OPIOIDS

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Rutgers – New Jersey Medical School
Fundamentals of Addiction Medicine Summer Series
Newark, NJ – July 24, 2013

Outline

1. The Opioid Family
2. Intoxication and Withdrawal
3. Epidemiology
4. Pharmacological Treatments
5. Treating CNCP
6. Conclusions

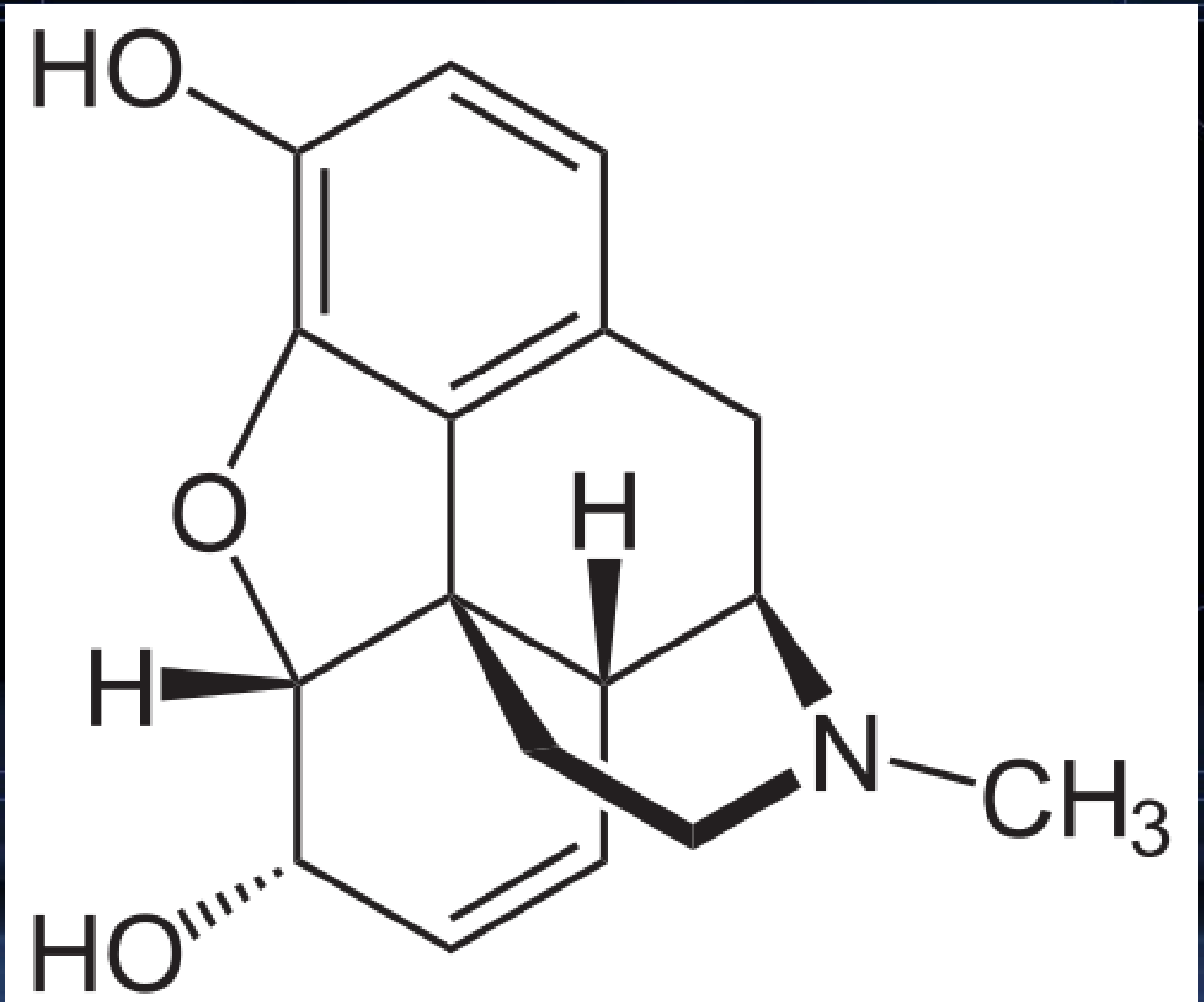
1

The Opioid Family

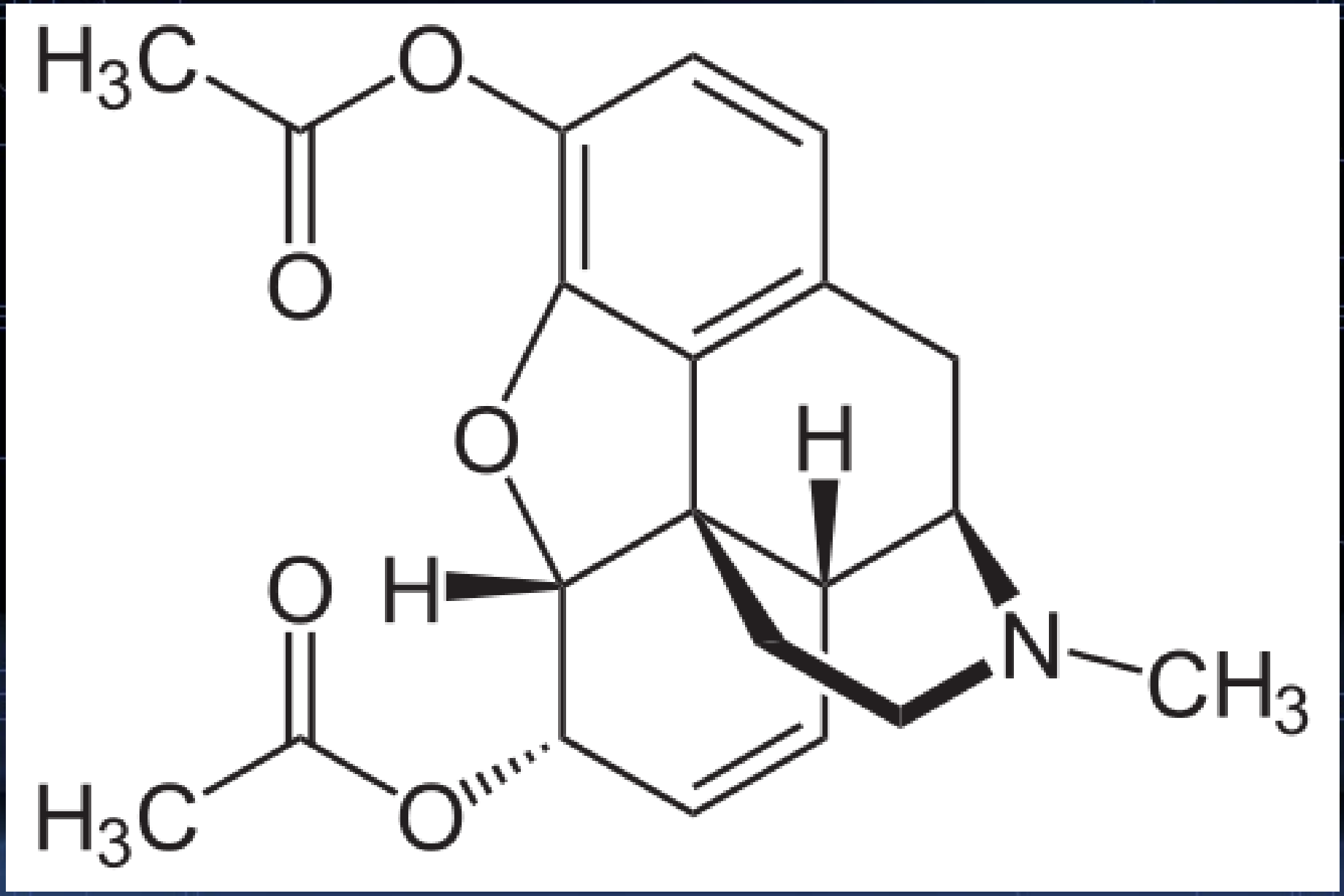
The Opium Poppy

Morphine circa 1887

Morphine



Di-Acetyl-Morphine (Heroin)



Types of Opioid Receptors

1. Mu
2. Kappa
3. Delta

Opioid Medications

1. Naturally Occurring Opioids
   - **Morphine**
   - **Codeine**
2. Semi-Synthetic Opioids
   - **Oxymorphone**
   - **Oxycodone**
   - **Hydromorphone**
   - **Hydrocodone**
3. Synthetic Opioids
   - **Fentanyl**
   - **(Tramadol)**
   - **Methadone**
   - **Buprenorphine**

Opioid Effects

1. Relief of physical pain
2. Relief of emotional pain
3. Euphoria
4. Decreased anxiety, calmness
5. Cough suppression

2

Intoxication and Withdrawal

Opioid Intoxication

1. Constricted pupils
2. Constipation
3. Nausea and vomiting (often projectile)
4. Respiratory depression
5. Coma and death

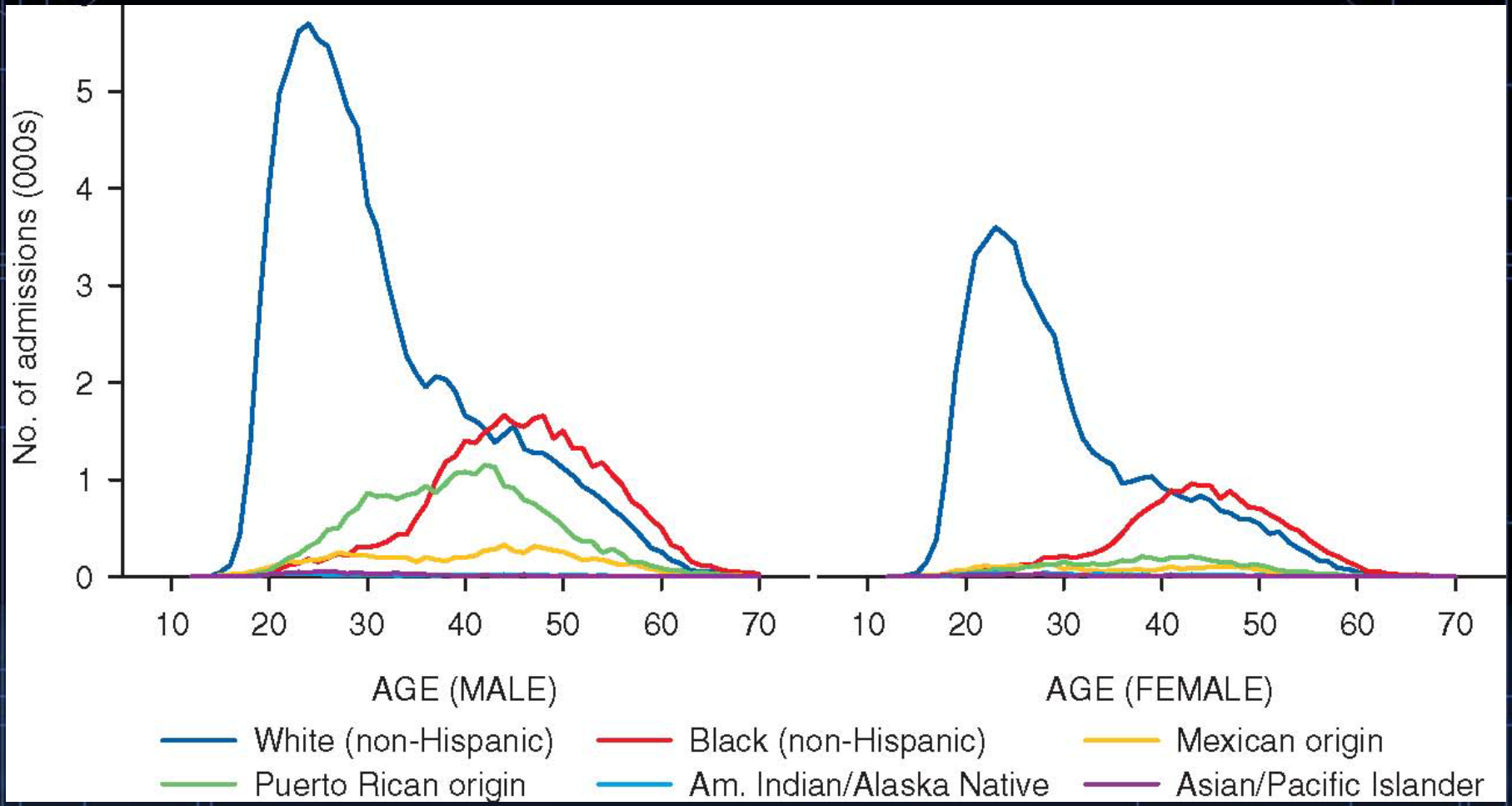
Opioid Withdrawal

1. Dilated pupils
2. Diarrhea
3. Flu-like symptoms (rhinorrhea, lacrimation)
4. Yawning
5. Unbearable body aches
6. Sweats and piloerection (“cold turkey”)

3

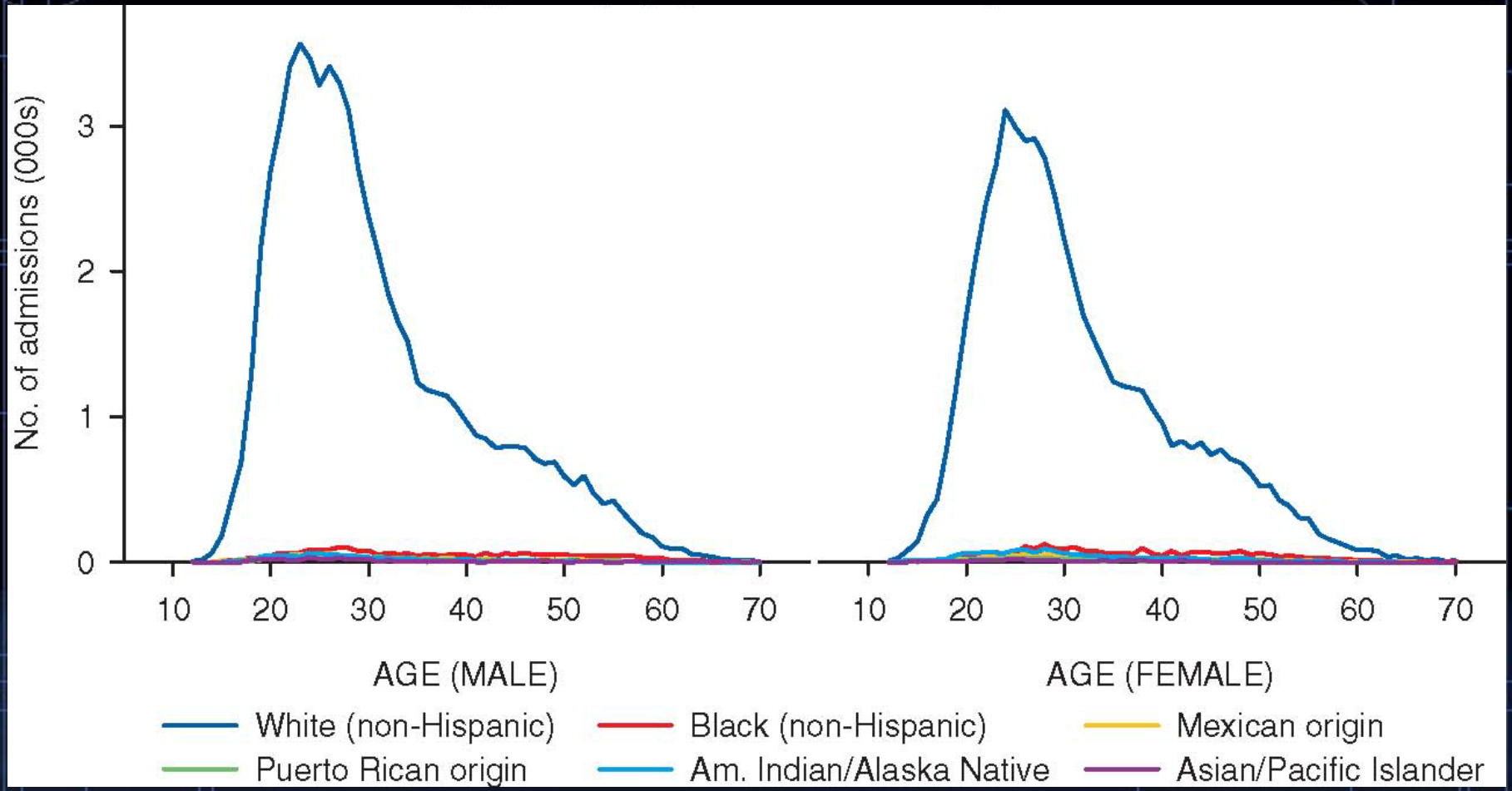
Epidemiology

Heroin Admissions



Substance Abuse and Mental Health Services Administration, *Treatment Episode Data Set (TEDS). 1999-2009. National Admissions to Substance Abuse Treatment Services*, DASIS Series: S-56, HHS Publication No. (SMA) 11-4646, Rockville, MD; SAMHSA, 2011.

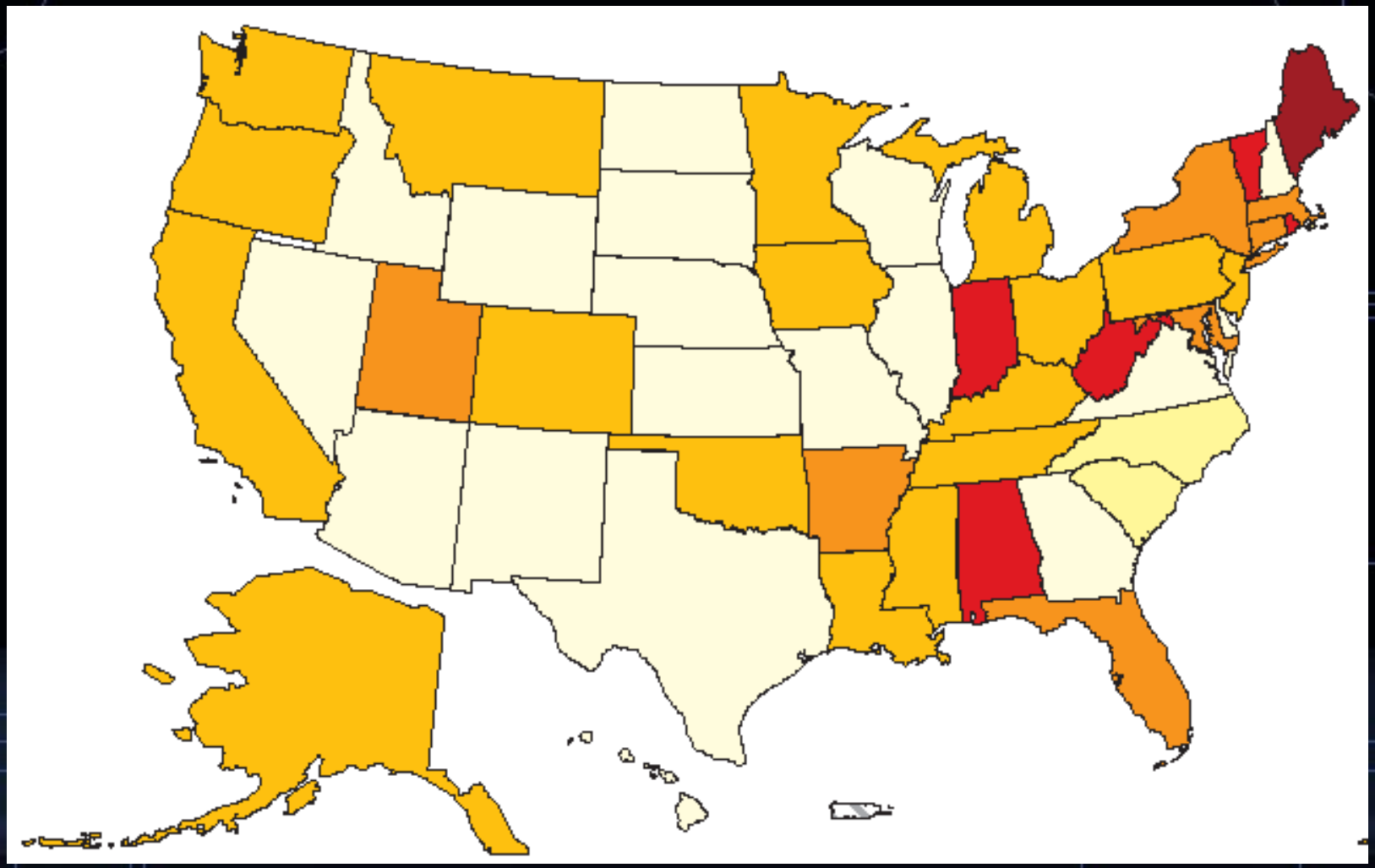
Non-Heroin Opioid Admissions



Substance Abuse and Mental Health Services Administration, *Treatment Episode Data Set (TEDS). 1999-2009. National Admissions to Substance Abuse Treatment Services*, DASIS Series: S-56, HHS Publication No. (SMA) 11-4646, Rockville, MD; SAMHSA, 2011.

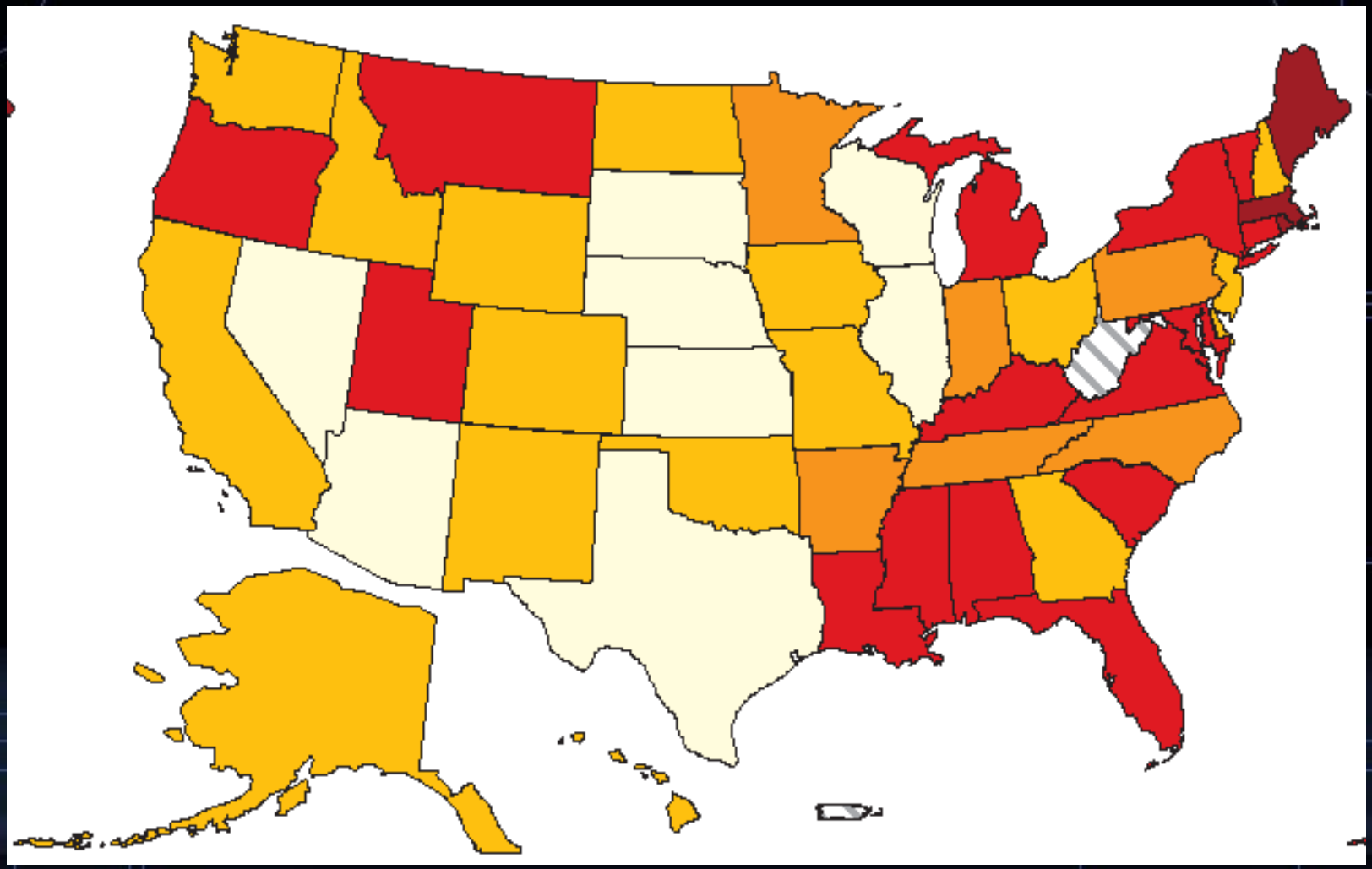
Admissions: 1999

Primary non-heroin opioid admission rates (per 100,000)



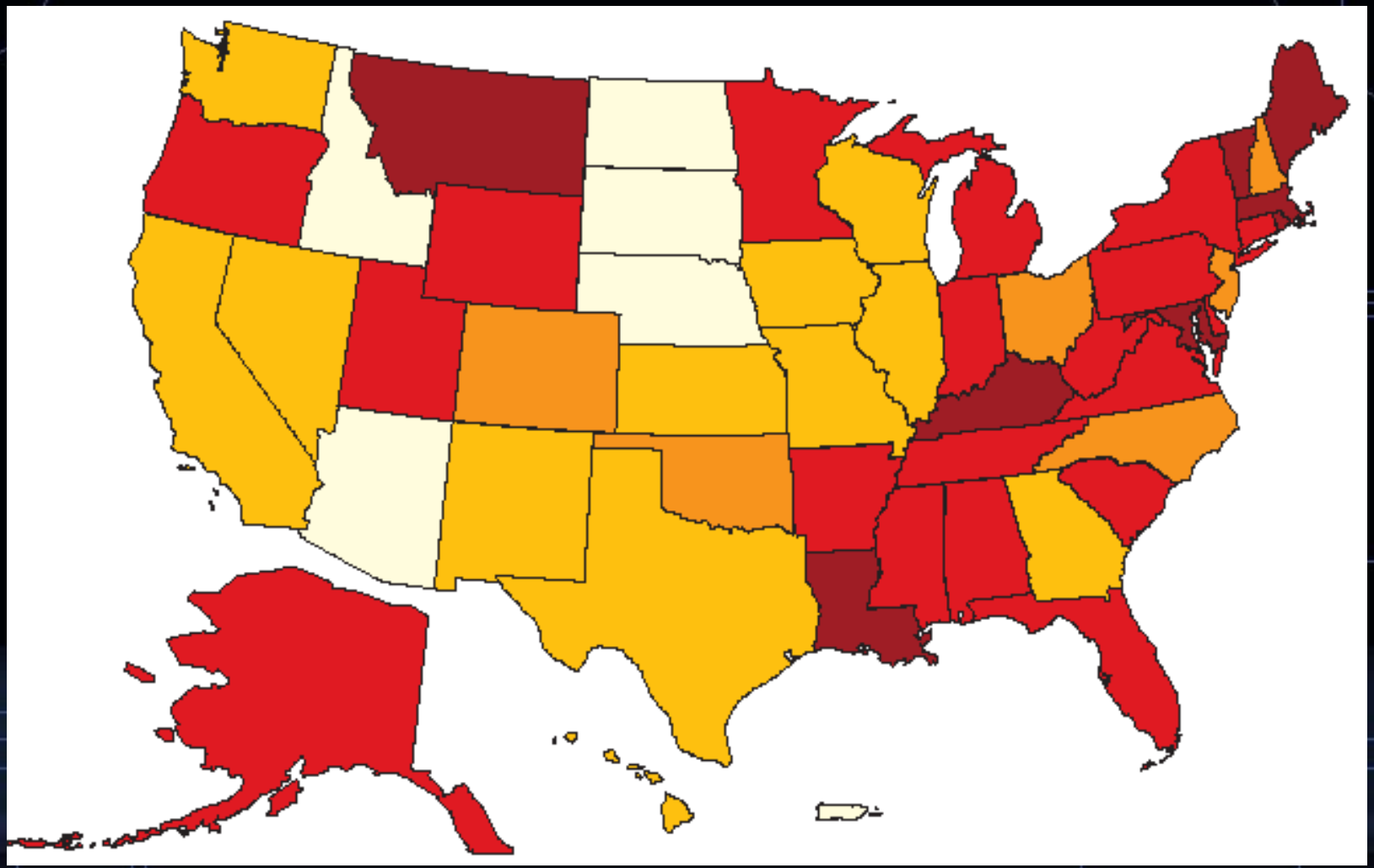
Admissions: 2001

Primary non-heroin opioid admission rates (per 100,000)



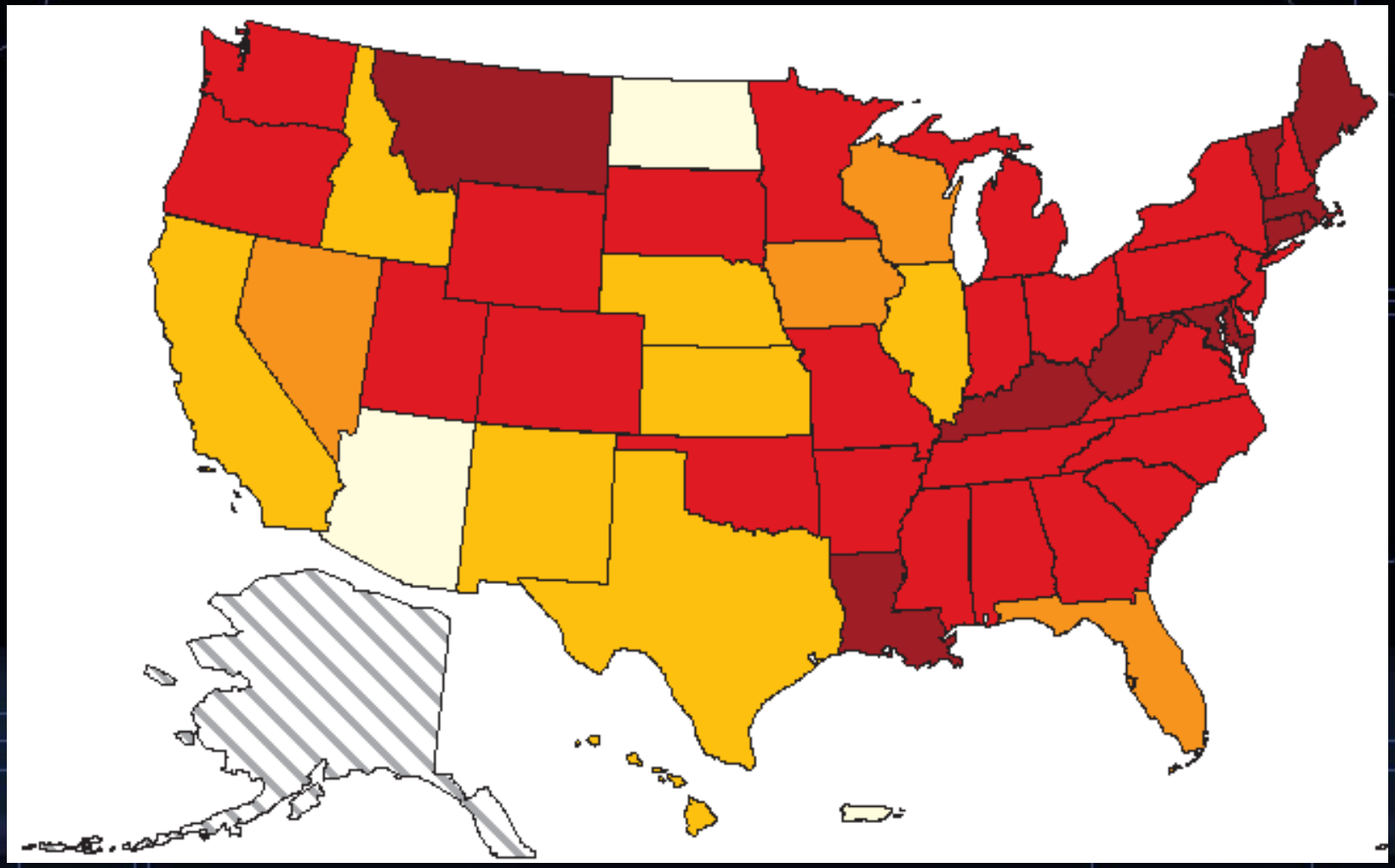
Admissions: 2003

Primary non-heroin opioid admission rates (per 100,000)



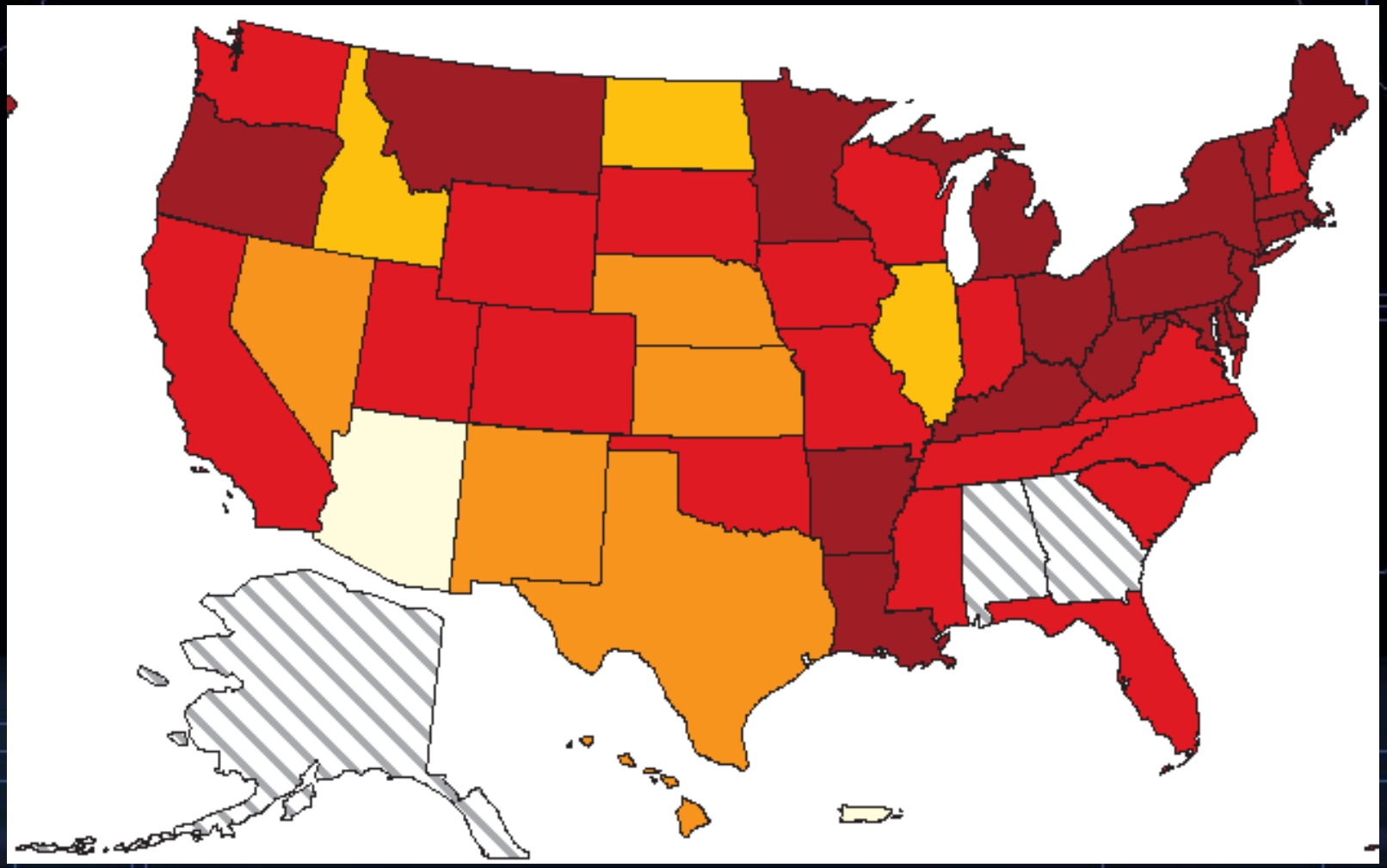
Admissions: 2005

Primary non-heroin opioid admission rates (per 100,000)



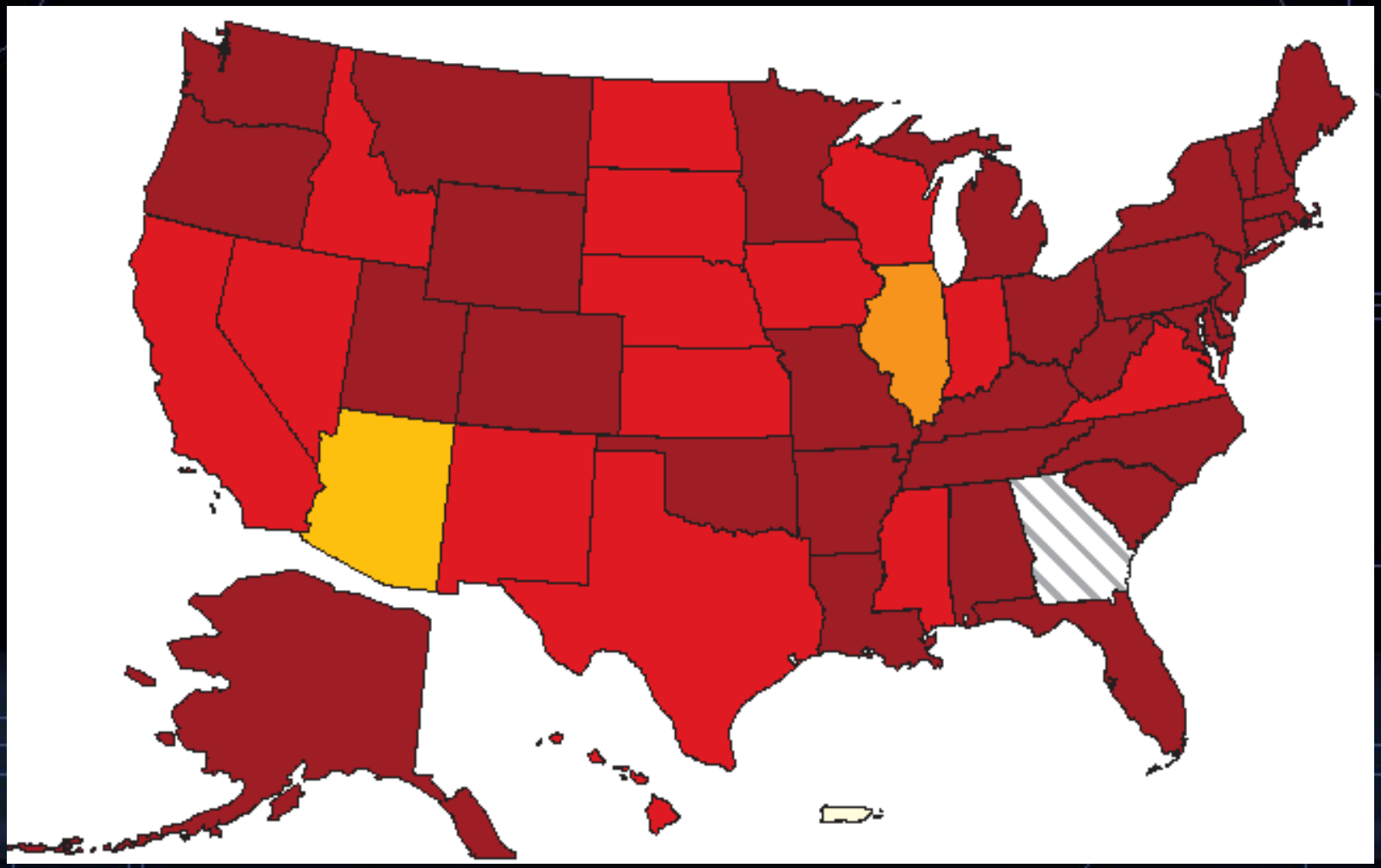
Admissions: 2007

Primary non-heroin opioid admission rates (per 100,000)



Admissions: 2009

Primary non-heroin opioid admission rates (per 100,000)

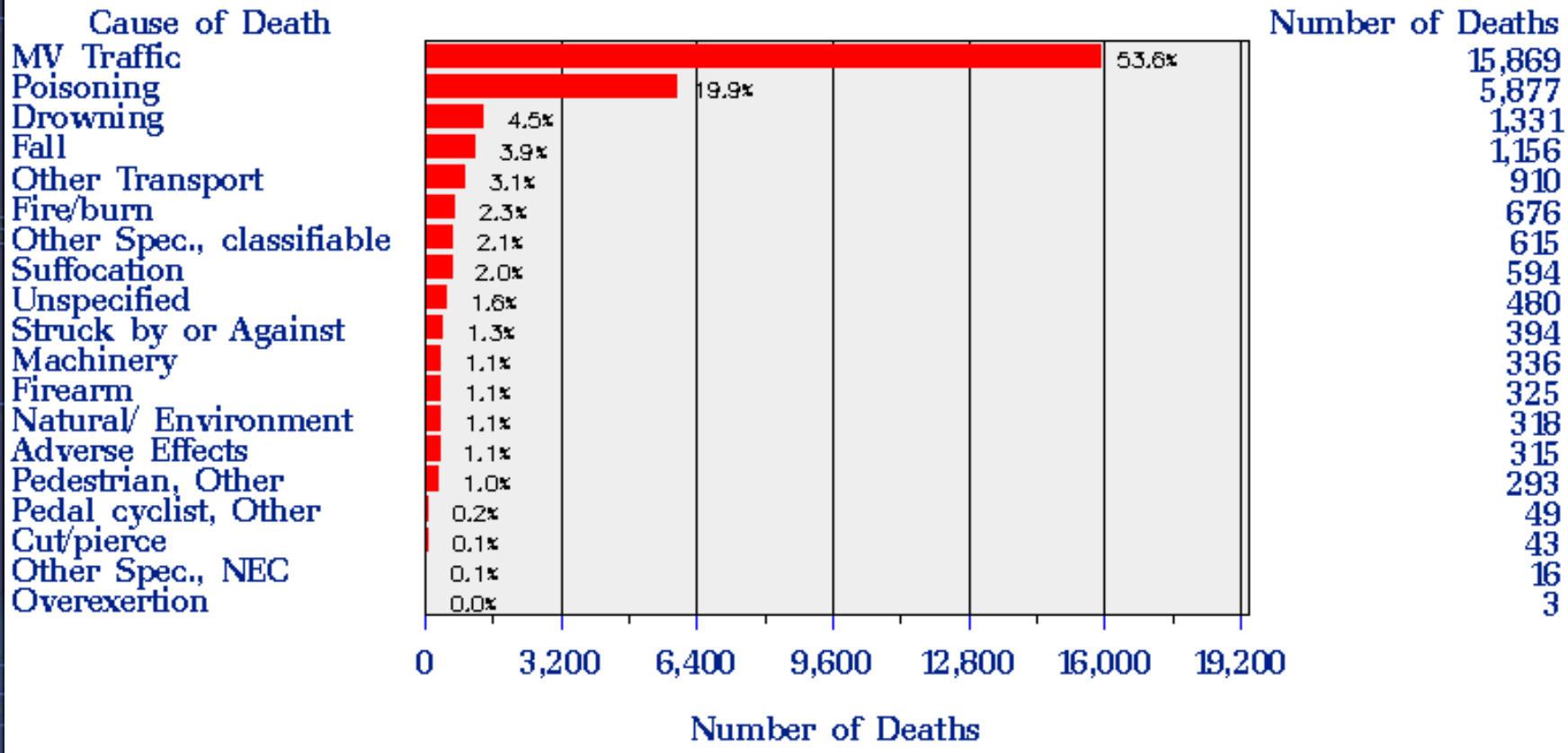


1998, United States

Unintentional Injuries and Adverse Effects

Ages 19–50, White, Non–Hispanic*, Both Sexes

Total Deaths: 29,600



NEC means Not Elsewhere Classifiable.

WISQARS™ Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention

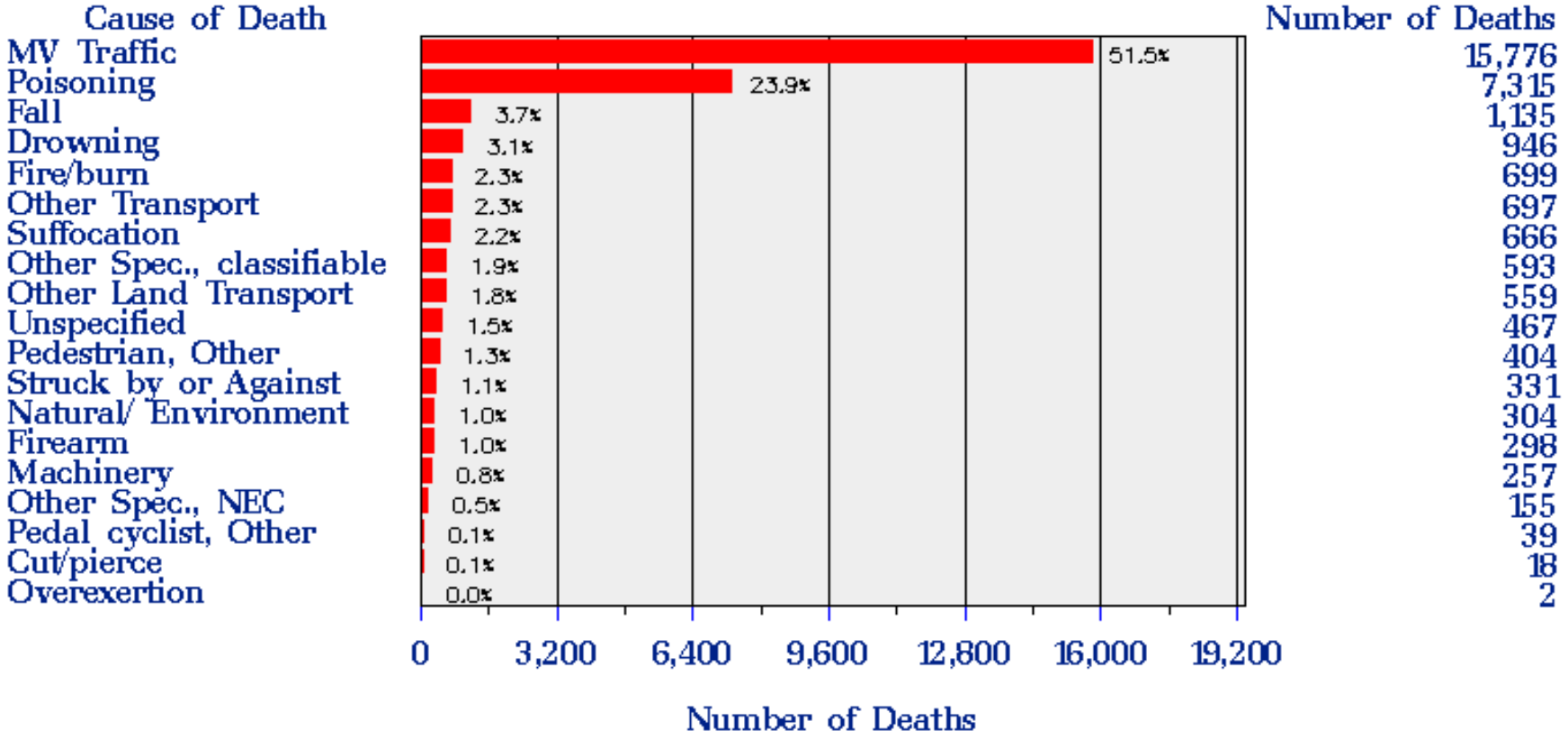
Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

2000, United States

Unintentional Injuries

Ages 19–50, White, Non–Hispanic, Both Sexes

Total Deaths: 30,661



NEC means Not Elsewhere Classifiable.

WISQARS™ Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention

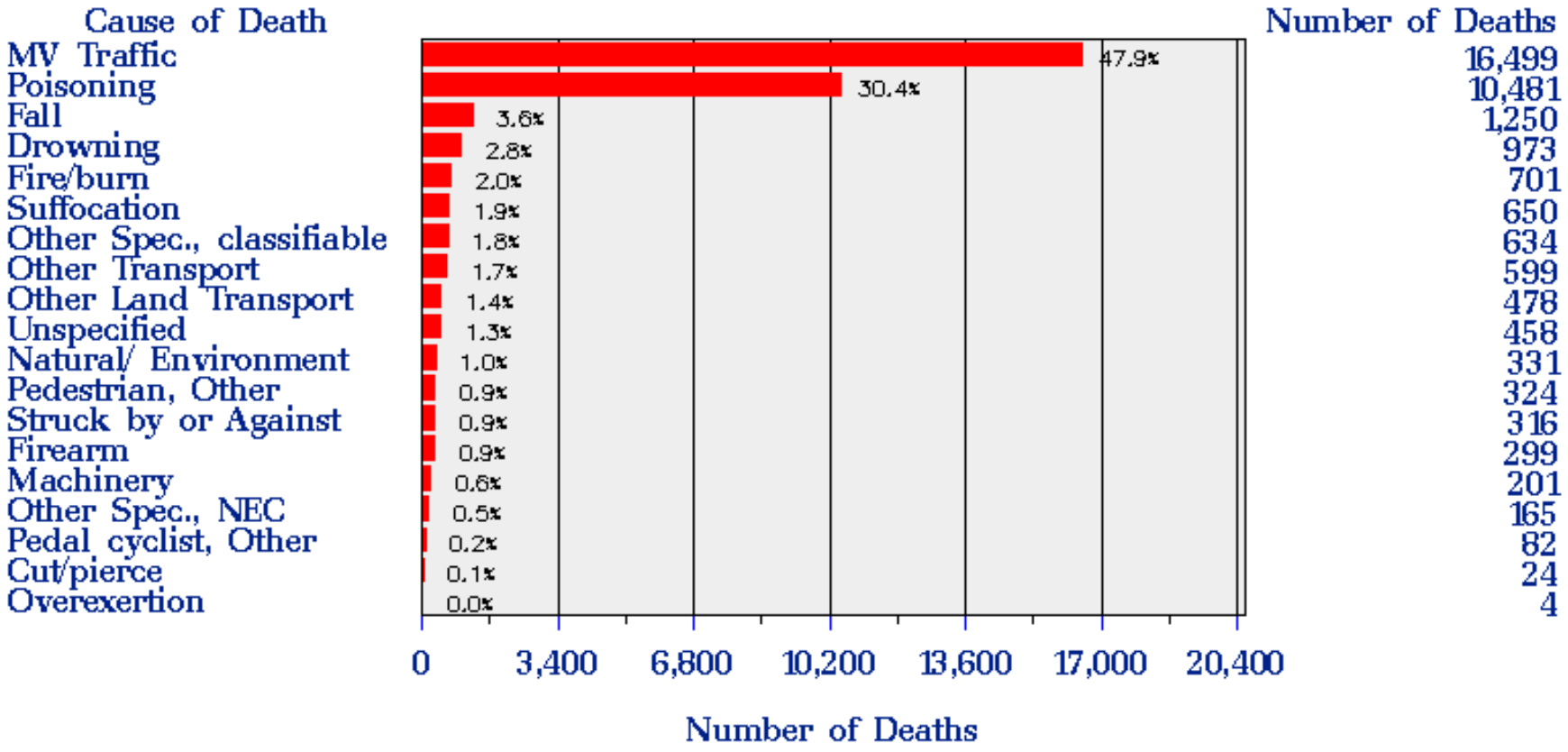
Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

2002, United States

Unintentional Injuries

Ages 19–50, White, Non–Hispanic, Both Sexes

Total Deaths: 34,469



NEC means Not Elsewhere Classifiable.

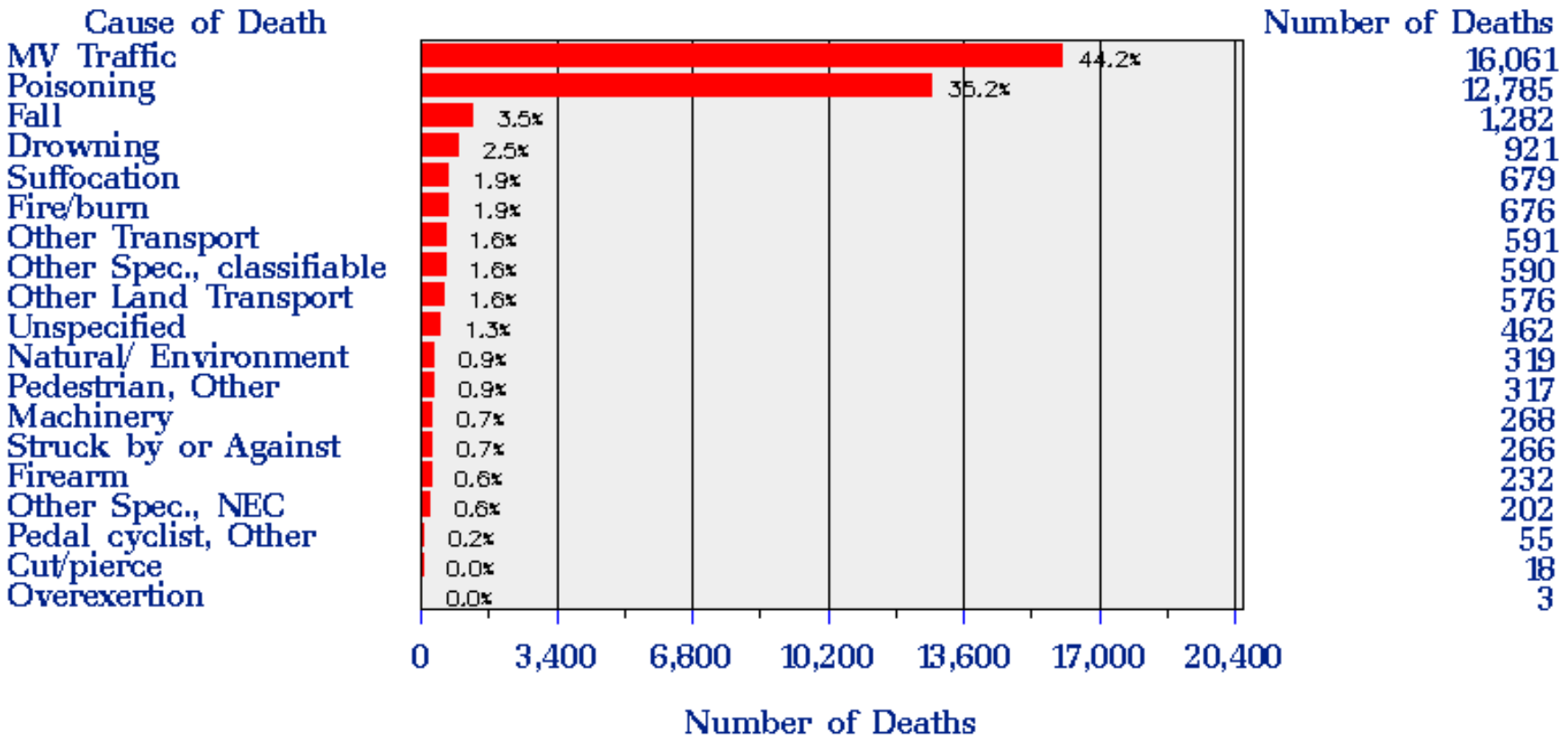
WISQARS™ Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention
Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

2004, United States

Unintentional Injuries

Ages 19–50, White, Non–Hispanic, Both Sexes

Total Deaths: 36,303



NEC means Not Elsewhere Classifiable.

WISQARS™ Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention

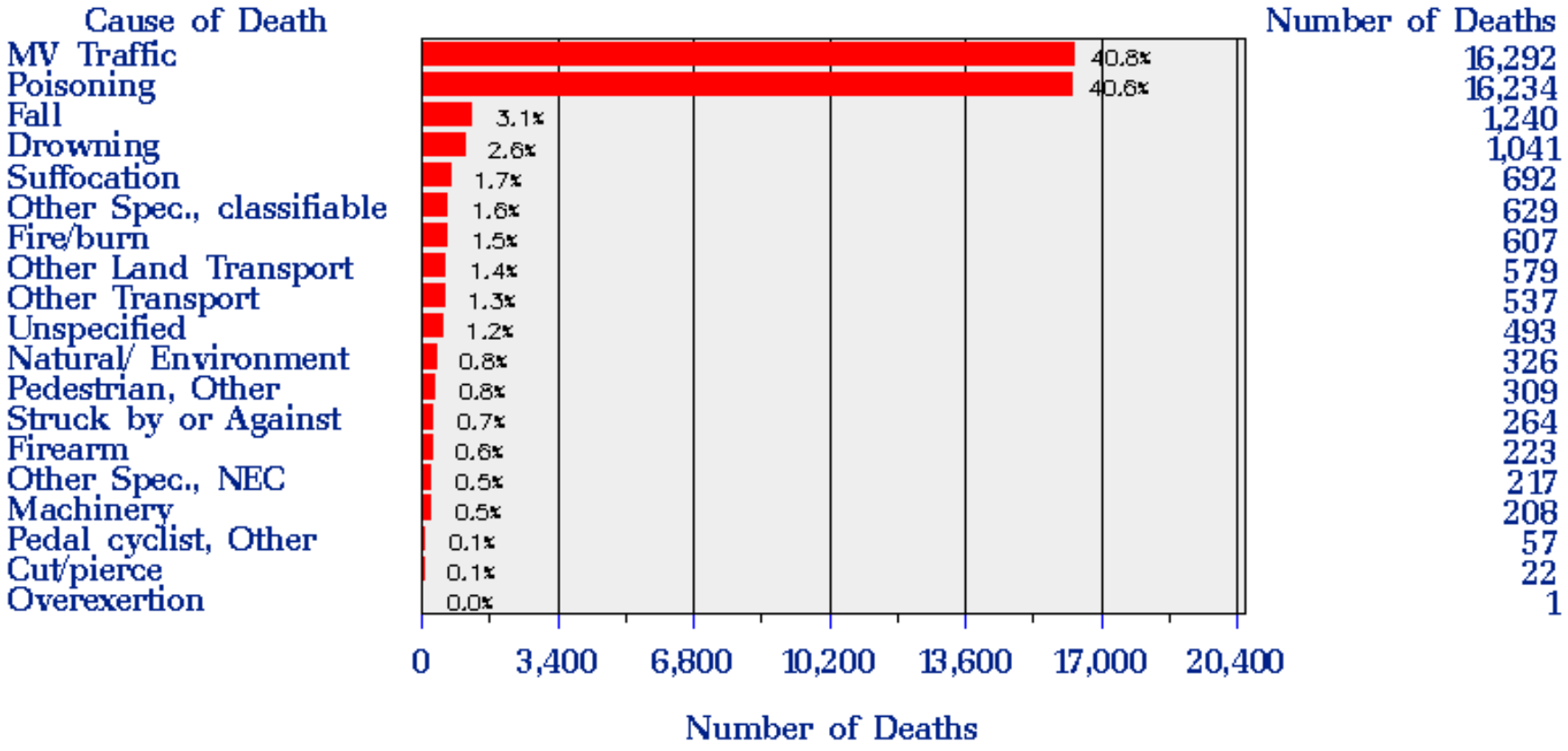
Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

2006, United States

Unintentional Injuries

Ages 19–50, White, Non–Hispanic, Both Sexes

Total Deaths: 39,971



NEC means Not Elsewhere Classifiable.

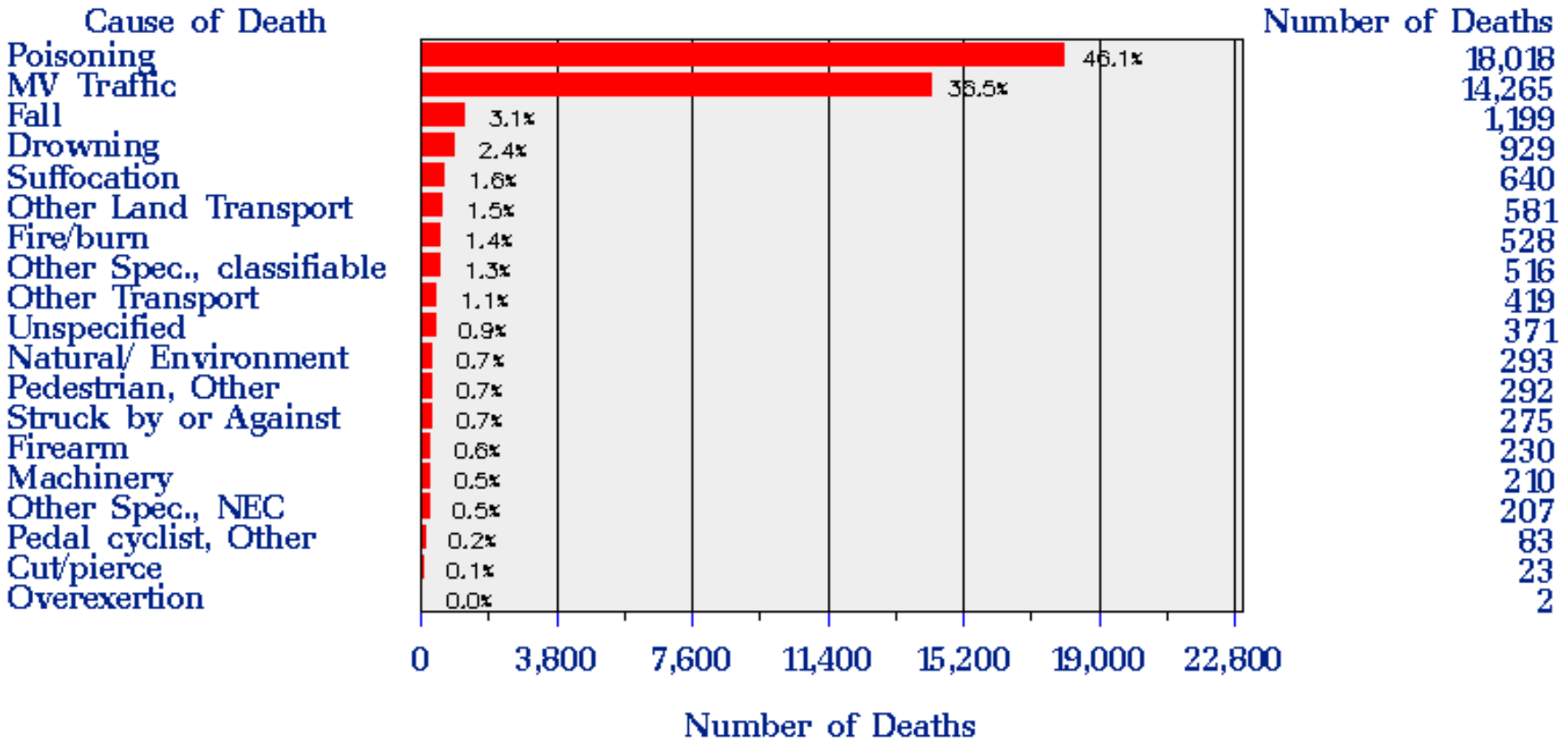
WISQARS™ Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention
Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

2008, United States

Unintentional Injuries

Ages 19–50, White, Non–Hispanic, Both Sexes

Total Deaths: 39,081

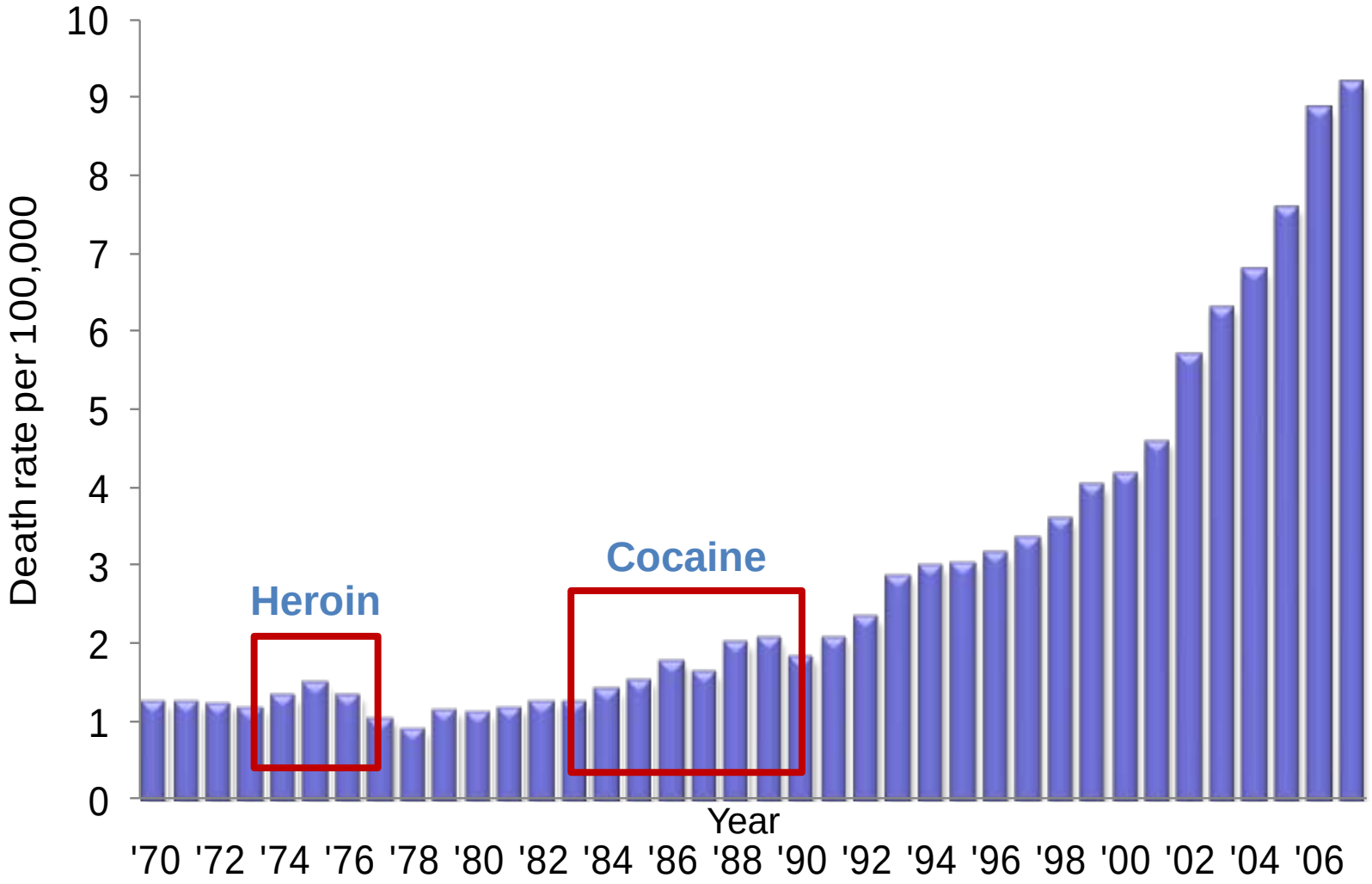


NEC means Not Elsewhere Classifiable.

WISQARS™ Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention

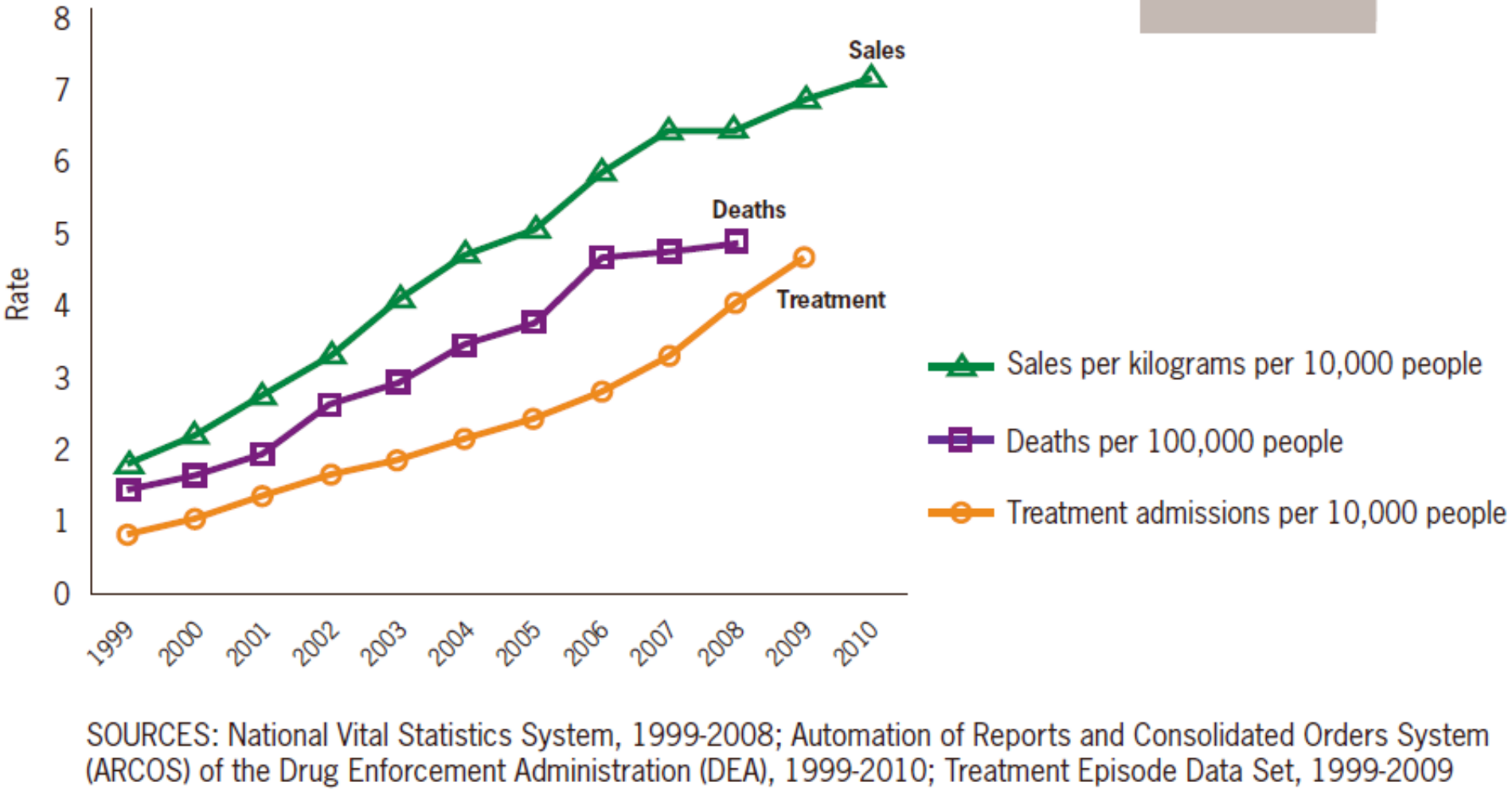
Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

Unintentional Drug Overdose Deaths United States: 1970–2007



National Vital Statistics System, http://wonder.cdc.gov

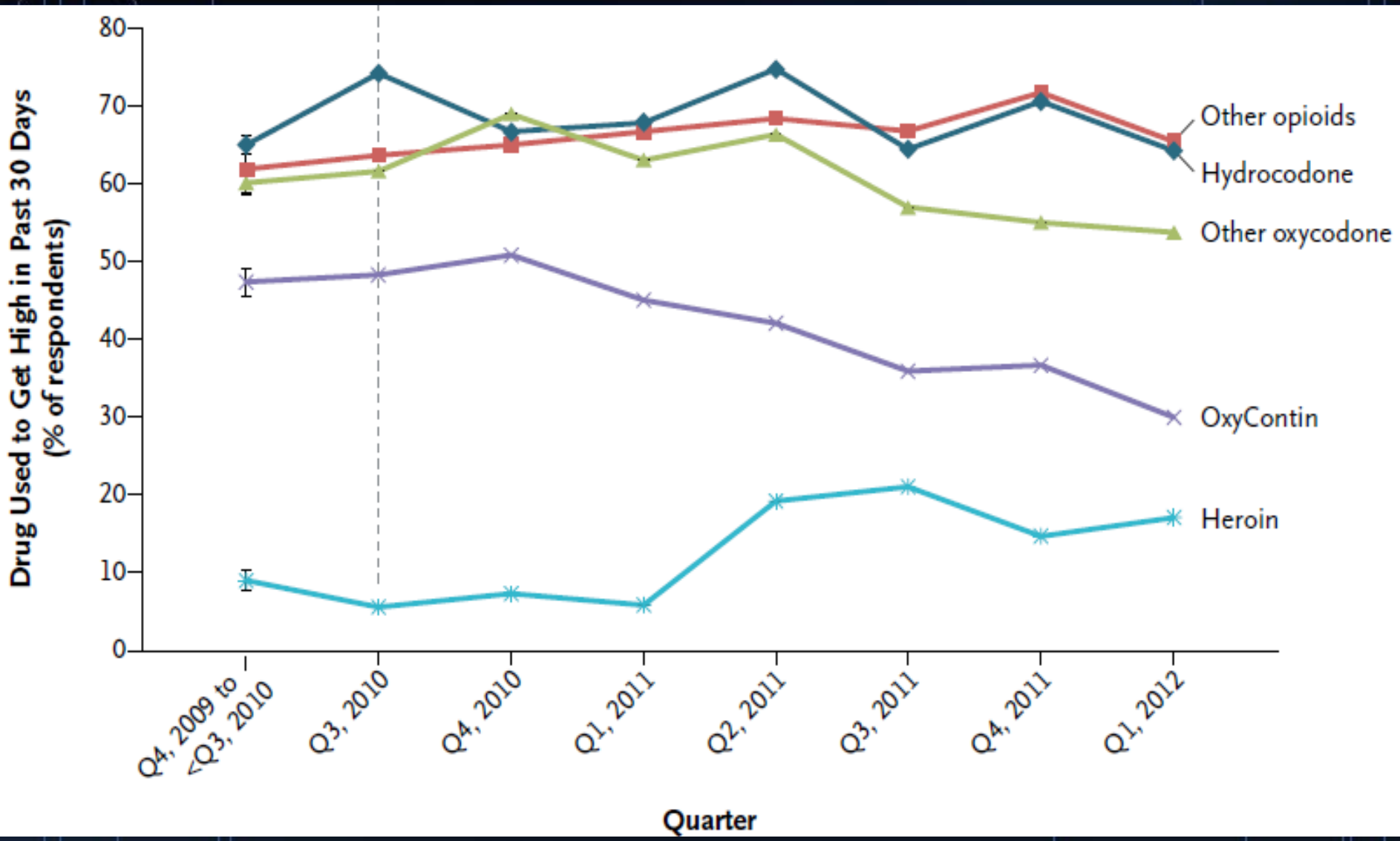
Prescription Opioids 1999-2010



SOURCES: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009

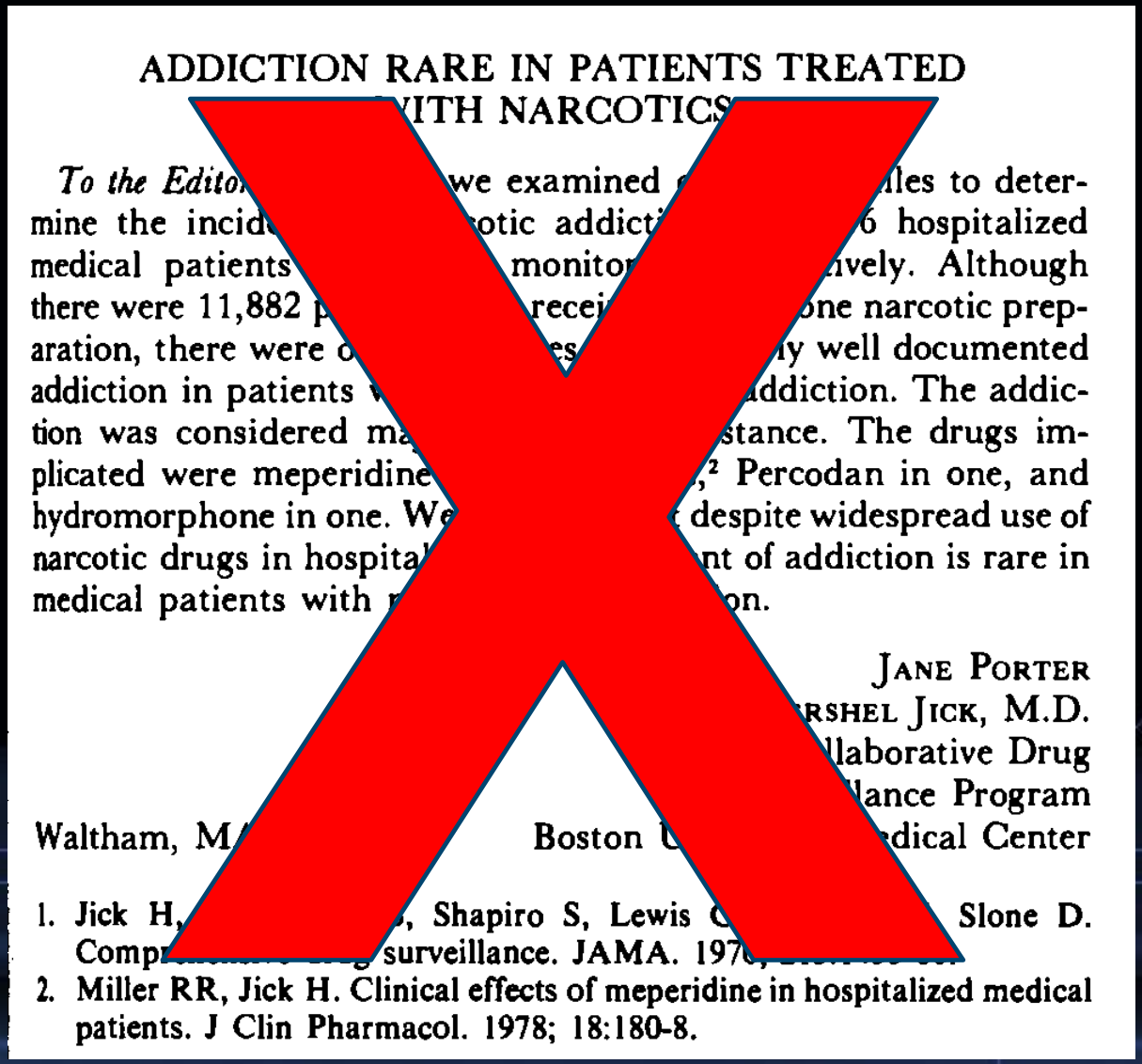
Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report*, November 1, 2011

Prescription Opioids 2012



Cicero et al, *N Engl J Med*, July 12, 2012

The Prescription Opioids Epidemic: The Root of the Disaster



ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

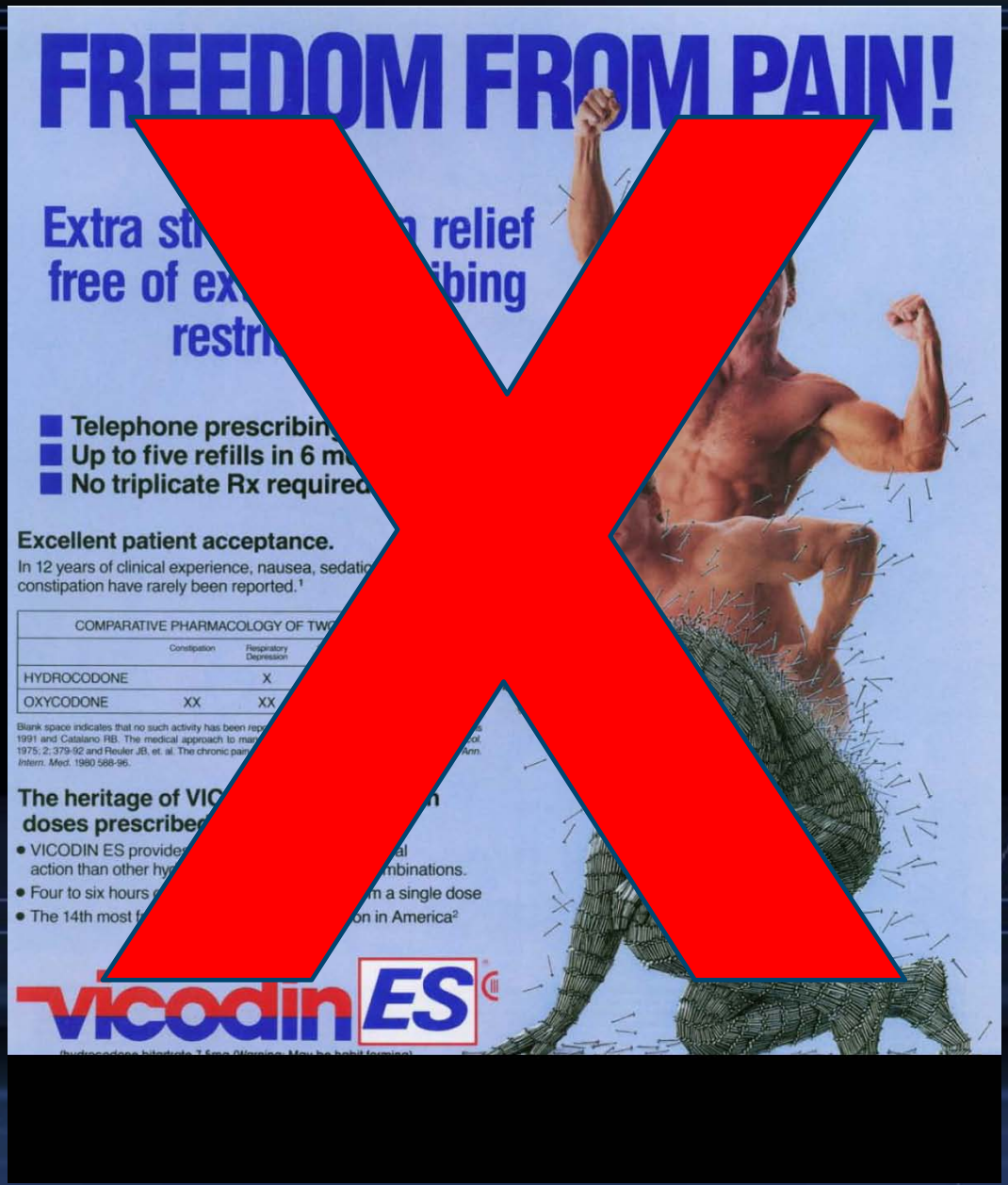
To the Editor: we examined [illegible] files to determine the incidence of addiction [illegible] 6 hospitalized medical patients [illegible] monitoring actively. Although there were 11,882 patients receiving one narcotic preparation, there were only well documented addiction in patients with addiction. The addiction was considered major in substance. The drugs implicated were meperidine in [illegible],[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, addiction of addiction is rare in medical patients with [illegible].

JANE PORTER
[illegible]RSHEL JICK, M.D.
[illegible]llaborative Drug
[illegible]llance Program
Waltham, MA [illegible] Boston [illegible]dical Center

1. Jick H, [illegible], Shapiro S, Lewis [illegible] Slone D. Comprehensive drug surveillance. JAMA. 197[illegible]
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol. 1978; 18:180-8.

Porter and Jick, *N Engl J Med*, January 10, 1980.

Pharma


FREEDOM FROM PAIN!
Extra st relief
free of ex ibing
restri
Telephone prescribi
Up to five refills in 6 m
No triplicate Rx required
Excellent patient acceptance.
In 12 years of clinical experience, nausea, sedati
constipation have rarely been reported.¹
COMPARATIVE PHARMACOLOGY OF TW
Constipation
Respiratory Depression
HYDROCODONE
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OXYCODONE
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4

Pharmacological Treatments

Three Options

- Agonist: Methadone
- Partial Agonist: Buprenorphine
- Antagonist: Naltrexone

Full Agonist Effects

Mu receptor → **Full agonist binding ...**

❶ activates the mu receptor

❷ is highly reinforcing

❸ is the most abused opioid type

❹ includes heroin, codeine, & others

Antagonist Effects

Mu receptor

Antagonist binding …

❶ occupies without activating

❷ is not reinforcing

❸ blocks abused agonist opioid types

❹ includes naloxone and naltrexone

Partial Agonist Effects

Mu receptor

Partial agonist binding ...

❶ activates the receptor at lower levels

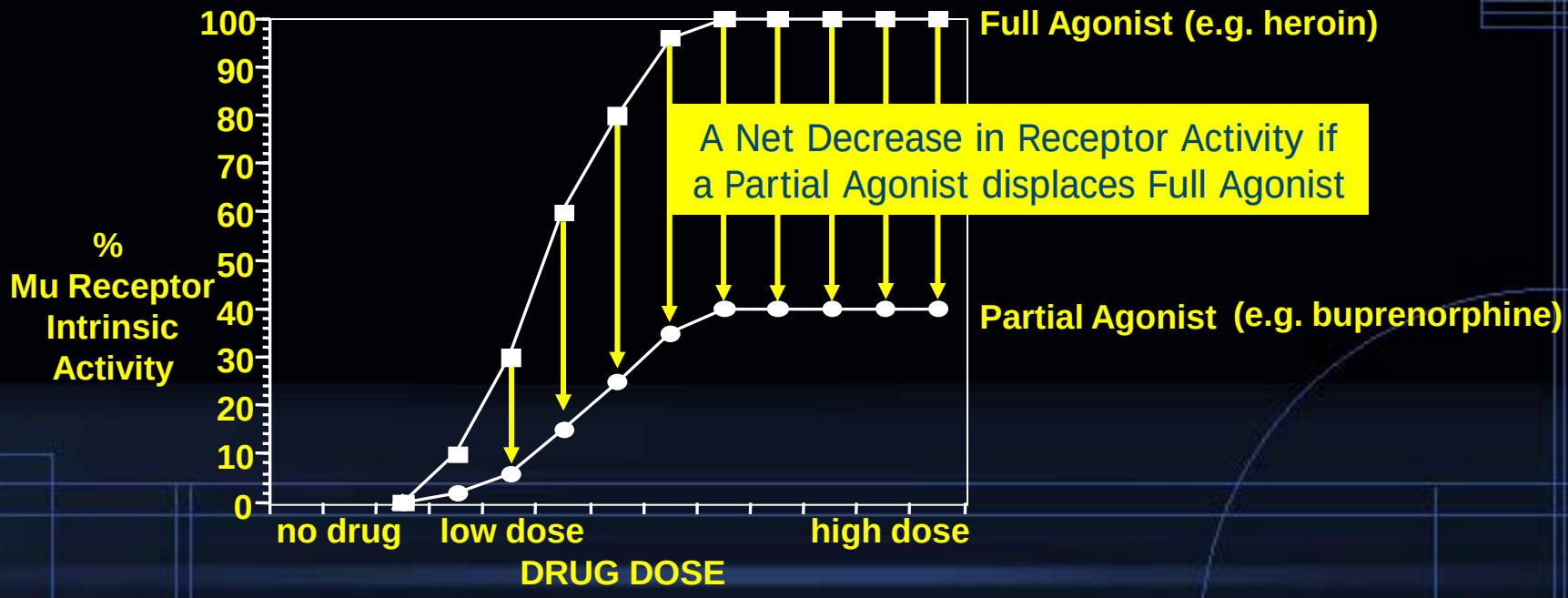
❷ is relatively less reinforcing

❸ is a less abused opioid type

❹ includes buprenorphine

Precipitated Withdrawal

- Buprenorphine will precipitate withdrawal only when it displaces a full agonist off the mu receptors.
- Buprenorphine only partially activates the receptors, therefore a net decrease in activation occurs and withdrawal develops.



Discrepancy Between Populations Abusing Opioids & Population Treated

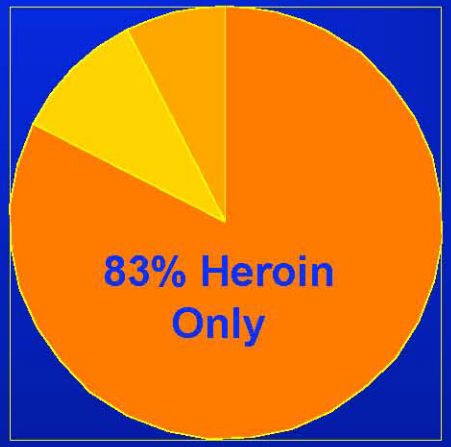
Opioid Abuse

NSDUH Past Month Use 2002

4,549,570 reported opioid abuse

Methadone Treatment

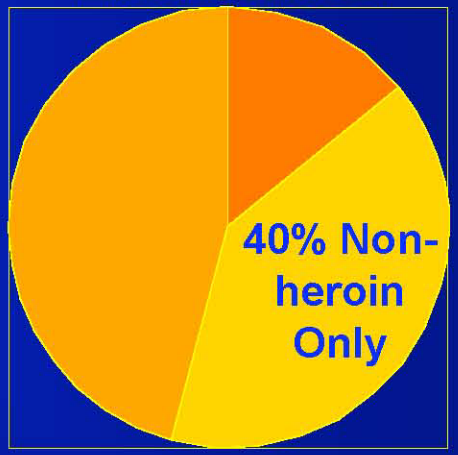
TEDS 2002 Admissions Involving Methadone Treatment



111,885 admissions involved methadone treatment

Treatment Under the Waiver (BUP)

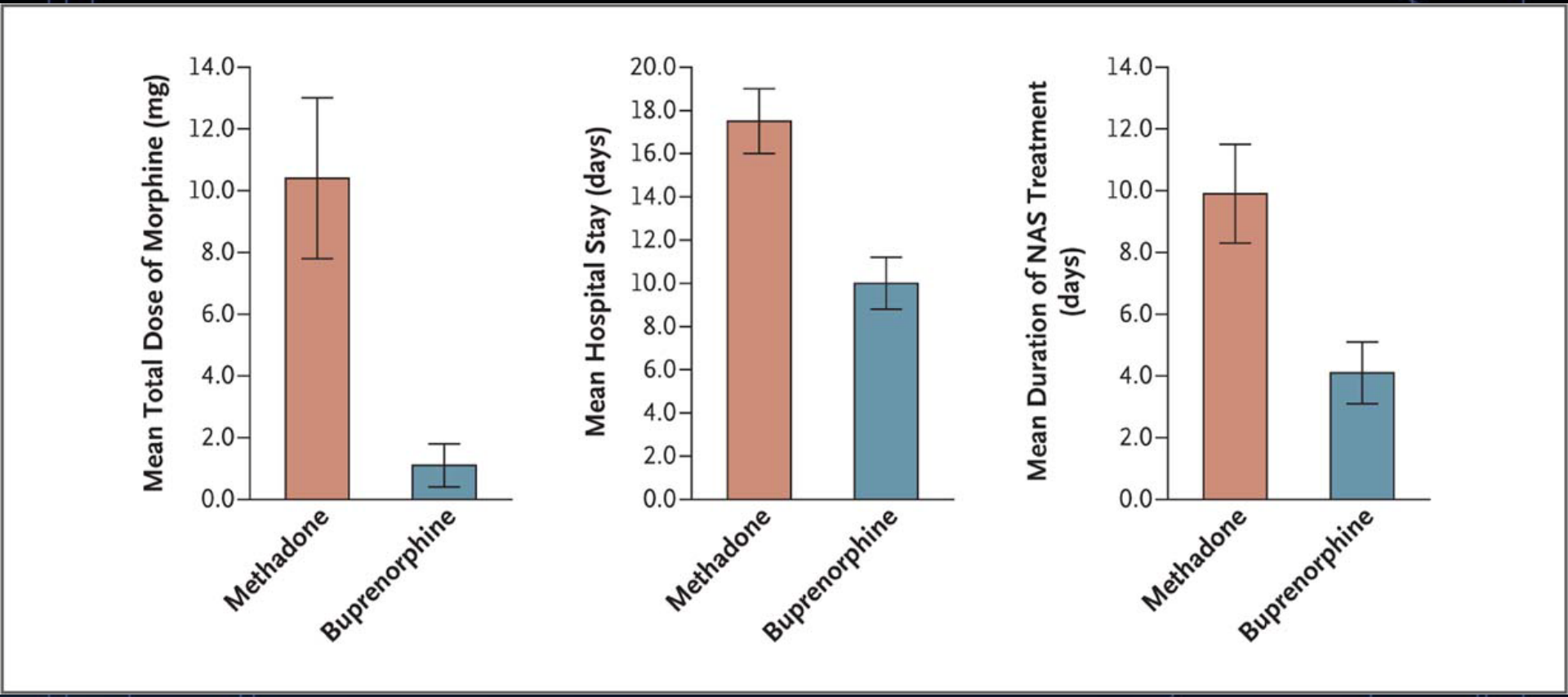
Patient Study BUP Evaluation 2005



434 patients recruited from 132 sites

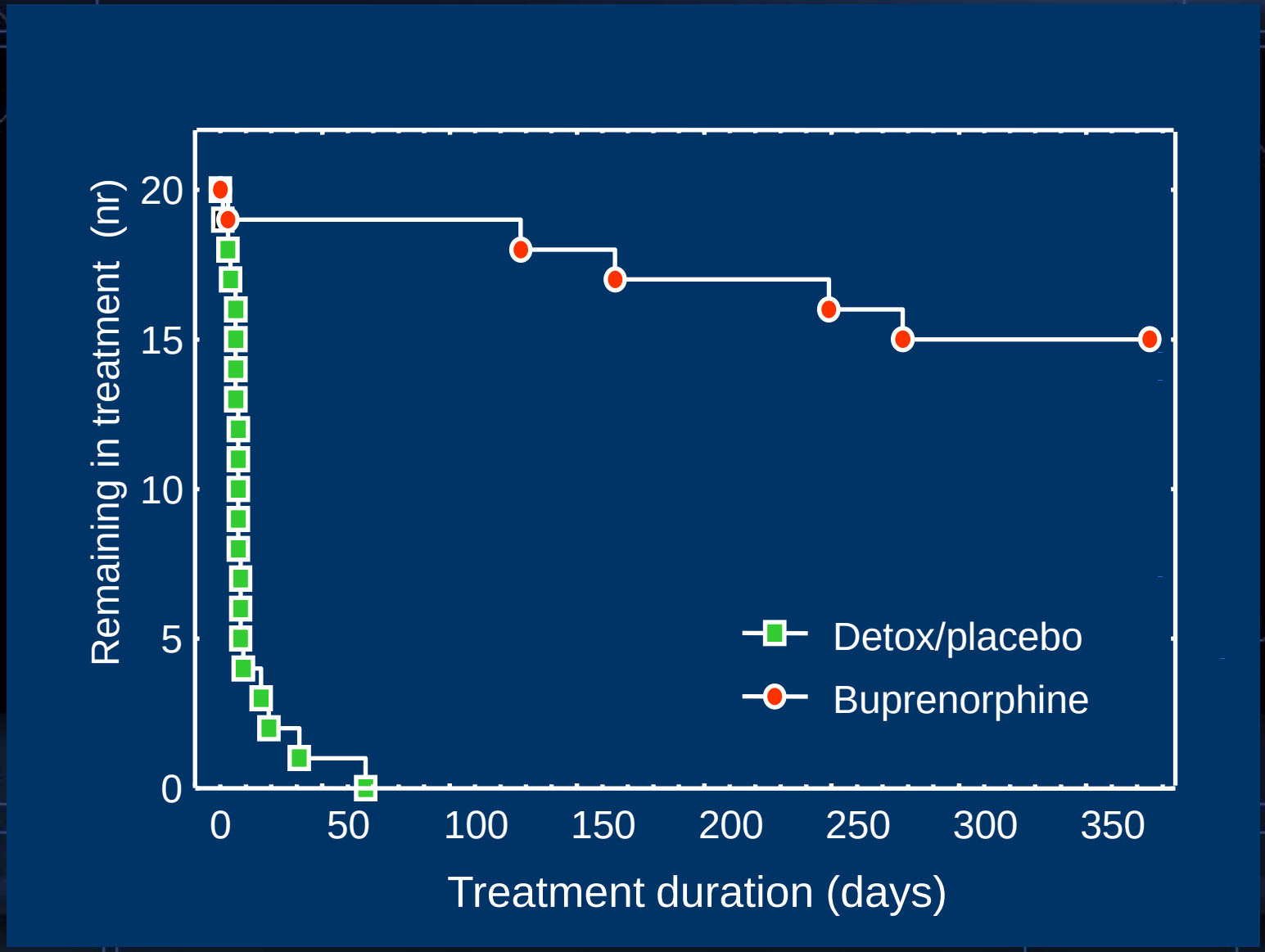
Heroin Only | Non-heroin Opioids Only | Heroin & Non-heroin Opioids

Neonatal Abstinence Syndrome



Jones et al, *N Engl J Med*, 2010

Maintenance v. Detoxification 1



Kakko J et al. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. Lancet 361(9358):662-8, 2003.

Maintenance v. Detoxification 2

	Detox/Placebo	Buprenorphine	Cox regression
Dead	4/20 (20%)	0/20 (0%)	χ^2=5.9; p=0.015

Kakko J et al. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. Lancet 361(9358):662-8, 2003.

5

Treating Chronic Non-Cancer Pain

Non-Opioid Strategies

1. NSAIDs and acetaminophen
2. Corticosteroids
3. Anticonvulsants and antidepressants
4. Capsaicin for neuropathic pain
5. Transdermal lidocaine
6. Physical Therapy
7. Exercise and Relaxation Techniques
8. Cognitive Behavioral Therapy

Chronic Opioid Therapy

Opioids are not first-line treatments for chronic non-cancer pain.

Three major problems:

1. Lack of Efficacy
2. Significant Health Risks
3. Addiction

Lack of Efficacy

- Evidence of long-term efficacy for chronic non-cancer pain (>16 weeks) is limited and of low quality.
- For many patients with chronic pain, analgesic efficacy is not maintained over long time periods.

Washington State Agency Medical Directors' Group
www.agencymeddirectors.wa.gov. Accessed January 9, 2013.

Significant Health Risks

- Fractures from falls (especially for patients over 60)
- Fatal unintentional overdose from respiratory depression
- Hyperalgesia
- Sexual dysfunction
- Hypogonadism
- Chronic constipation and fecal impaction
- Chronic dry mouth and tooth decay
- Dry skin and pruritus

The 2009 Article

- American Pain Society and American Academy of Pain Medicine multi-disciplinary expert panel
- Chronic Opioid Therapy (COT) in Chronic Noncancer Pain (CNCP)
- 14 Areas of Concern
- 25 Recommendations
  - 21 “Low-quality evidence”
  - 4 “Moderate-quality evidence”

Chou et al, *J Pain*, 2009

1. Opioid Risk Tool

		Mark each box that applies	Item score if female	Item score if male
1. Family history of substance abuse	• Alcohol	☐	1	3
	• Illegal drugs	☐	2	3
	• Prescription drugs	☐	4	4
2. Personal history of substance abuse	• Alcohol	☐	3	3
	• Illegal drugs	☐	4	4
	• Prescription drugs	☐	5	5
3. Age (mark box if 16-45)		☐	1	1
4. History of preadolescent sexual abuse		☐	3	0
5. Psychological disease	• Attention-deficit disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia	☐	2	2
	• Depression	☐	1	1

Total Score _____ Risk Category _____

Low Risk: 0 to 3 Moderate Risk: 4 to 7 High Risk: 8 and above

Source: Webster LR, Webster R. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. *Pain Med*. 2005;6(6):432.

2. Morphine Equianalgesic Doses

1. Naturally Occurring Opioids

Morphine	**30**
Codeine	**200**

2. Semi-Synthetic Opioids

Oxymorphone	**10**
Oxycodone	**20**
Hydromorphone	**7.5**
Hydrocodone	**30**

For MED over 100 per day, reassess!

3. Depression

- Depression often manifests as physical pain, indistinguishable to the patient from somatic pain
- Assessment focuses on accompanying symptoms of:
  - Loss of pleasure
  - Loss of energy
  - Sadness
  - Appetite and sleep disturbances
  - Guilt and thoughts of death

4. Urine Toxicology Exams

Use of which one of the following can turn a Urine Toxicology Examination positive for both codeine and morphine?

A. Heroin

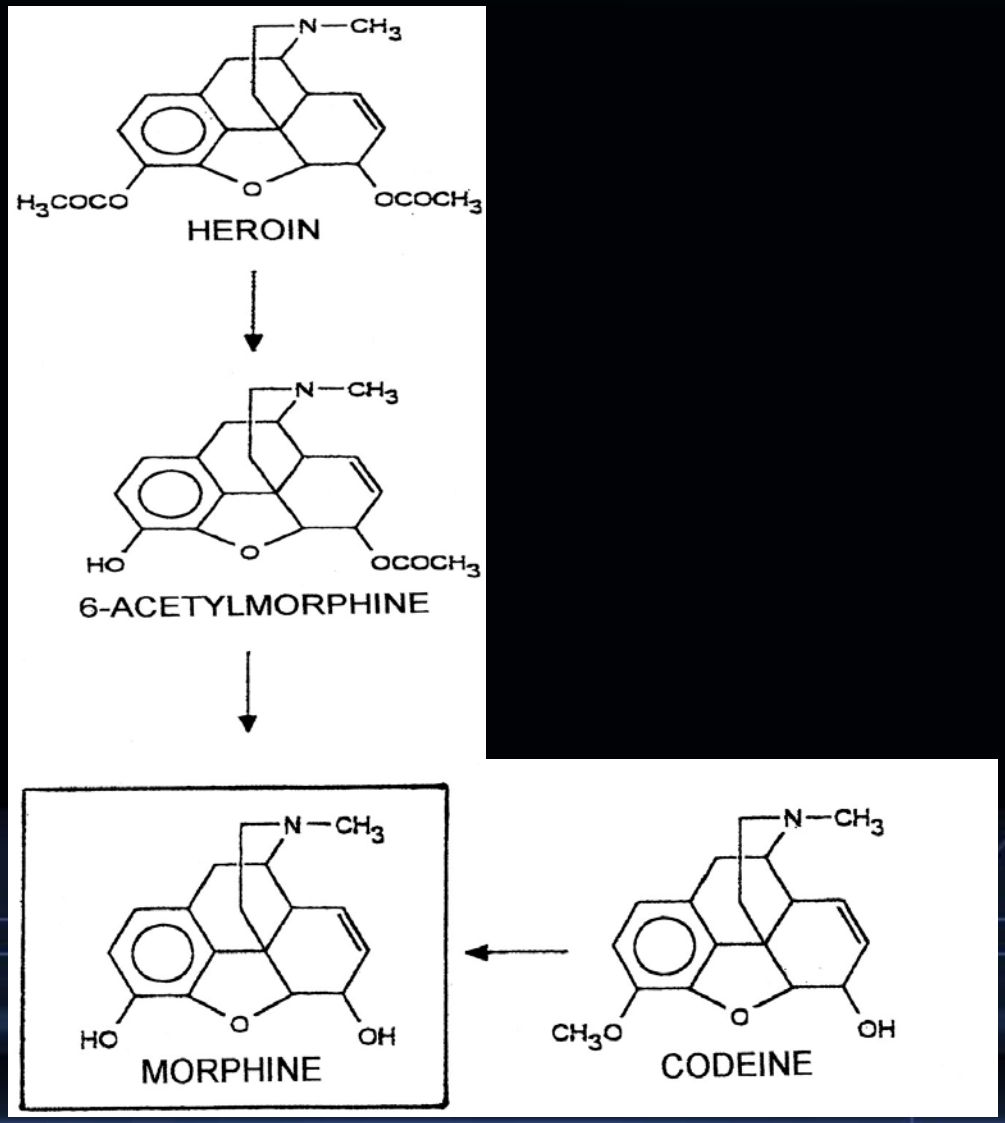
B. Hydrocodone

C. Oxycodone

D. Poppy seed bagels

E. All of the above

Opioid Metabolism



Adapted from: Staub et al, *Clinical Chemistry*, 2001

Urine Toxicology Detection Limits

Alcohol	7-12 hours
Alcohol (Ethyl glucuronide, EtG test)	4 days
Amphetamines/Methamphetamines	2 days
Benzodiazepines (Short-acting)	3 days
Benzodiazepines (Long-acting)	30 days
Cocaine	2-4 days
Heroin (Morphine)	2 days
Methadone	3 days
Marijuana (Single use)	3 days
Marijuana (Long-term heavy use)	>30 days

Moeller. *Mayo Clin Proc*. 2008; Anders, et al. *Alcohol and Alcoholism,* 2009.

5. Acetaminophen Warning

Hepatotoxicity can result from prolonged use of combination opioid/acetaminophen products.

- Short-term use (<10 days) – 4,000 mg/day
- Long-term use – 2,500 mg/day

Washington State Agency Medical Directors' Group
www.agencymeddirectors.wa.gov. Accessed January 9, 2013.

And One More …

An opioid dependent patient has decided to undertake an opioid discontinuation trial. She asks for specific advice while she is still taking opioids.

All of the following are good recommendations, EXCEPT:

A. Fill your prescriptions at one pharmacy
B. Keep medications in a secure location, preferably locked.
C. Avoid alcohol, benzodiazepines, muscle relaxants, and monoamine oxidase inhibitors (MAOIs)
D. Discard unused medication down the toilet
E. All of the above are excellent recommendations!

6

Conclusions

1. Opioids relieve physical and emotional pain by activating the μ opioid receptor.

2. Prescription opioid use has now become a nation-wide epidemic.

3. Opioids have been shown to be neither effective nor safe in the treatment of chronic non-cancer pain.

4. In 2013, buprenorphine maintenance is the first line pharmacological treatment of opioid addiction.

Thank you