# *Focus on Methadone*

## Therapeutic, Safety & Pharmacokinetic Considerations


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# MedWatch Alert:

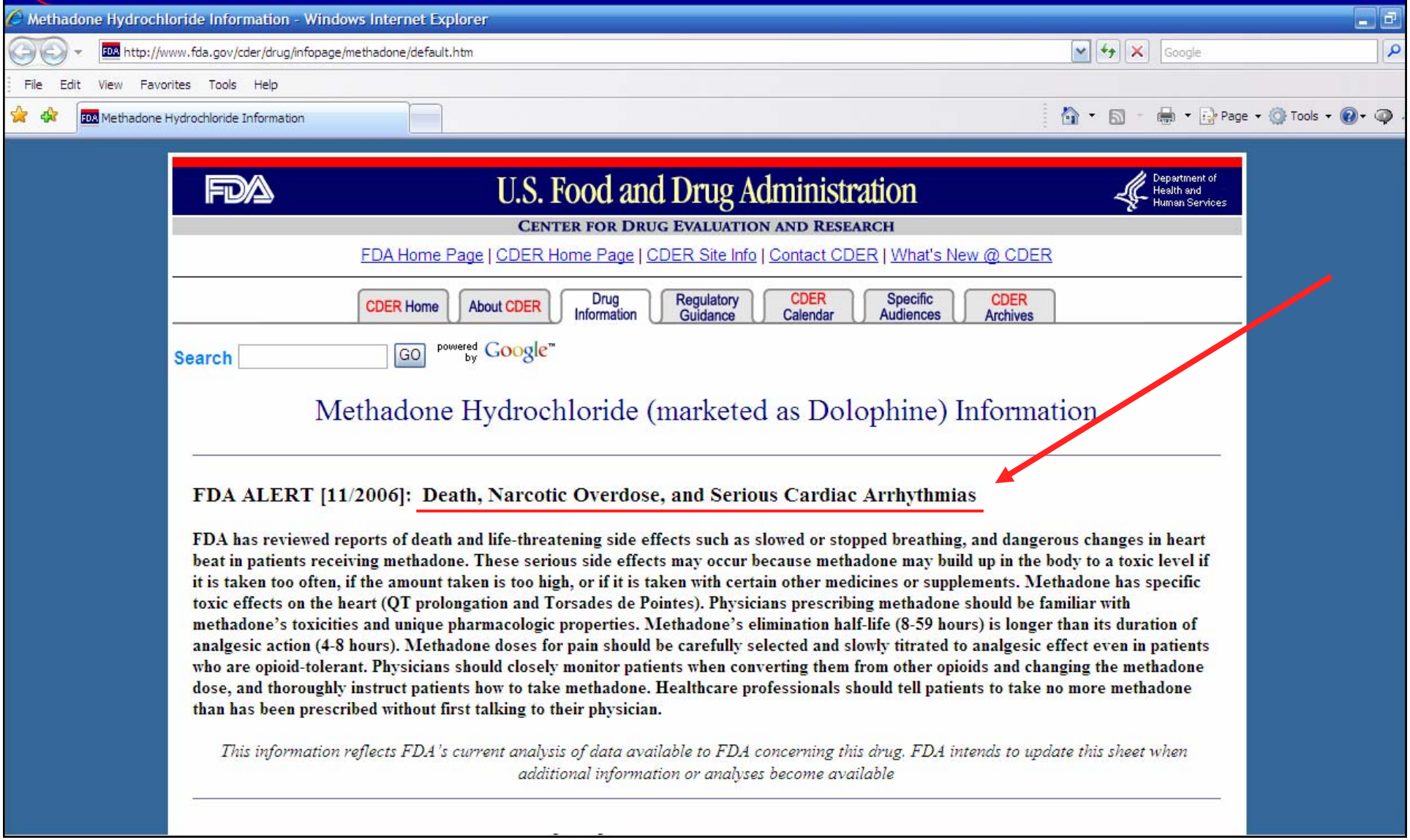
FDA Public Health Advisory
November 2006

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

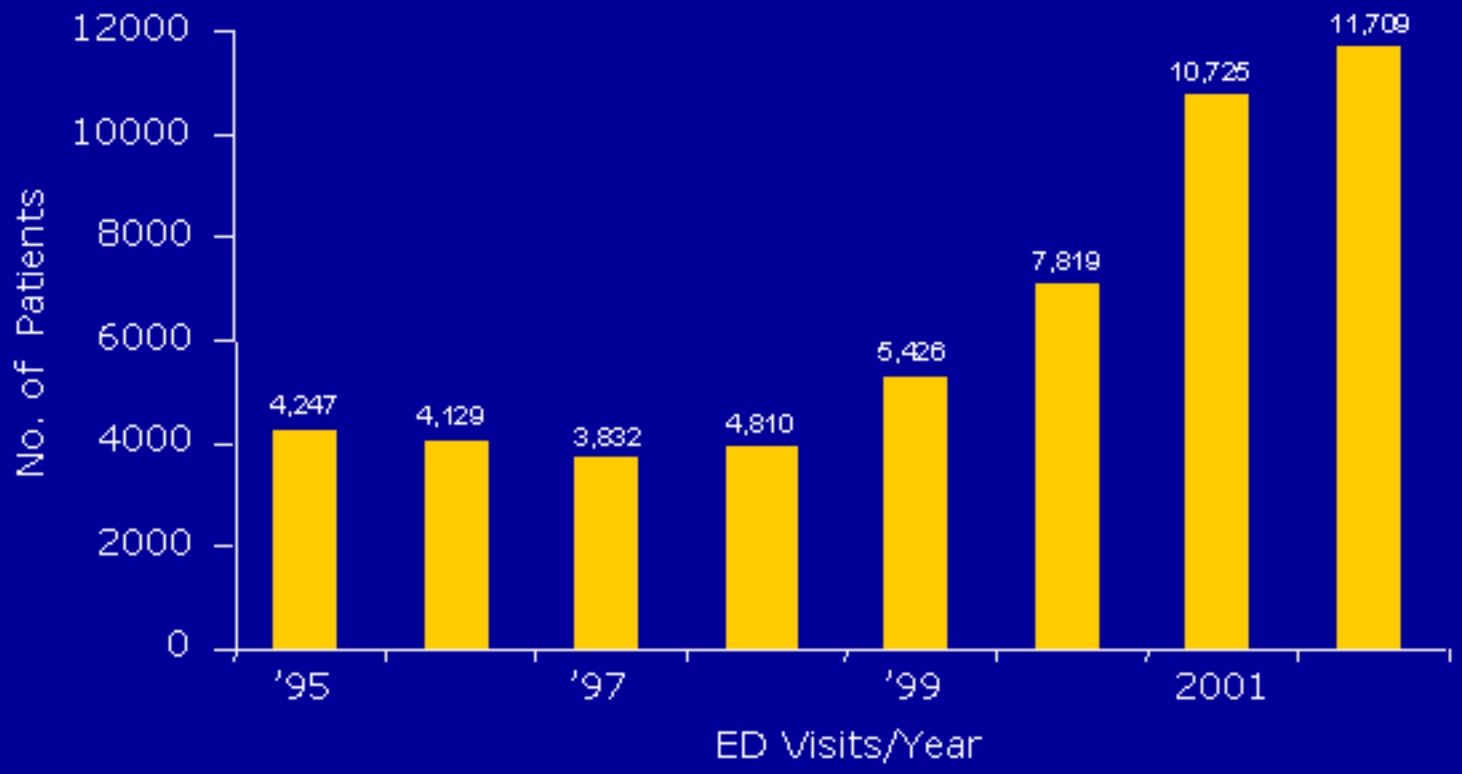
What prompted this warning?

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 Feburary 28, 2007.

# http://www.fda.gov/cder/drug/infopage/methadone/default.htm



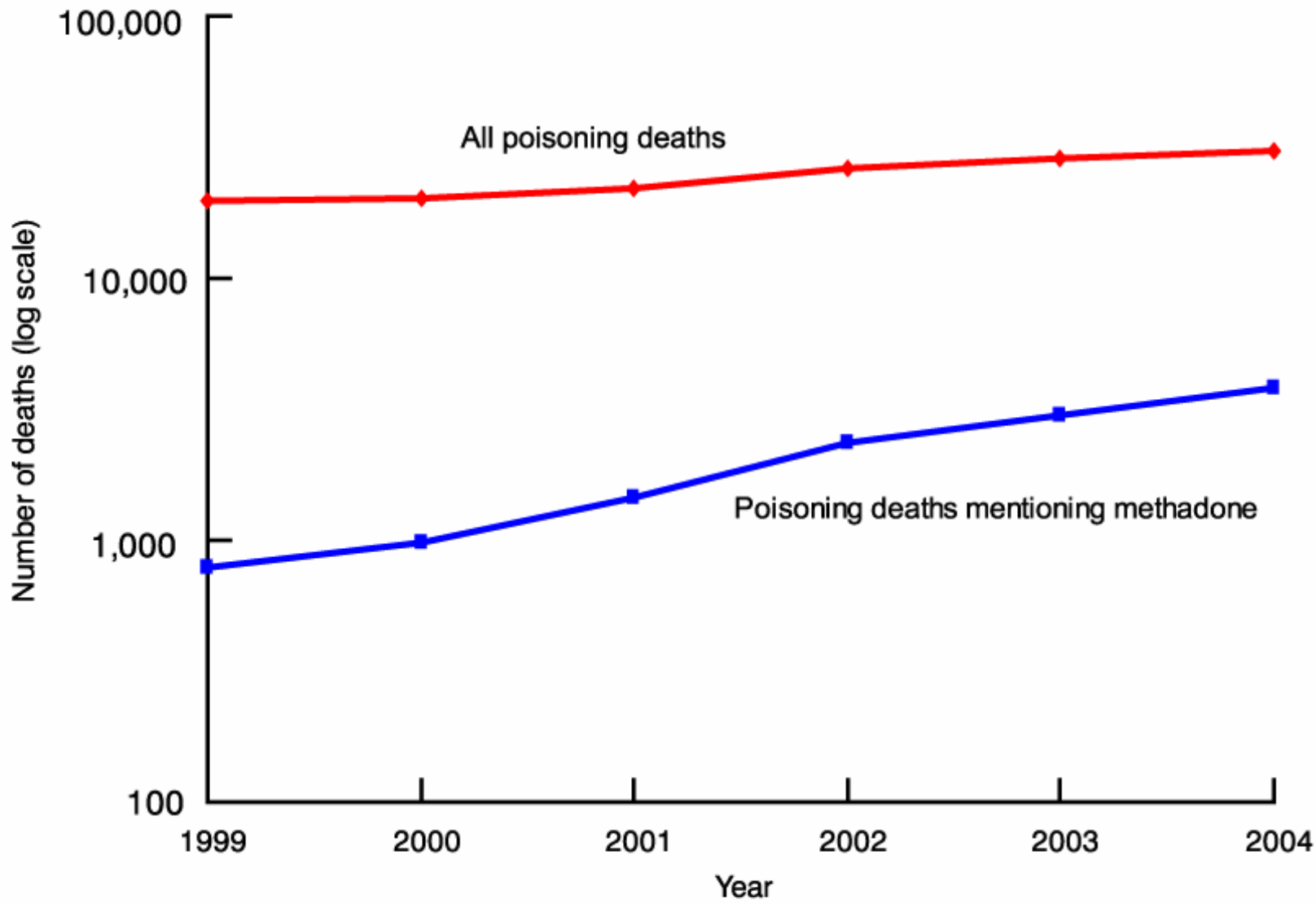
# Methadone-Related ED Visits: Trend




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

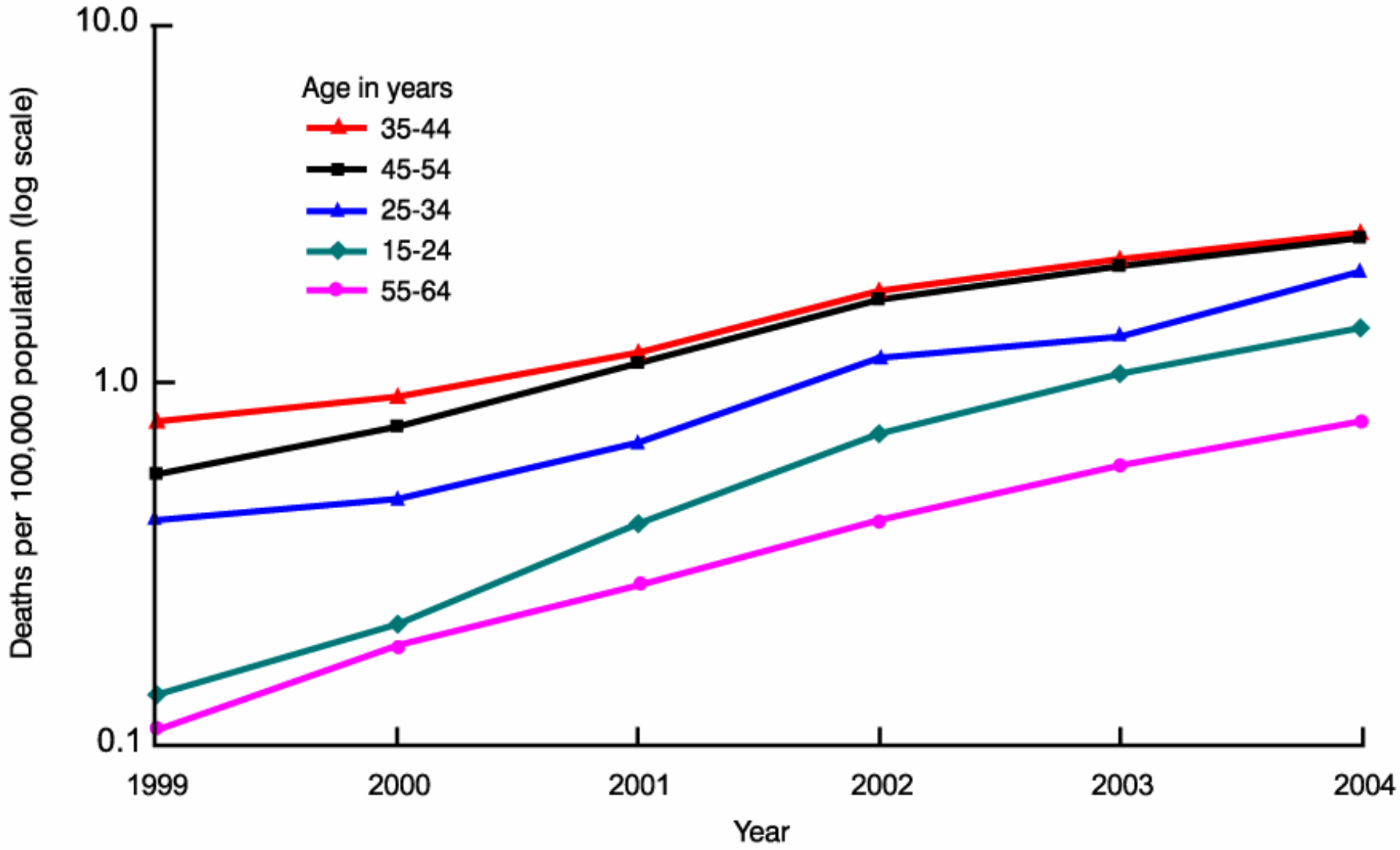
US Dept. of Health & Human Services/SAMHSA/OAS: Emergency Department Trends From the Drug Abuse Warning Network, 1995-2002, Table 2.8.0, Pub. D-24, July 2003.

# 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.

# Overview of Topics

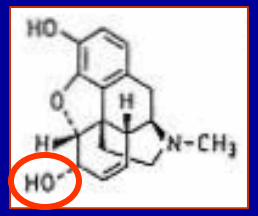
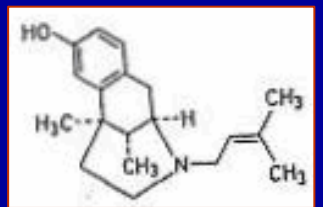
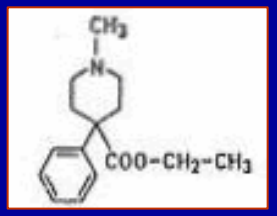
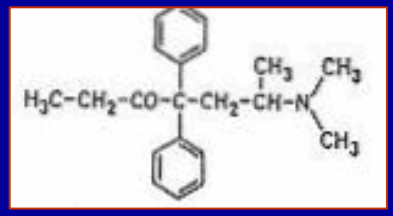
- Goals of Therapy
- Opioid/Opiate Pharmacotherapy
  - chemistry
  - Therapeutics
  - Advantages/disadvantages
- Methadone
- Special dosing considerations and precautions
- Unique pharmacokinetics
- Drug interactions

# Goals of Therapy for Acute Vs Chronic Pain

Levy, 1985

| | ACUTE | CHRONIC |
|---|---|---|
| Therapeutic Goal | Pain relief | Pain prevention |
| Sedation | Often desirable | Usually undesirable |
| Rapid Onset of Effect | Important | Unnecessary |
| Desired Duration of Effect | 2-4 hours | As long as possible |
| Timing | PRN | Regularly (anticipation) |
| Dose | Usually standard | Individually titrated |
| Route | Parenteral / Oral | Oral / Transdermal |
| Side Effect Profile | Minimize risk for constipation/respira-tory depression | Minimize risk for constipation/respir-atory depression |

# Chemical Classes of Opioids

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

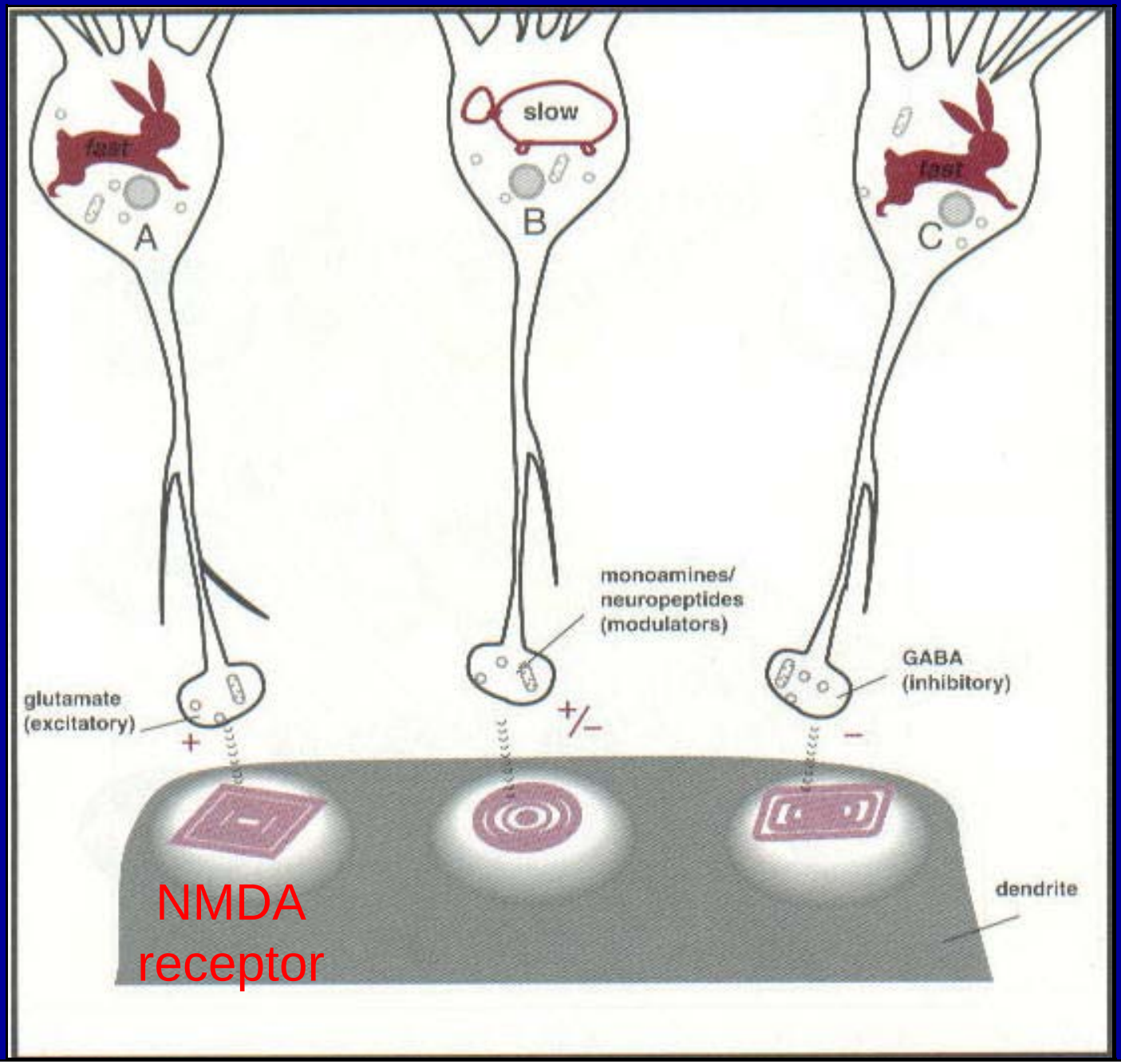
*These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.

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.

**Courtesy of Dr. J. Fudin 2003**

# Neurotransmitter Signals



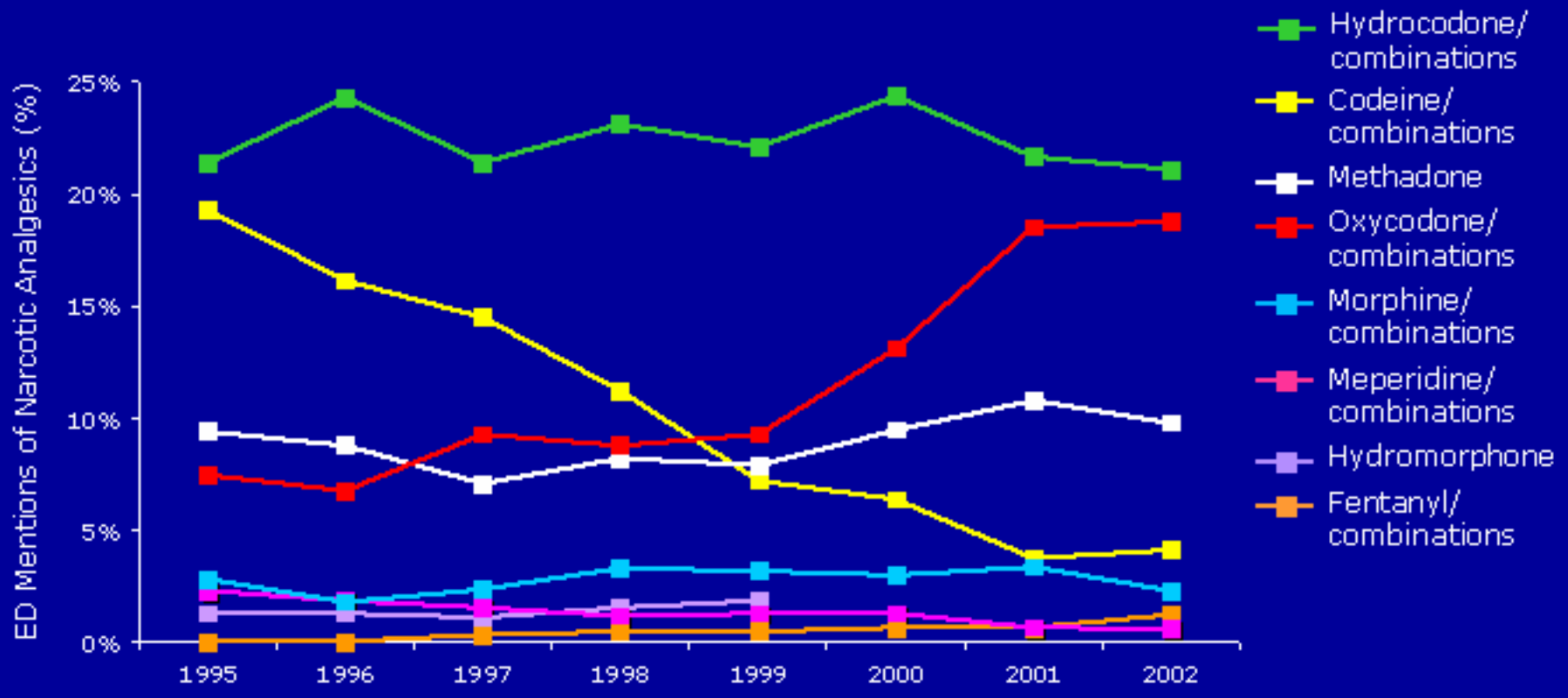

Stephen Stahl. Essentials of Psycho-pharmacology

# Analgesic Choices

*Executive Summary*

- Extended Release Products:
  - Fentanyl (Duragesic®)
  - Morphine-ER (Kadian®, MS Contin®, Oramorph SR® others)
  - 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

# 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.

# Metabolic Pathway from Drug Elimination

| DRUG | Opioid Class | Major Metabolic Pathway |
|---|---|---|
| Morphine | Phenanthrene (w/ -OH) | Glucuronidation |
| Hydromorphone | Phenanthrene | Glucuronidation |
| Codeine | Phenanthrene (w/ -OH) | Demthylation, glucuronidation |
| Levorphanol | Phenanthrene | Glucuronidation |
| Oxycodone | Phenanthrene | Demethylation, glucuronidation, keto-reduction |
| Oxymorphine | 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. Pharmacokinetc 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

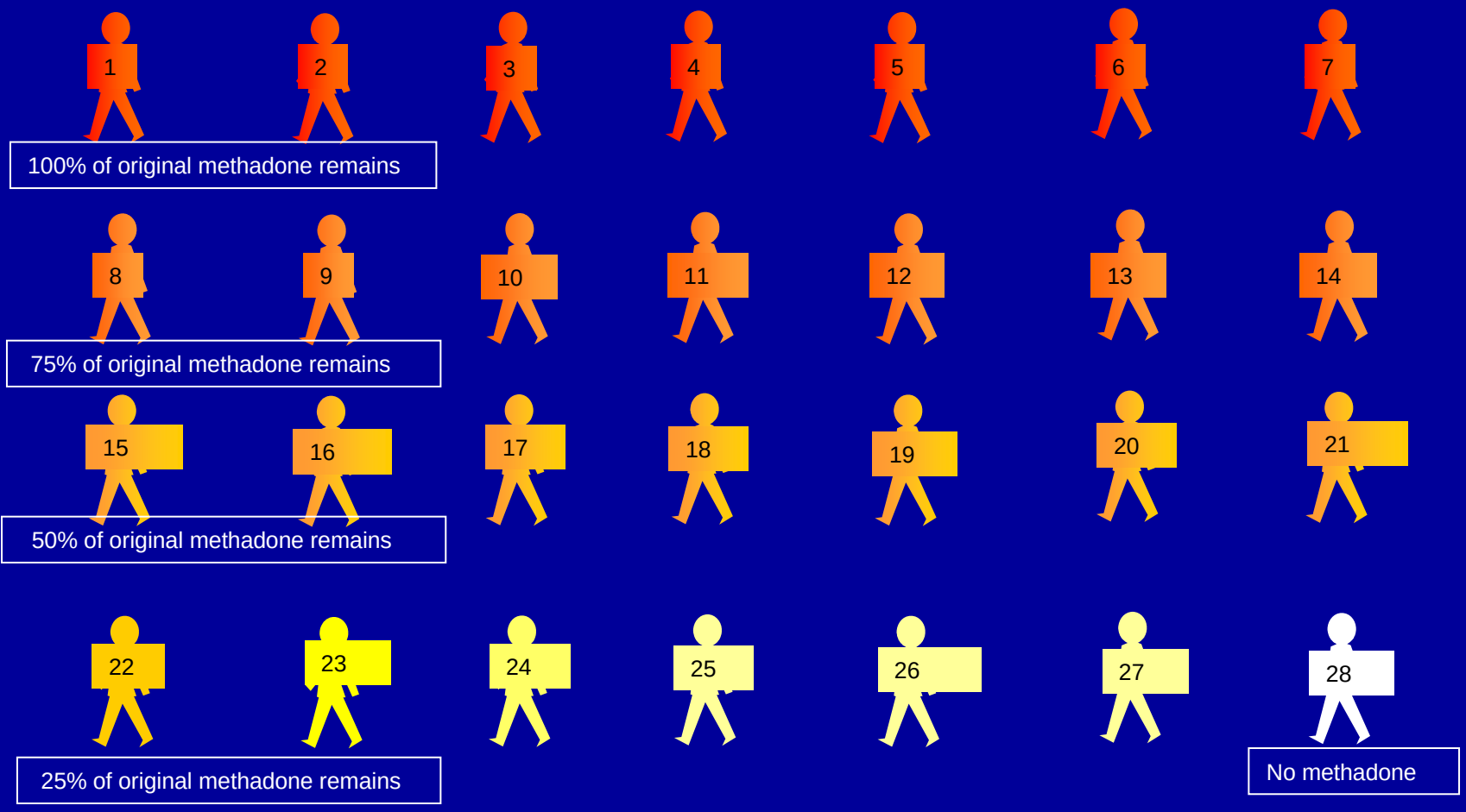
- Morphine (compare to oxycodone)
  - morphine-3-glucuronide (M3G)
    - no analgesic activity
  - morphine-6-glucuronide (M6G)
    - active metabolite eliminated by kidneys
- Meperidine
  - metabolized to nor-meperidine
  - nor-meperidine is renally cleared
    - ergo, Rx accumulation ⇒ CNS excitability ⇒ 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.[1]
- The morphine-to-methadone conversion ratio increases as the previous dose of morphine increases.[2]
- 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.[3]
- 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, AHCPR (1994); Cancer pain: a monograph on the management of cancer pain, Health & Welfare Canada (1984); Twycross (1990);Levy (1985).
2. The oal 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 ≠ 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

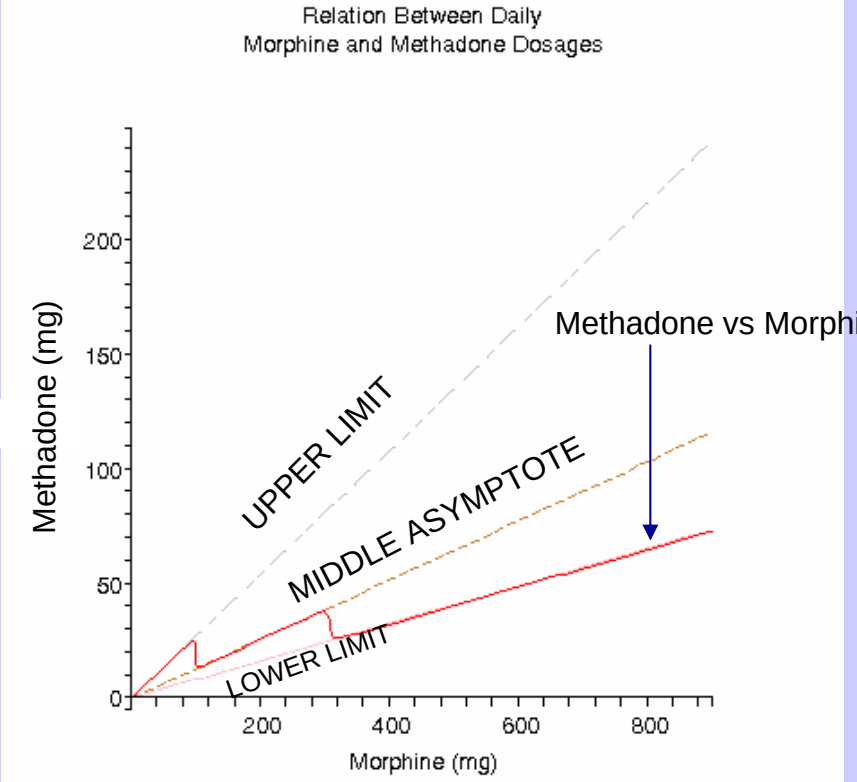
# "Fudin Factor"

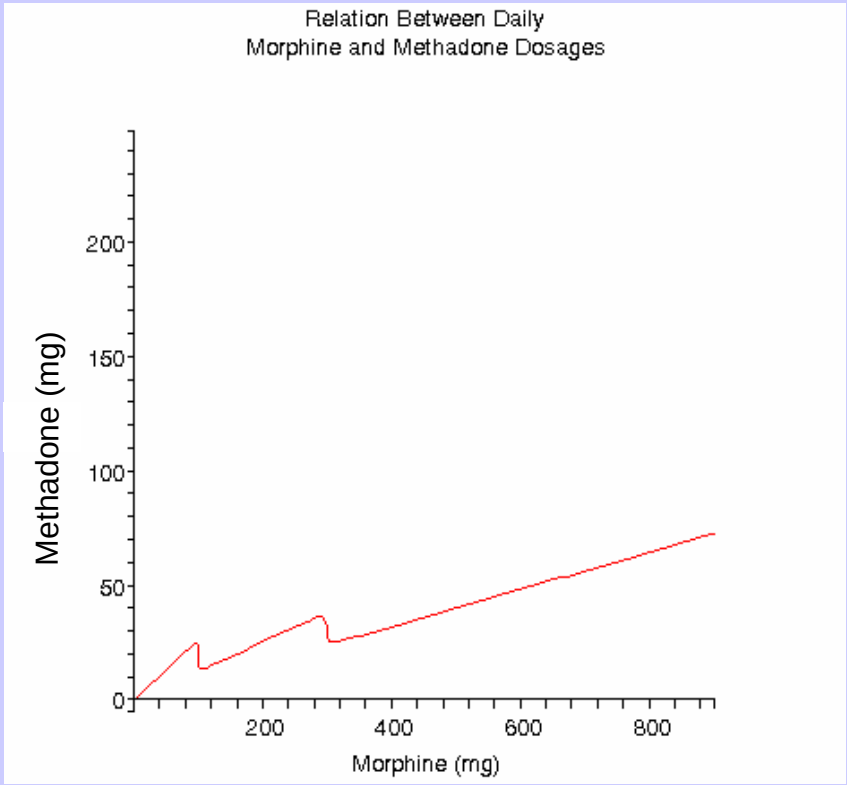
# A Methadone Conversion Formula

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**

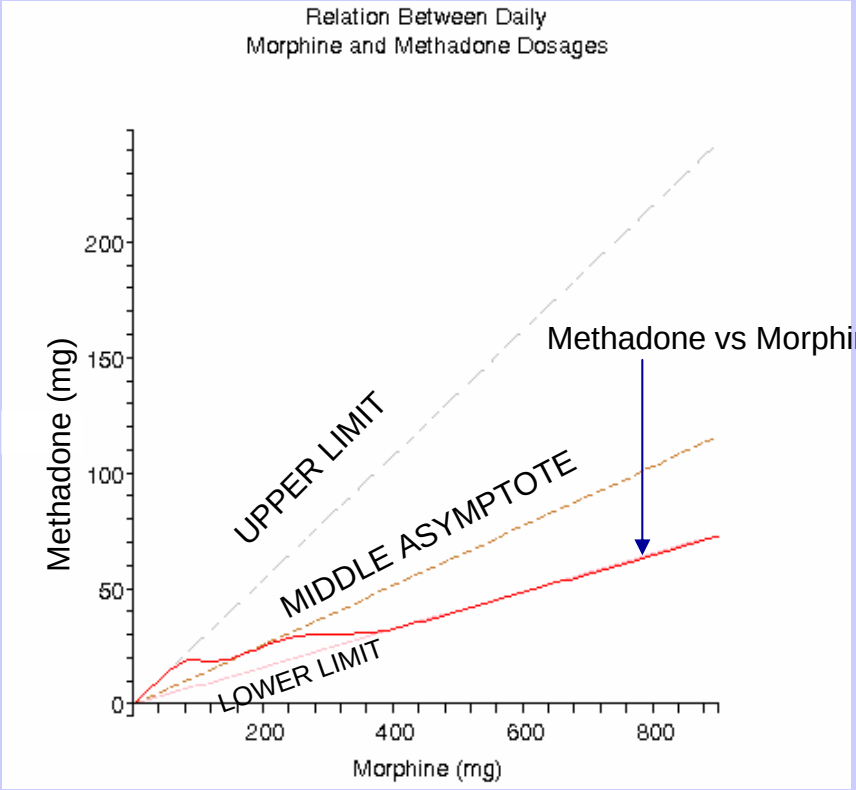
# "Fudin Factor"

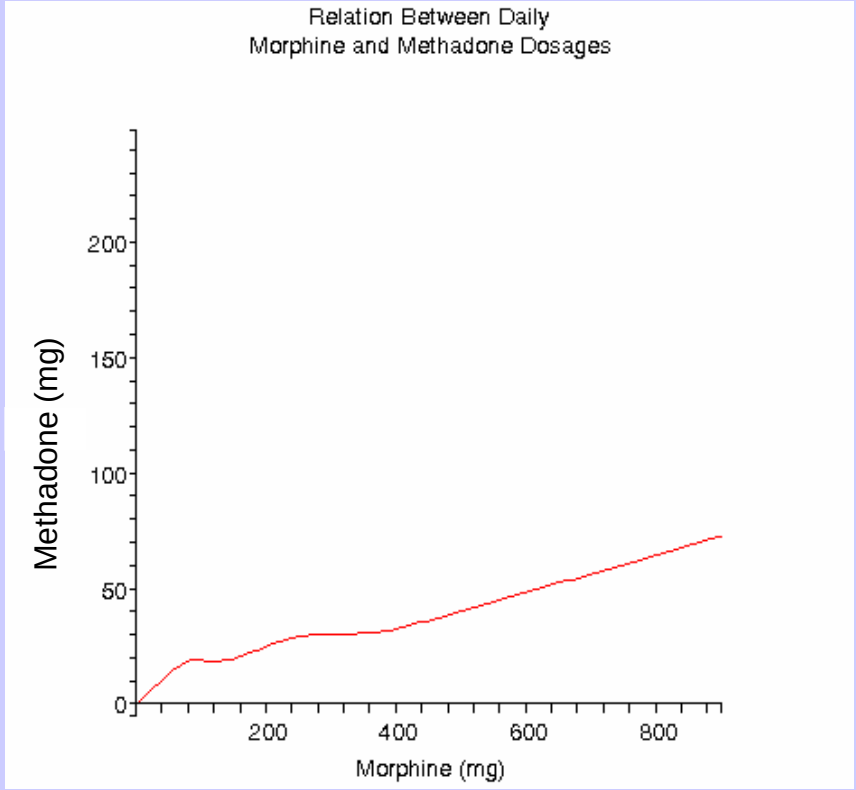
# A Methadone Conversion Formula

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

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

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.[1]
- Two prospective studies on methadone excluded patients with kidney and liver disease.[2,3]


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, Stravrakis 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.**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