4

15.1 ng/mL +/- 4.7

32.6 ng/mL +/- 4.7

None of the above.

Answers:

A

B

C

C

B

## Opioid Metabolites

### OXYCODONE<sup>1,2,3,24</sup>

Noroxycodone, Oxymorphone, Oxycodyl

### MORPHINE<sup>4,5,6,24,25</sup>

Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, Codeine, 7,8-dihydromorphinone

### FENTANYL<sup>7,8,9,24</sup>

Norfentanyl, 4-N-(N-propionylanilino) piperidine, 4-N-(N-hydroxypropionylanilino) piperidine, 1-(2-phenethyl)-4-N-(N-hydroxypropionylanilino) piperidine

### HYDROMORPHONE<sup>10,11,12,24</sup>

Hydromorphone-3-glucuronide, Hydromorphone-3-glucoside, Dihydroisomorphine-6-glucuronide, Dihydroisomorphine-6-glucoside, Dihydroisomorphine, \*Dihydromorphine

### CODEINE<sup>13,14,24</sup>

Morphine, Norcodeine, Normorphine, Hydrocodone, Codeine 6-glucuronide

### HYDROCODONE<sup>15,16,17,24</sup>

Hydromorphone, Norcodeine, 6-beta-hydrocodol, 6-alpha-hydrocodol, 6-beta-hydromorphol, 6-alpha-hydromorphol

### METHADONE<sup>18,19,20,24</sup>

EDDP (2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium), EMDP (2-ethyl-5-methyl-3,3-diphenylpyraline)

### HEROIN<sup>21,22,23,24</sup>

6-acetylmorphine, Morphine, Morphine-3-glucuronide, Normorphine, 6-acetylmorphine 3-glucuronide, Normorphine glucuronide

\*hydromorphone is 7,8-dihydromorphinone: Please note that morphine metabolism to hydromorphone has been confirmed in 8 mammals other than humans. New data in humans is pending publication.

Revised from Fudin J. Opioid Pharmacokinetics and Expected Metabolites. Available at <http://www.paindr.com/06-2005%20Opioid%20Metabolite%20Chart.pdf>. Last Accessed August 14, 2006.

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## Opioid Pharmacokinetics and Expected Metabolites (Updated 06-2005)

Data collected, collated, and organized by Jason Palmer, Pharm.D. Candidate / Revised, reviewed, & reformatted by Jeffrey Fudin, R.Ph., BS, Pharm.D., DAAPM

DRUG	Half-Life (Hrs <sup>A</sup> )	Time to Steady State (Hrs <sup>A</sup> )	Metabolites	Time to Peak Conc. (Hrs <sup>A</sup> )	Serum Predictability	Sample Time After Dose (Hrs <sup>A</sup> )	24 Hour Dose vs. Expected Serum Conc. (ng/mL)
OXYCODONE <sup>1,2,3,24</sup>	IR=3.2 CR=4.5-8	IR = 17.5 CR = 24-36	Noroxycodone, Oxymorphone, Oxycodol	IR = 1.6 CR = 2.1-3.2	Y	IR = 1.4 +/-0.7 CR = 3.2 +/-2.2	IR 20mg = 15.6 +/-4.4 CR 20mg = 15.1 +/-4.7
MORPHINE <sup>4,5,6,24,25</sup>	2-4	24	Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, Codeine, 7,8-dihydromorphinone	IR = 1 CR = 2-3	Y	IR = 1.0 CR = 4.4	IR 40mg = 11.1 +/-8.4 CR 100mg = 36.9 +/-15.5
TRANSDERMAL FENTANYL <sup>7,8,9,24</sup>	16-25	72	Norfentanyl, 4-N-(N-propionylanilino) piperidine, 4-N-(N-hydroxypropionylanilino) piperidine, 1-(2-phenethyl)-4-N-(N-hydroxypropionylanilino) piperidine	24-72	Y	25mcg/hr=38.1hrs 50mcg/hr=34.8hrs 75mcg/hr= 33.5hrs 100mcg/hr=36.8hrs	(600mcg = 0.6 +/-0.3) (1200mcg = 1.4 +/- 0.5) (1800mcg = 1.7 +/- 0.7) (2400mcg = 2.5 +/- 1.2) [XXXXmcg <sup>D</sup> ]
HYDROMORPHONE <sup>10,11,12,24</sup>	2.5	12.5	Hydromorphone-3-glucuronide, Hydromorphone-3-glucoside, Dihydroisomorphine-6-glucuronide, Dihydroisomorphine-6-glucoside, Dihydroisomorphine, Dihydromorphine <sup>E</sup>	48-60 min.	Y	IR = 1.47 CR = 4.78	IR 48 mg = 19.7 +/- 4.04 CR 48 mg = 17.76 +/- 3.07
CODEINE <sup>13,14,24</sup>	2.5-3.5	12.5-17.5	Morphine, Norcodeine, Normorphine, Hydrocodone, Codeine 6-glucuronide	1-2	Y	IR = 1.1	IR 180mg = 222.9 +/- 48.9
HYDROCODONE <sup>15,16,17,24</sup>	3.8-4.5	19-22.5	Hydromorphone, Norcodeine, 6-beta-hydrocodol, 6-alpha-hydrocodol, 6-beta-hydromorphol, 6-alpha-hydromorphol	1.3	?	N/A	N/A
METHADONE <sup>18,19,20,24</sup>	24	~5 days	EDDP (2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium), EMDP (2-ethyl-5-methyl-3,3-diphenylpyraline)	2-4	Y	SS blood draw @ 24 hr post-dose, before subsequent dose, & after initial dose.	Linear drug levels increase 260ng/mL for every 1mg/kg consumed
HEROIN <sup>21,22,23,24</sup>	~3 min.  1.7-5.3 min	~15 min.	6-acetylmorphine, Morphine, Morphine-3-glucuronide, Normorphine, 6-acetylmorphine 3-glucuronide, Normorphine glucuronide	10 minutes for I.M. dose <sup>B</sup>	Y	112mcg/min continuous infusion = 5min <sup>C</sup>	Heroin level = 57 ng/mL <sup>C</sup> 6-acetylmorphine level=15ng/mL <sup>C</sup>

IR = Immediate Release Products, CR = Continuous Release products, SS = Steady State

A-Hours, unless otherwise indicated

B-Can detect heroin and 6-acetyl morphine within 10-15 minutes of parenteral administration

C-Administered IV in a single patient over 180 minutes

D-Cummulative amount of fentanyl release from patch dose in 24 hours.

E-hydromorphone is 7,8-dihydromorphinone: Please note that morphine metabolism to hydromorphone has been confirmed in 8 mammals other than humans.

New data in humans is pending publication.

**Courtesy of Jeffrey Fudin, RPh, BS, PharmD, DAAPM and Jason Palmer, Pharm.D. Candidate.**

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