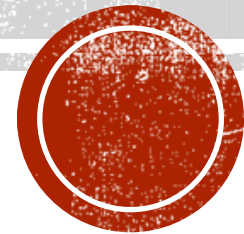


SUBSTANCE USE AND SUICIDE RISK

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Professor, School of Pharmacy



DISCLOSURES

- No financial conflicts of interest



LEARNING OBJECTIVES

- Discuss the current opioid overdose crisis in the United States.
- Review the challenges associated with treating substance use disorders along with chronic pain.
- Highlight methods currently employed to reduce morbidity and mortality associated with illicit and prescription opioid use.

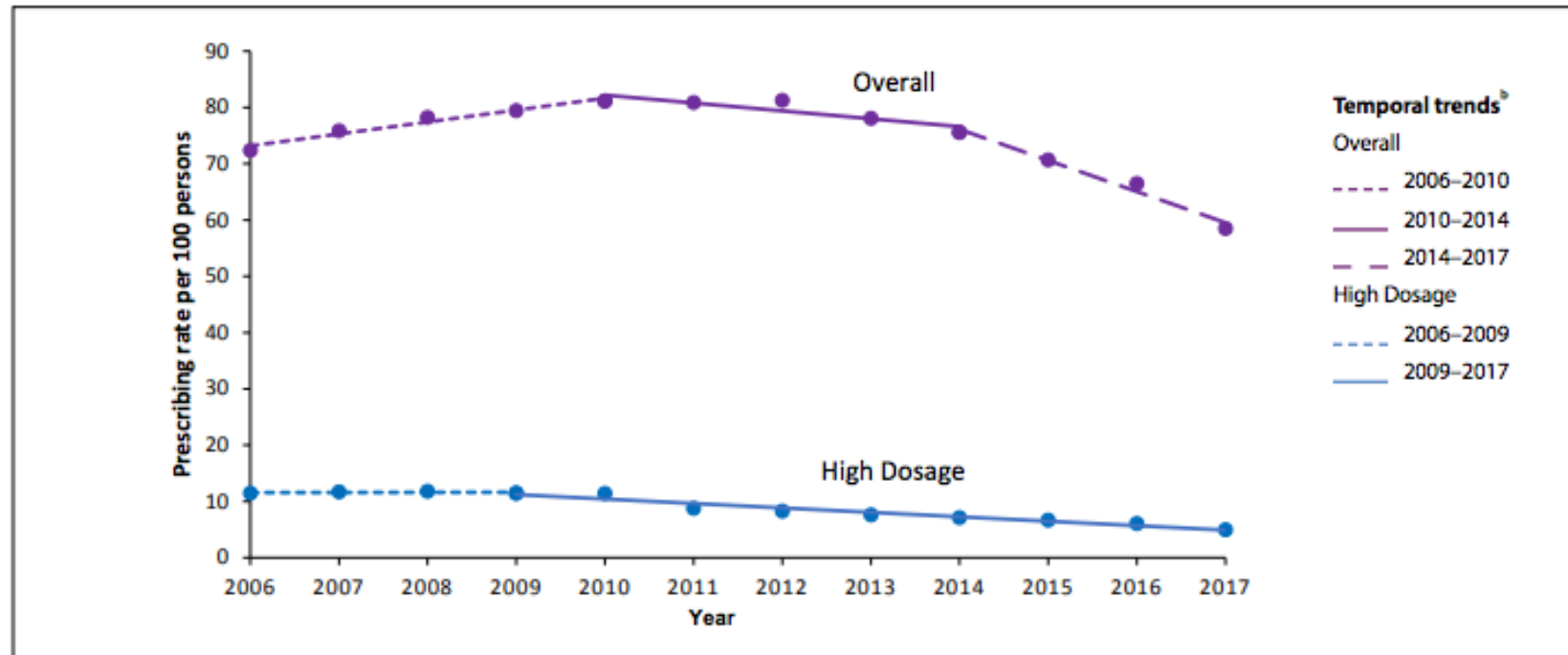


START WITH GOOD NEWS

Trends in Opioid Prescribing

FIGURE 1A

Annual opioid prescribing rates overall and for high-dosage prescriptions^a (≥ 90 MME/day)^b — United States, 2006–2017



Source: IQVIA™ Transactional Data Warehouse.

^aHigh-dosage prescriptions were defined as opioid prescriptions resulting in a daily dosage of ≥ 90 morphine milligram equivalents.

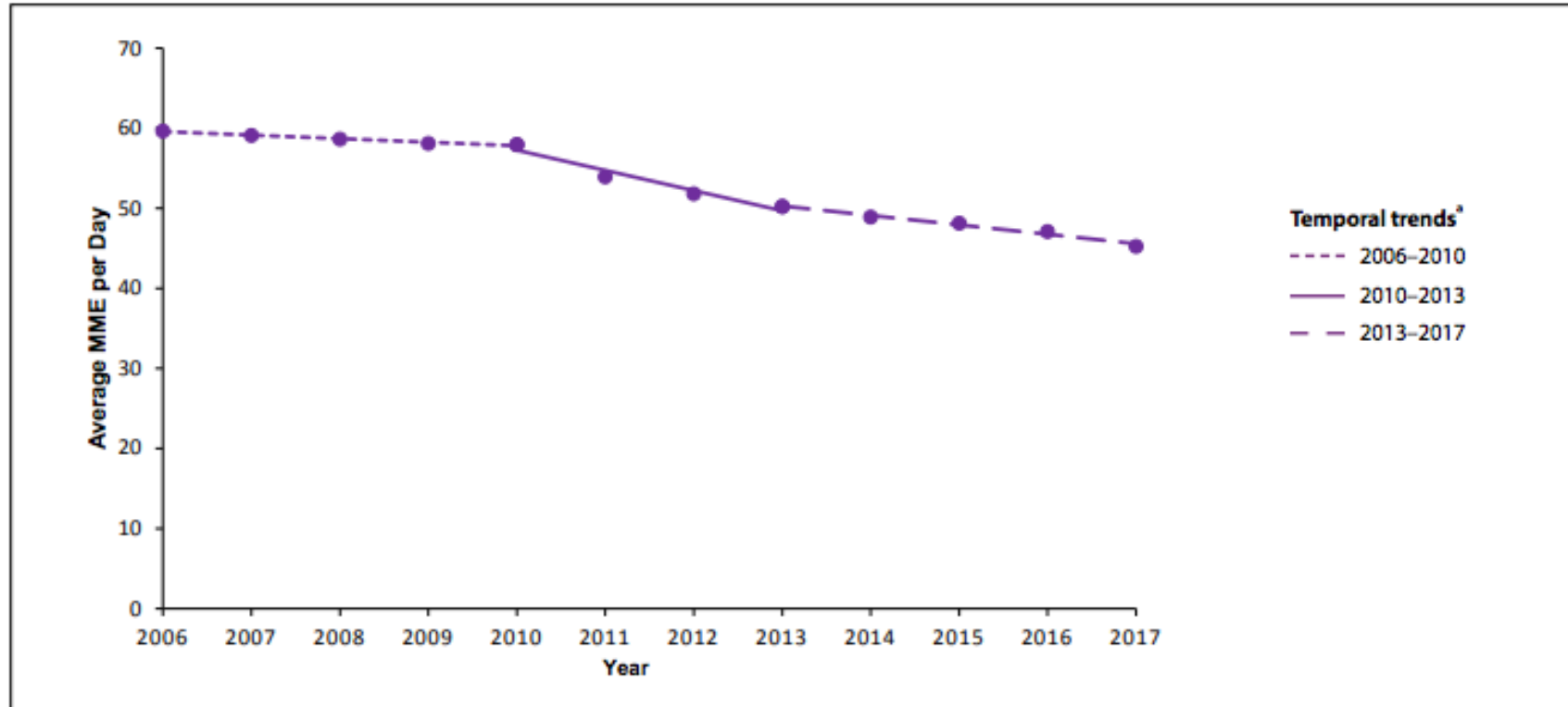
^bTemporal trends from 2006 to 2017 were evaluated by applying joinpoint regression methodology. This modeling approach simultaneously identified statistically significant trends as well as shifts in trends that occurred within a time series. A maximum of two joinpoints was allowed, and the permutation method was used for model selection. Different line dashes correspond to year groupings as determined by joinpoint regression.



MORE GOOD NEWS

FIGURE 1C

Average daily morphine milligram equivalents (MME) per opioid prescription^a — United States, 2006–2017



Source: IQVIA™ Transactional Data Warehouse.

Abbreviation: MME, morphine milligram equivalents.

^a Temporal trends from 2006 to 2017 were evaluated by applying joinpoint regression methodology.

This modeling approach simultaneously identified statistically significant trends as well as shifts in trends that occurred within a time series. A maximum of two joinpoints was allowed, and the permutation method was used for model selection. Different line dashes correspond to year groupings as determined by joinpoint regression.



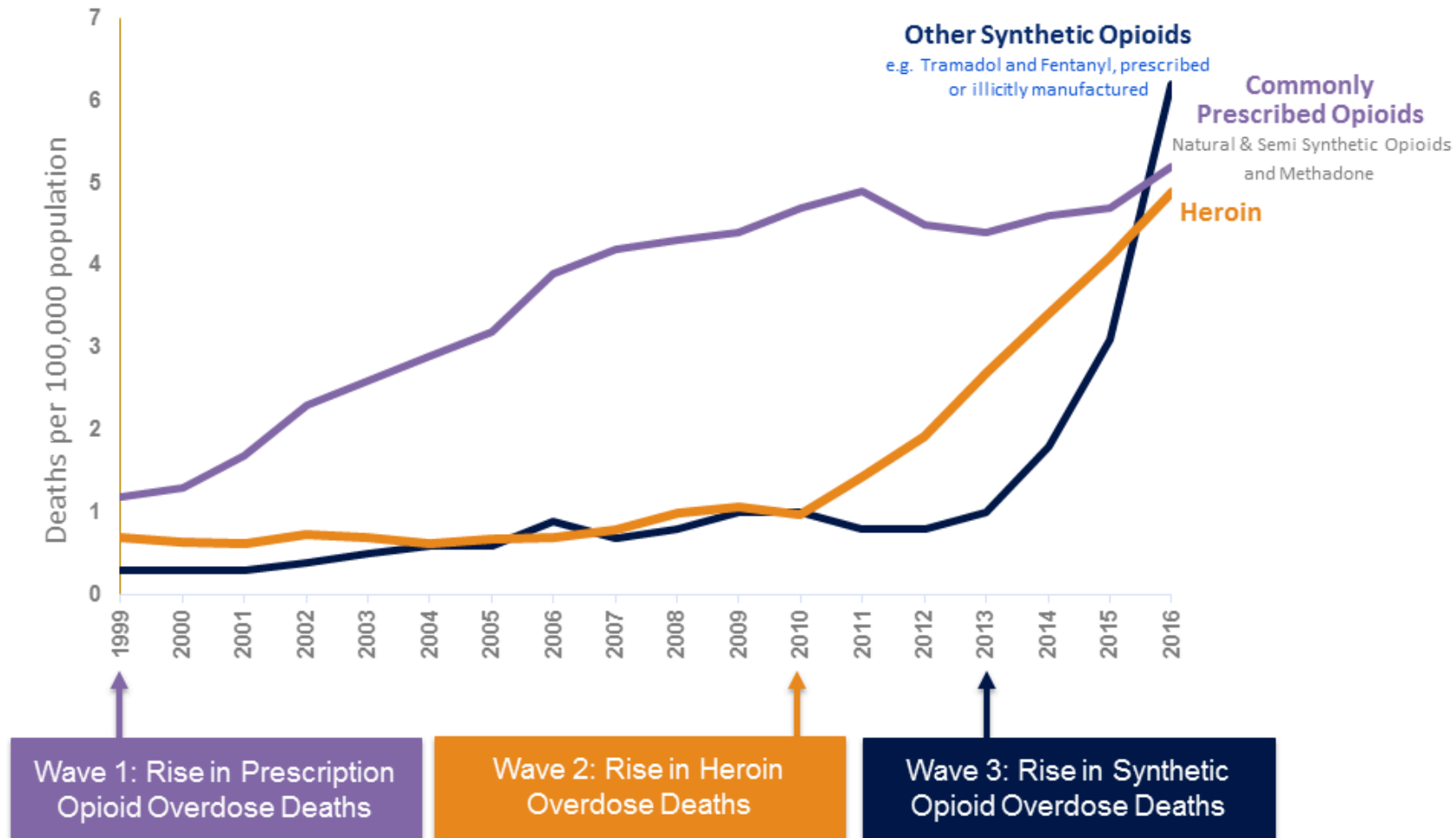
WHAT IS AN “MME”

- “Morphine Milligram Equivalent”
- A less than perfect way to compare relative risk of harms based on equianalgesic dosing
- One milligram of oral morphine is equivalent to:
 - 0.25 mg hydromorphone (Dilaudid)
 - 0.75 mg of oxycodone (Oxycontin, Roxicodone)
 - 0.33 mg of oxymorphone (Opana)
 - 0.25 mg of methadone
 - 3 mcg of fentanyl (0.003mg)



THE BAD NEWS

3 Waves of the Rise in Opioid Overdose Deaths

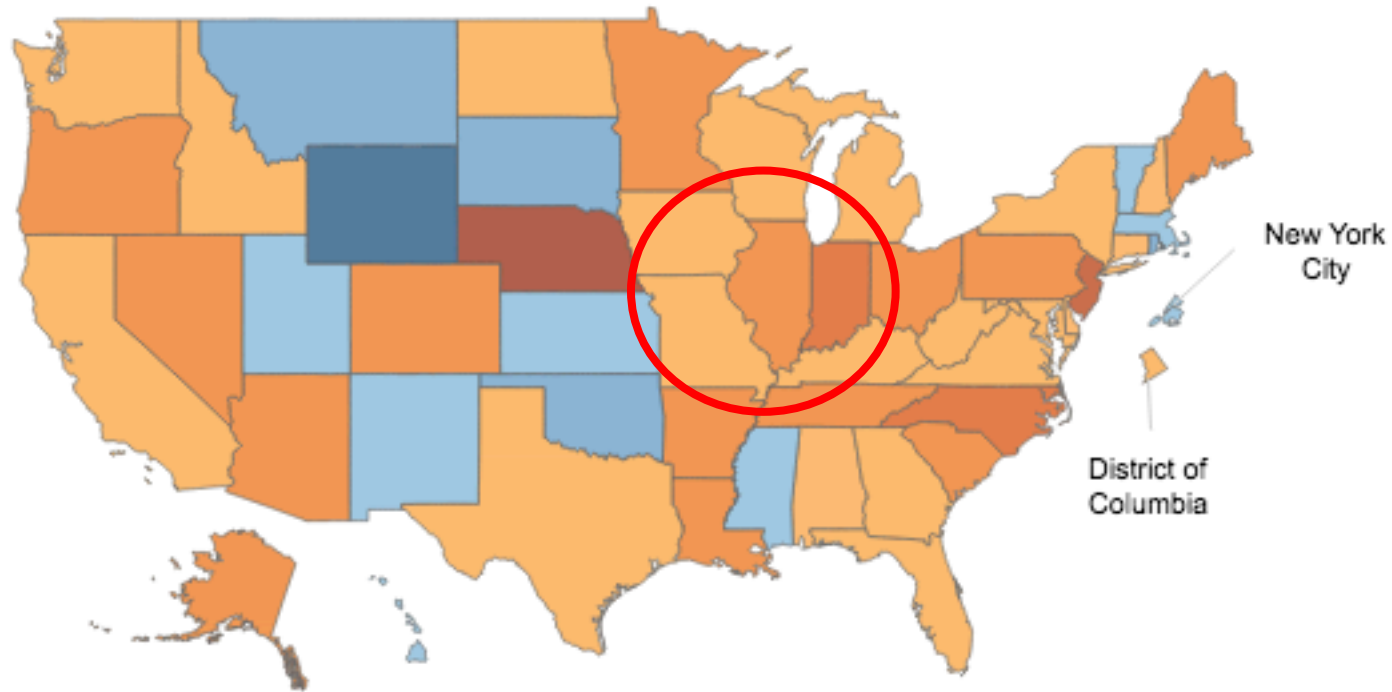


SOURCE: National Vital Statistics System Mortality File.



MORE BAD NEWS

Figure 1b. Percent Change in Reported 12 Month-ending Count of Drug Overdose Deaths, by Jurisdiction:
January 2017 to January 2018



Select predicted
or reported
number of deaths

- Predicted
- Reported

Percent Change for
United States

6.3

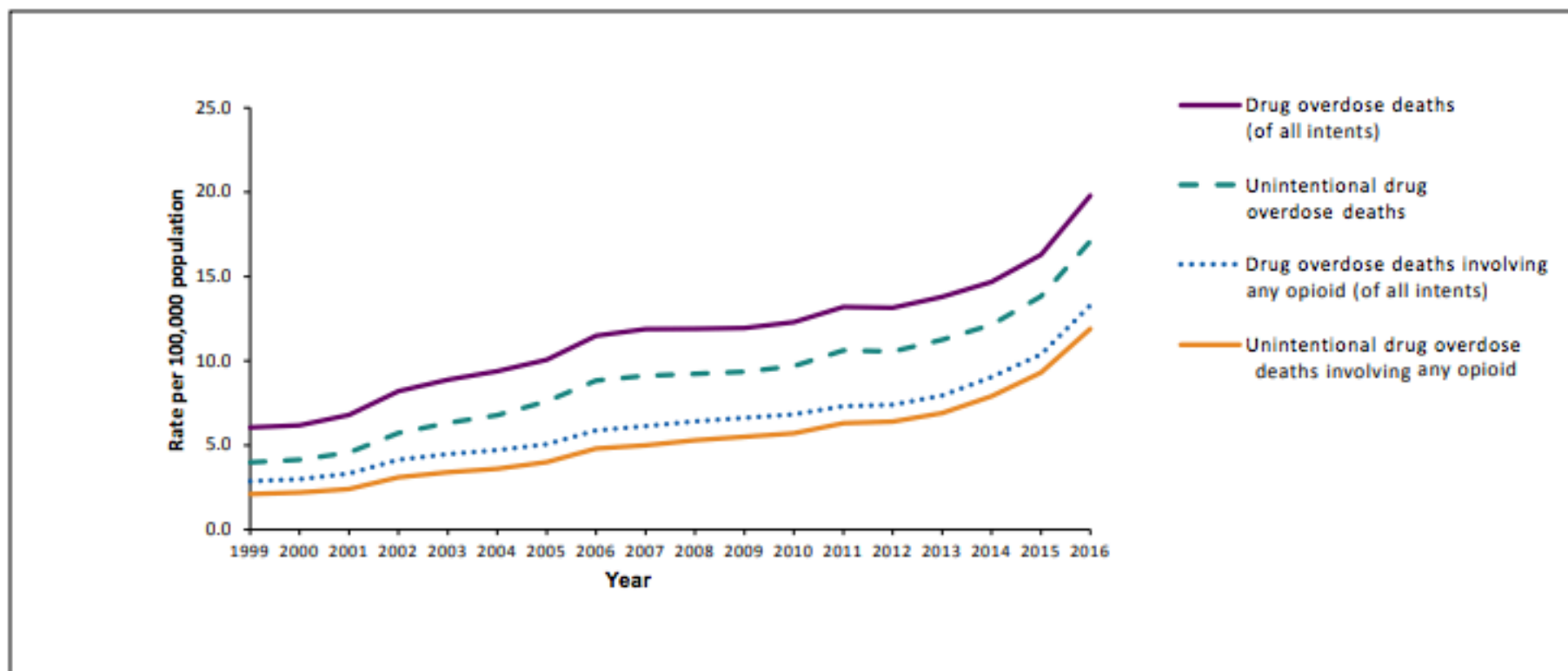
Legend for Percent Change in Drug Overdose Deaths Between 12-Month Ending Periods



Trends in Drug Overdose Deaths

FIGURE 2A

Age-adjusted rates^a of drug overdose deaths^b and drug overdose deaths involving any opioid^c for all intents and for unintentional intent by year — United States, 1999–2016



Source: National Vital Statistics System, Mortality File, CDC WONDER.

^a Rate per 100,000 population age-adjusted to the 2000 U.S. standard population using the vintage year population of the data year.

^b Deaths are classified using the International Classification of Diseases, Tenth Revision (ICD-10). All drug overdose deaths are identified using underlying cause-of-death codes X40–X44 (unintentional), X60–X64 (suicide), X85 (homicide), and Y10–Y14 (undetermined). Unintentional drug overdose deaths are identified using underlying cause-of-death codes X40–X44. Note that overall drug overdose deaths and opioid overdose deaths include deaths of any intent. In 2016, 5.7% of drug overdose deaths had undetermined intent; this is a decrease from 14.7% of drug overdose deaths that had an undetermined intent in 1999. Some of these deaths may be unintentional drug overdose deaths.

^c Drug overdose deaths, as defined, that involve opium (T40.0), heroin (T40.1), natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids excluding methadone (T40.4), and other and unspecified narcotics (T40.6). Specification on death certificates of drugs involved with deaths varies over time. In 2016, approximately 15% of drug overdose deaths did not include information on the specific type of drug(s) involved. Some of these deaths may have involved opioids.



OPIUM WARS

- 18 March 1839 through 29 August 1842
- Waged due to trade imbalance between Great Britain and China
 - Only commodity imported from Britain via India
 - Qing Yongzheng Emperor prohibited due to rising recreational use and abuse
- East India Company sought to prevent prohibition



MORPHINE FIRST ISOLATED ALKALOID

- Discovered in 1804 by Friedrich Sertuner
 - pharmacist's apprentice
- Originally called Morphium, for the Greek god morpheus
- Used extensively in the U.S. Civil War along with opium
 - "Soldier's Disease"
 - Estimated 400,000 U.S. soldiers addicted to morphine or opium by 1865 (1.2%)



HEROIN

(DIAMORPHINE, DIACETYLMORPHINE)

- First synthesized by Charles Alder Wright in 1874
 - boiled anhydrous morphine with acetic anhydride
- Sought to develop non-addictive alternative to morphine
- Wright was a chemistry and physics researcher
- Heinrich Dreser (Bayer Labs) further developed and marketed as a non-addictive cough suppressant



A SAFER ALTERNATIVE TO MORPHINE



Am. J. Ph.]

7

[December, 1901

BAYER Pharmaceutical Products **HEROIN—HYDROCHLORIDE**

is pre-eminently adapted for the manufacture of cough elixirs, cough balsams, cough drops, cough lozenges, and cough medicines of any kind. Price in 1 oz. packages, \$4.85 per ounce; less in larger quantities. The efficient dose being very small (1-48 to 1-24 gr.), it is

The Cheapest Specific for the Relief of Coughs

(In bronchitis, phthisis, whooping cough, etc., etc.)

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IS THE CURRENT "EMERGENCY" REALLY NEW?

44

CALIFORNIA STATE JOURNAL OF MEDICINE Vol. XII, No. 1

turbance of the stomach or the kidneys. Arheol is marketed only in the form of Arheol Capsules, 0.2 Gm. Alexandre Astier, Paris, France (Jour. A. M. A., Nov. 22, 1913, p. 1900).

Gluten Food A, Barker's.—A wheat-gluten flour, containing not more than 4 per cent. of carbohydrates and 87 per cent. protein.

Gluten Food B, Barker's.—A wheat-gluten flour, containing not more than 7 per cent. carbohydrates and 85 per cent. protein.

Gluten Food C, Barker's.—A wheat-gluten flour, containing not more than 12 per cent. of carbohydrates and 83 per cent. protein.

Barker's gluten foods are indicated when a

USE OF HEROIN SPREADING RAPIDLY AMONG DRUG FIENDS.

Washington, D. C.—According to information gathered by the U. S. Department of Agriculture, there has been a sudden and very significant increase in the use by persons with a drug habit of the little-known but very dangerous drug called "heroin." The sales of this drug have recently increased greatly, particularly in those States which have rigid laws preventing the indiscriminate sale of morphine and cocaine. Investigation of the subject establishes the fact that many drug victims who formerly used morphine and cocaine, and who



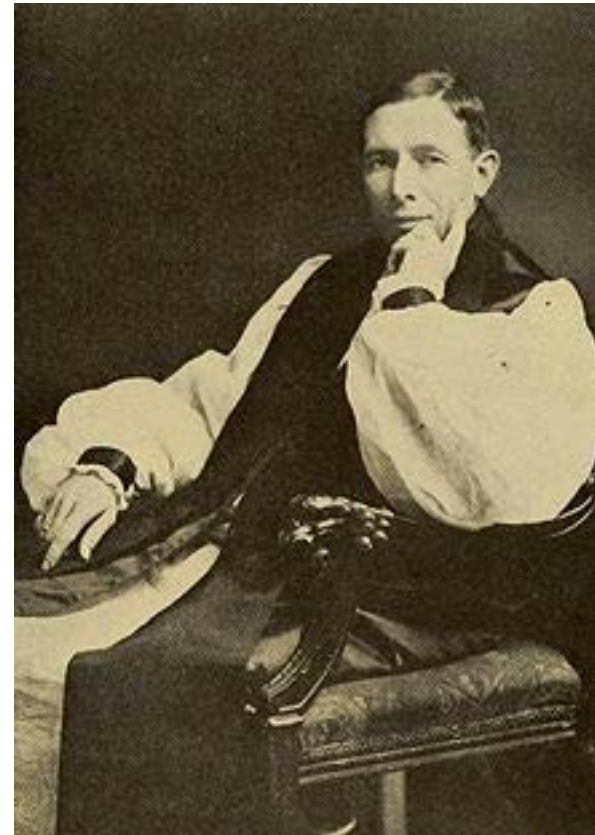
HAMILTON WRIGHT

- First U.S. Opium Commissioner
- Served as U.S. Delegate to the International Opium Commission
- “Of all the nations of the world, the U.S. consumes the most habit-forming drugs per capita...”
 - Wright, New York Times, 1911
- Addicts in NYC (1920) collected scrap



MODERN CONTROLS

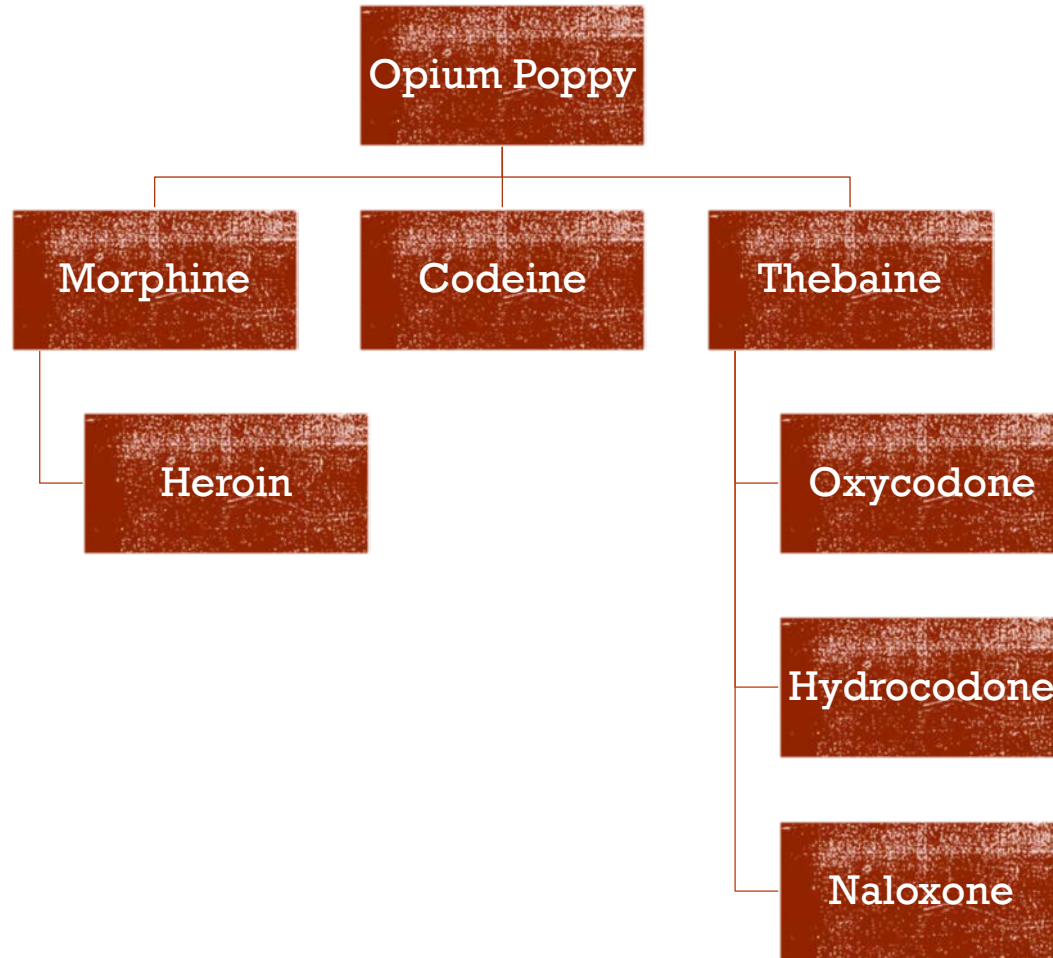
- **Brent Commission (1901)**
 - Philippines acquired by US
 - Significant opium addiction
- **Int. Opium Convention (1912)**
 - Orchestrated by T. Roosevelt
 - Called for international controls
- **Harrison Narcotics Tax Act (1914)**
 - Regulated opium and coca
- **Single Convention on Narcotic Drugs (1961)**
- **Controlled Substances Act (1970)**



Charles Henry Brent



OPIUM (*PAPAVER SOMNIFERUM*)



Many other alkaloids with little to no analgesic or euphoric properties



REGULATED AND ILLICIT OPIUM CULTIVATION



POPPY STRAW



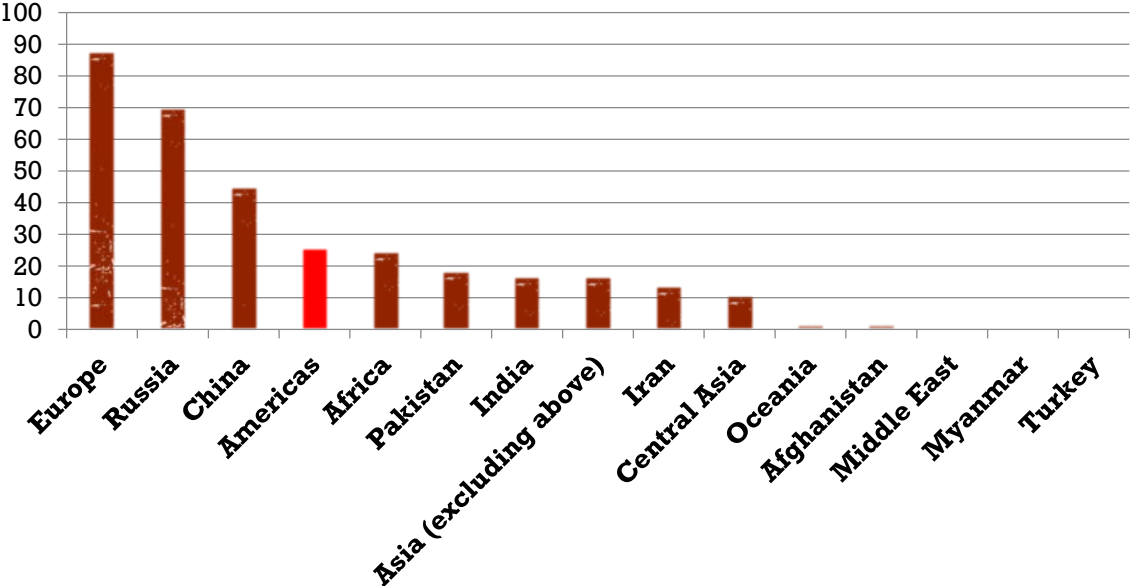
Labor intensive scoring and harvesting of opium latex no longer required



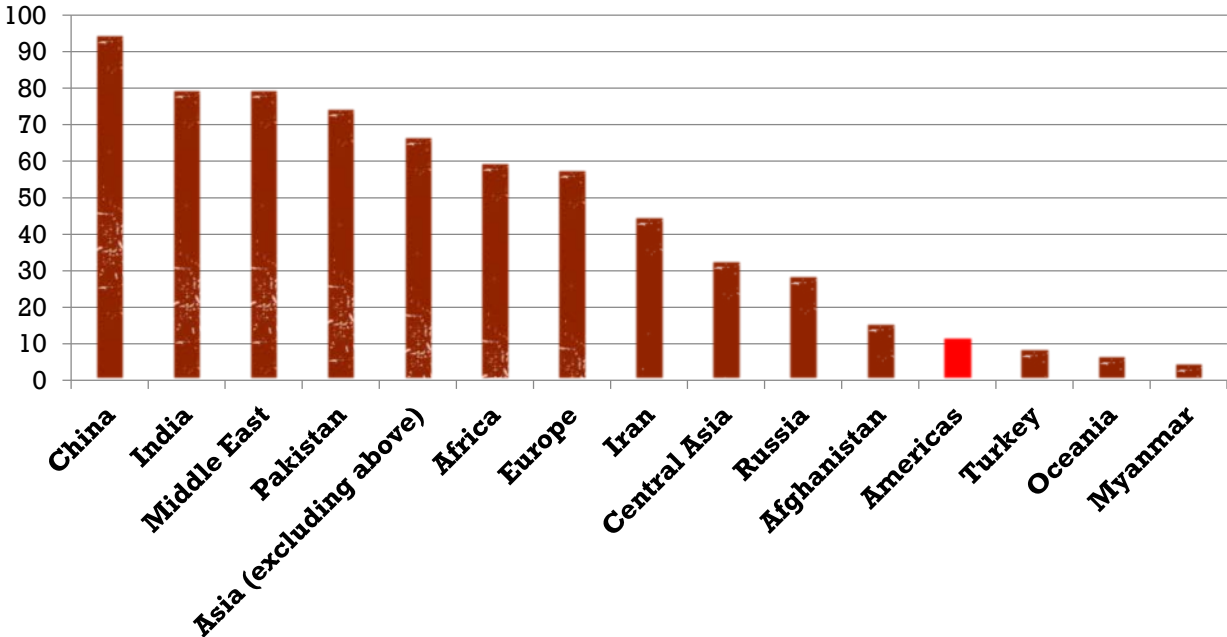
GLOBAL CONSUMPTION, 2008

IN METRIC TONS

Heroin Consumption



Opium Consumption



U.S. OPIUM IMPORTATION

- Special DEA license required
 - Mallinckrodt, Noramco (Johnson & Johnson), Abbott, Purdue, and Cody
 - Of these, three are active with Mallinckrodt representing 70-90% of import
- Must follow “80/20” rule requiring licit importation from India and Turkey (80%) and others (20%)
- Mallinckrodt and Noramco try to block all new importation licenses
- DEA sets annual quotas for importation and production

Top 10 Indian Exports to US

India's exports to the US amounted to \$42.6 billion or 13.4% of its overall exports.

1. Gems, precious metals, coins: \$8 billion
2. Oil: \$4.4 billion
3. Pharmaceuticals: \$3.8 billion
4. Other textiles, worn clothing: \$2.2 billion
5. Machines, engines, pumps: \$2 billion
6. Clothing (not knit or crochet): \$2 billion
7. Organic chemicals: \$1.6 billion
8. Iron or steel products: \$1.6 billion
9. Knit or crochet clothing: \$1.6 billion
10. Gums, resins: \$1.6 billion





Jillian Berman [Become a fan](#) [✉](#) [👍](#)
Jillian.Berman@huffingtonpost.com

How A Big Drug Company Inadvertently Got Americans Hooked On Heroin

Posted: 02/24/2014 7:55 am EST | Updated: 02/25/2014 11:59 am EST

ADDICTION

OxyContin users switching to heroin after drug is redesigned

By **Alex Crees** · Published July 12, 2012 · FoxNews.com



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We make technology simple,
so you can invest confidently.

Lea

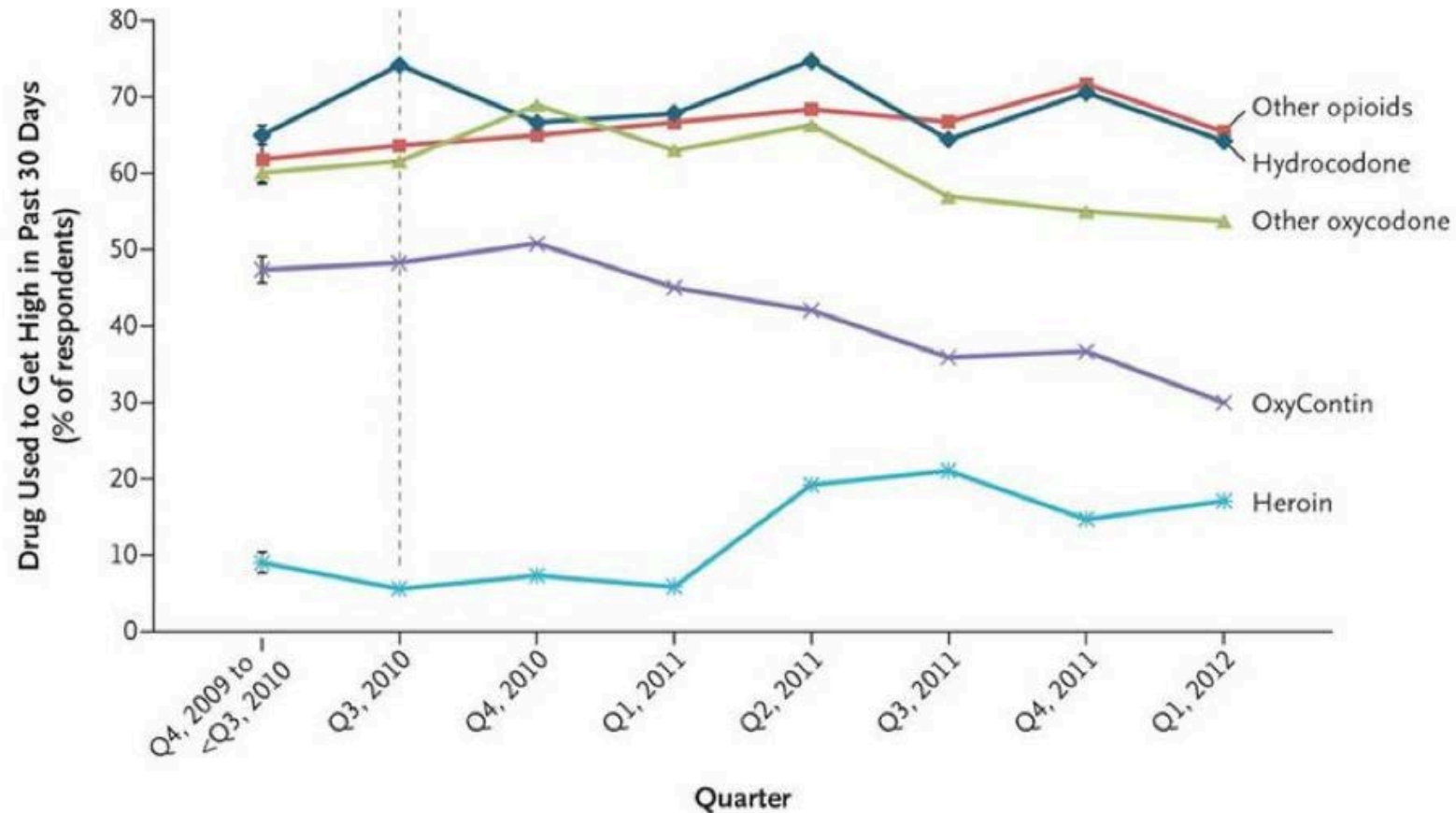
By **MICHELLE CASTILLO** / CBS NEWS / July 12, 2012, 6:13 PM

With OxyContin farther from their grasp, more users switching to heroin

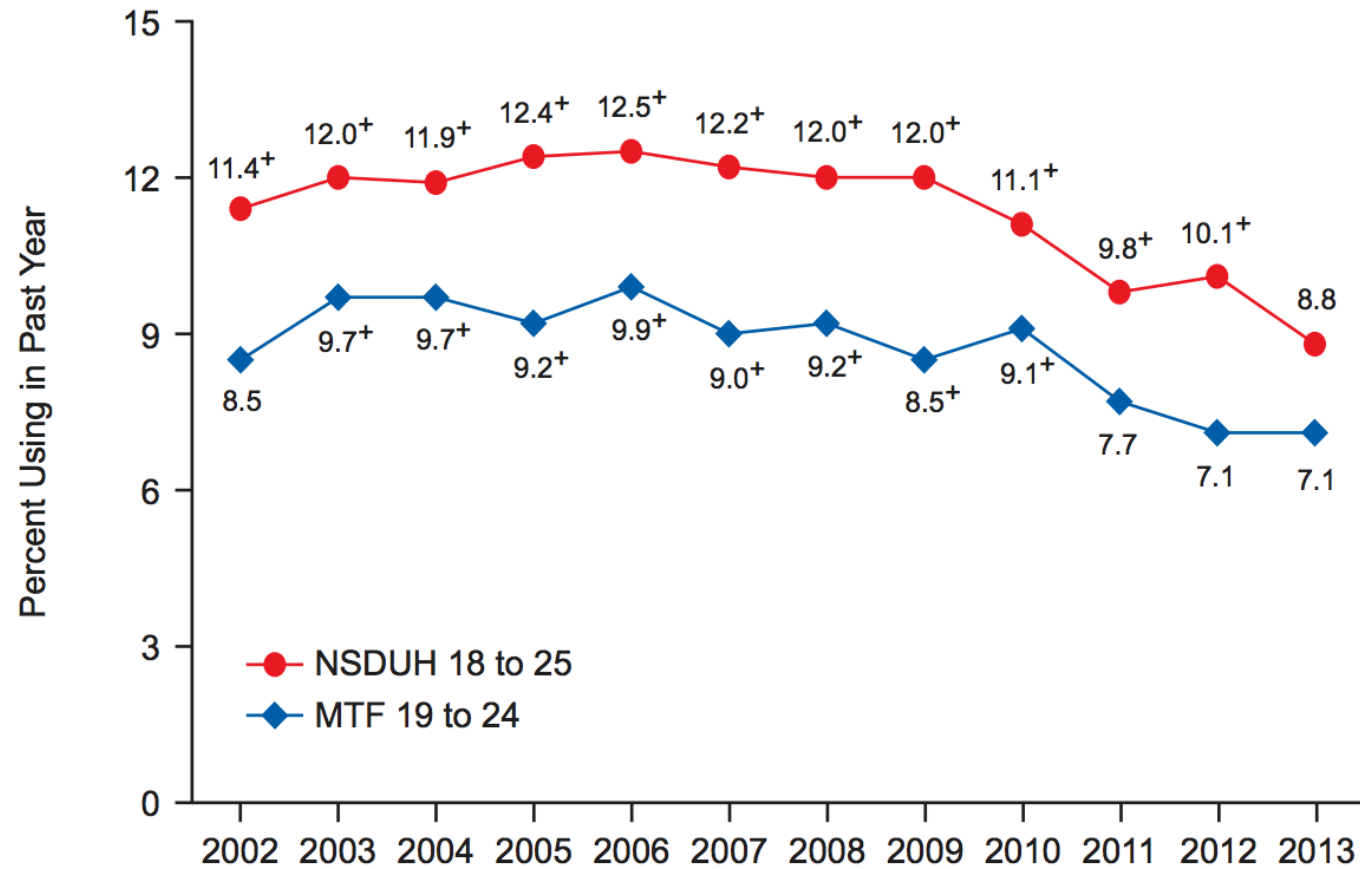


DRUGS USED TO GET HIGH

(ALL RESPONDERS)



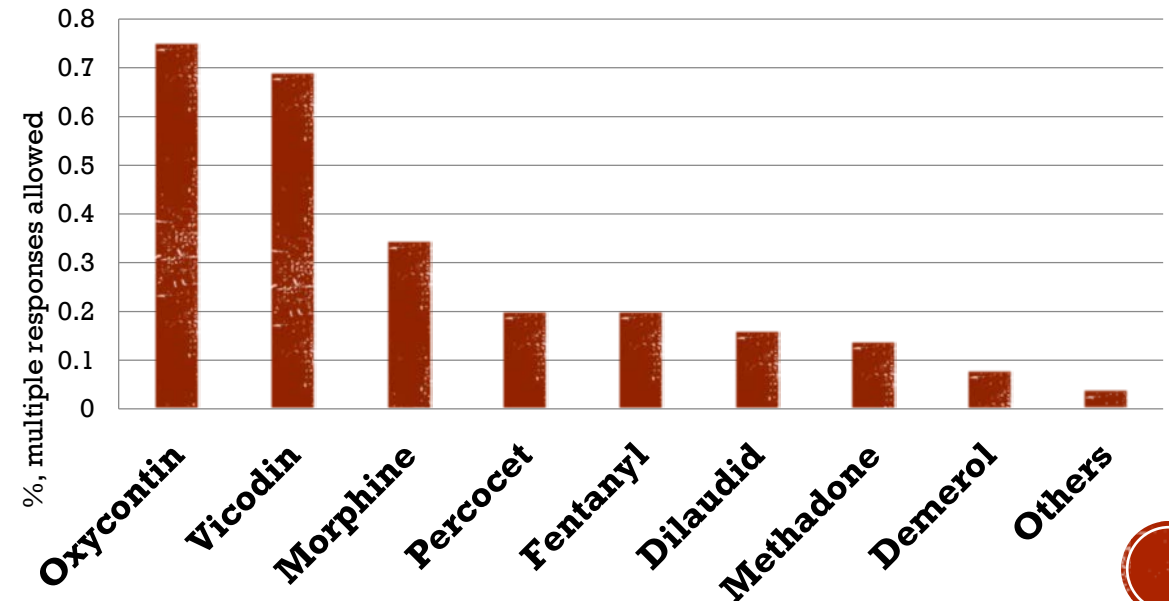
PAST YEAR NON-MEDICAL USE OF OPIOIDS, U.S.



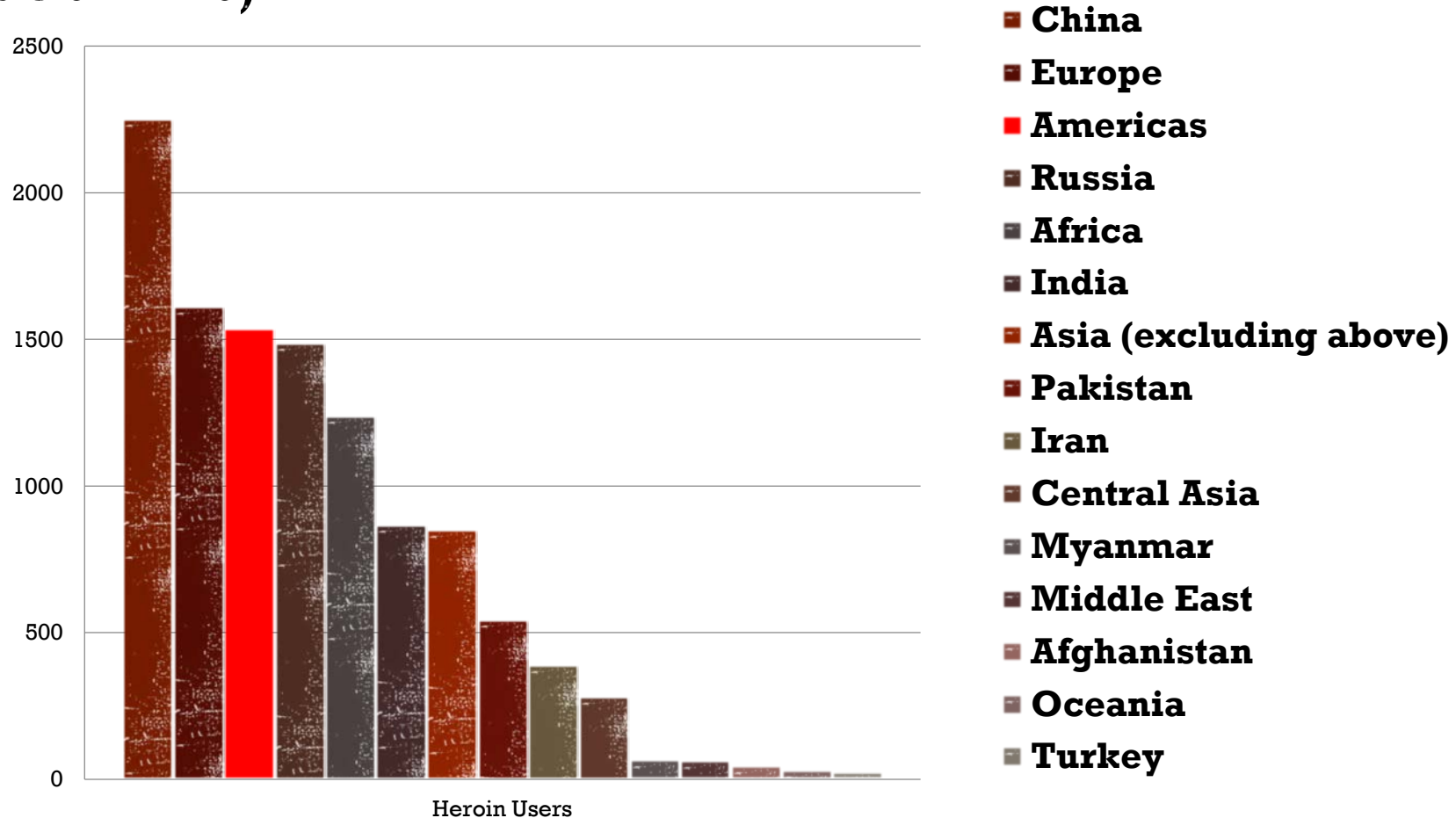
PRESCRIPTION OPIOIDS AND HEROIN ABUSE

- Quantitative questionnaire using street outreach, venue-recruitment, and needle-exchange advertisement (n = 123)
- Median age 29 yrs (75% male, 53% white, 28% hispanic, 19% black or other)
- 39.8% reported problematic prescription opioid use prior to first heroin use

Prior Prescription Opioid Abuse, by Drug



GLOBAL HEROIN USERS, 2008 (IN THOUSANDS)

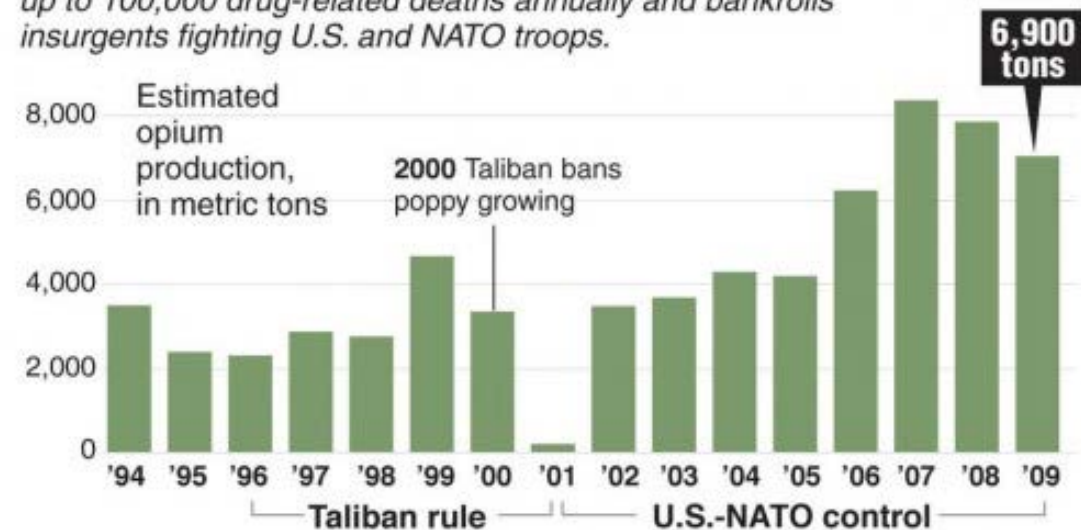


IS THE U.S. TO BLAME?

- Illicit opium
 - 90% Afghanistan
 - 5% Mexico
- Licit opium
 - 70% India
 - 20% France

Afghanistan's deadly crop

Afghanistan produces 90 percent of the world's opium*. The drug causes up to 100,000 drug-related deaths annually and bankrolls insurgents fighting U.S. and NATO troops.



Source: U.N. Office on Drugs and Crime
Graphic: Judy Treible

*Heroin is made from opium

© 2009 MCT





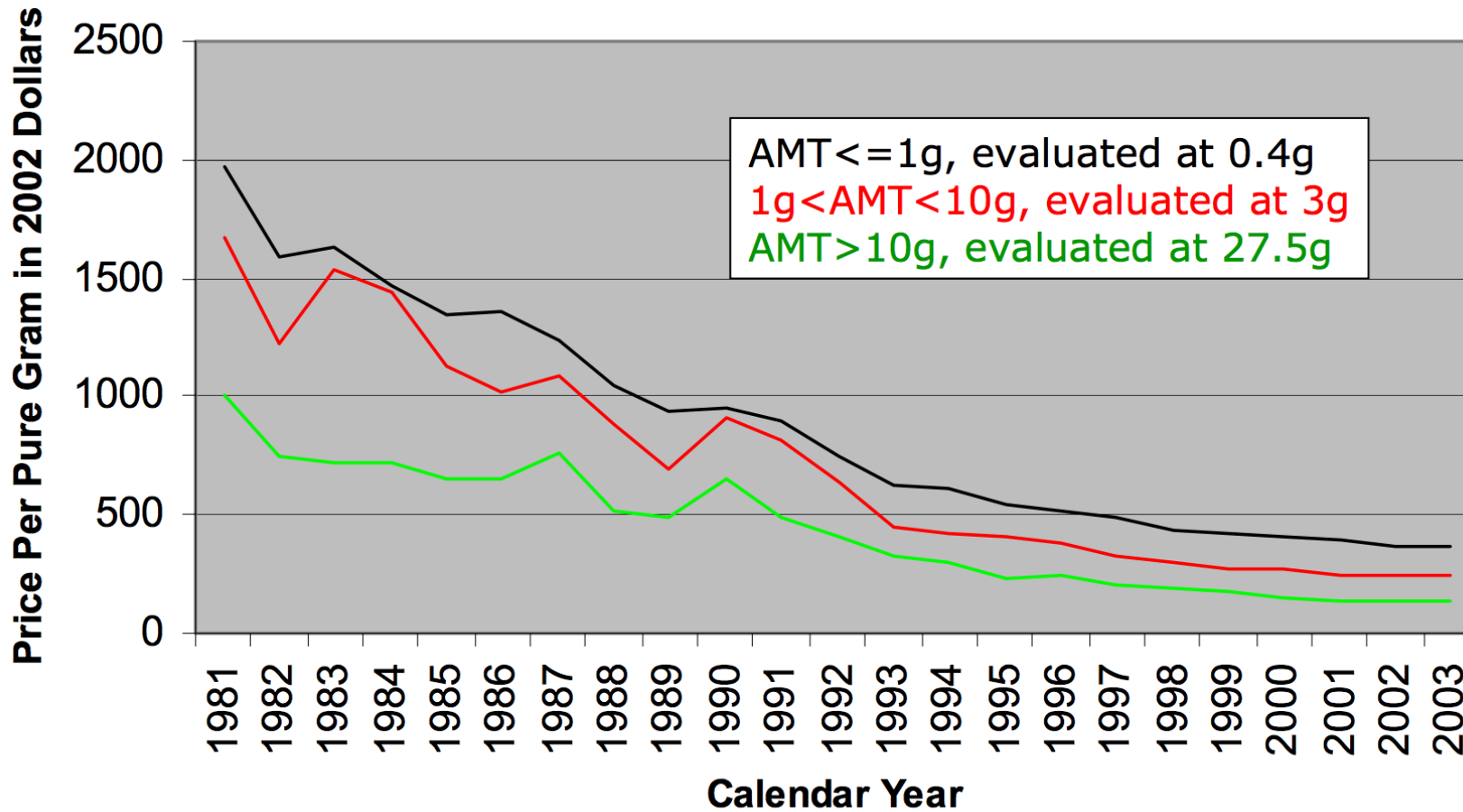
OTHER CONSPIRACY THEORIES

Ahmed Wali Karzai and the Overseas Private Investment Corporation

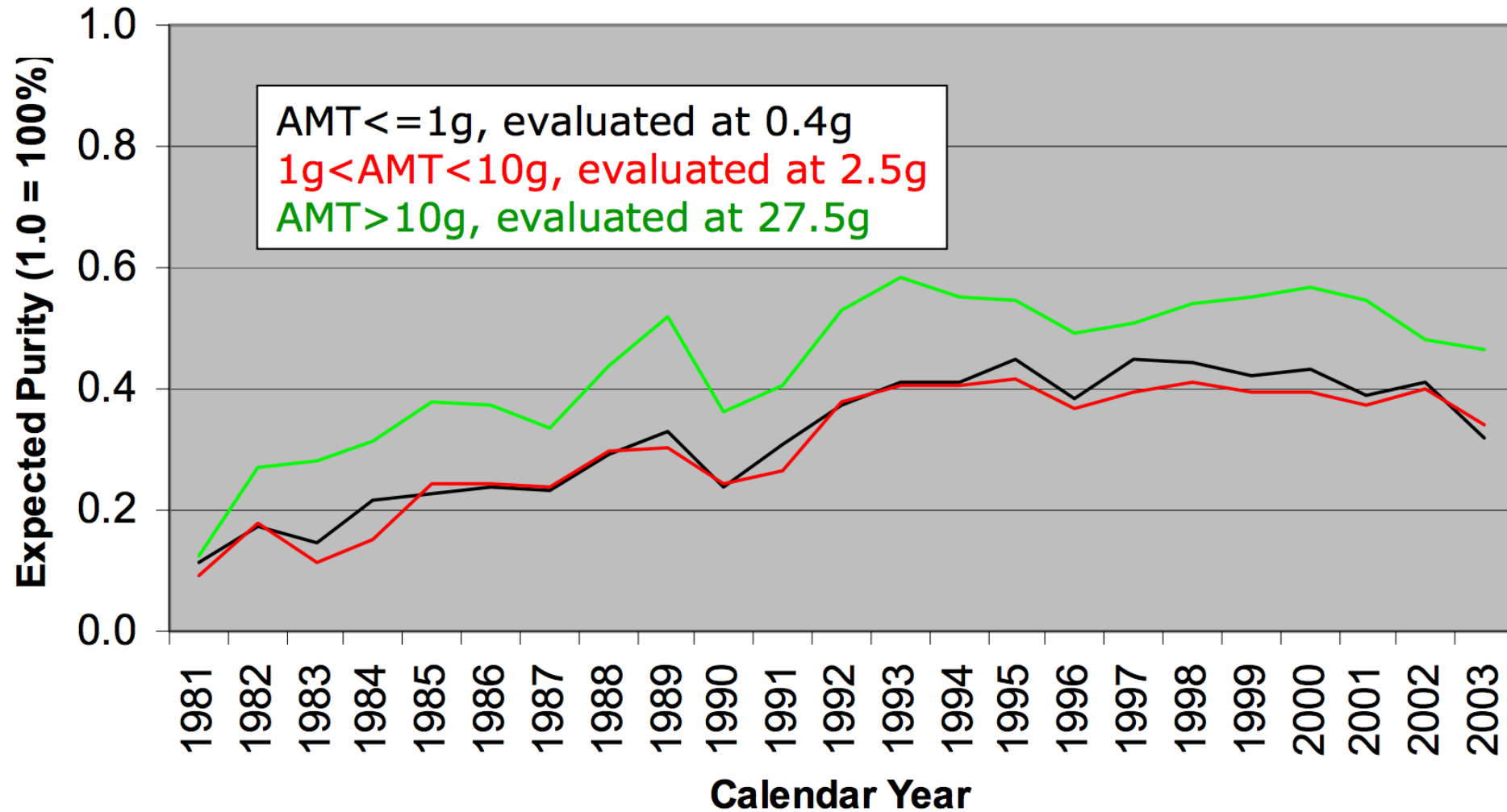


HEROIN COST

(BLACKMARKET, 2002 USD)



HEROIN PURITY



INTRAVENOUS MORPHINE VS. DIACETYLMORPHINE

- Randomized, DB, cross-over study (n = 39)
- Participants were long-standing IV opioid users
- Group A: started on morphine, titrated to effect
- Group B: started on diacetylmorphine, titrated to effect
 - At cross-over, both groups preferred diacetylmorphine
 - Diacetylmorphine preferred due to lower rates of itching, flushing, urticaria, and nausea
 - Euphoria negatively correlated with dose in both groups



INTRAVENOUS MORPHINE VS. DIACETYLMORPHINE... AGAIN

VAR parameter	Heroin group <i>M</i> (<i>SD</i>)	Morphine group <i>M</i> (<i>SD</i>)	<i>t</i> -Tests heroin vs morphine ^a
Euphoria [<i>t</i> -1]→euphoria [<i>t</i>]	2.06*** (1.42)	1.59** (2.1)	<i>t</i> =0.75 (<i>P</i> =0.461)
Euphoria [<i>t</i> -2] →euphoria [<i>t</i>]	0.49 (1.32)	0.84 (1.77)	<i>t</i> =0.65 (<i>P</i> =0.518)
Adverse effects [<i>t</i> -1] →adverse effects [<i>t</i>]	0.64* (1.19)	1.32** (1.1)	<i>t</i> =1.70 (<i>P</i> =0.099)
Adverse effects [<i>t</i> -2] →adverse effects [<i>t</i>]	-0.17 (1.06)	0.02 (0.91)	<i>t</i> =0.57 (<i>P</i> =0.575)
Euphoria [<i>t</i> -1] →adverse effects [<i>t</i>]	-0.01 (1.06)	-0.41 (1.42)	<i>t</i> =0.93 (<i>P</i> =0.359)
Euphoria [<i>t</i> -2] →adverse effects [<i>t</i>]	0.01 (1.27)	0.01 (1.35)	<i>t</i> =0.00 (<i>P</i> =0.999)
Adverse effects [<i>t</i> -1] →euphoria [<i>t</i>]	-0.09 (1.44)	-0.16 (1.26)	<i>t</i> =0.14 (<i>P</i> =0.892)
Adverse effects [<i>t</i> -2] →euphoria [<i>t</i>]	0.71** (0.85)	-0.62* (0.9)	<i>t</i> =4.39 (<i>P</i> <0.001)
Linear trend of euphoria	1.00 ^{ab} (1.96)	0.39 (2.33)	<i>t</i> =0.81 (<i>P</i> =0.422)
Linear trend of adverse effects	-0.81 ^b (1.45)	-1.15* (2.13)	<i>t</i> =0.54 (<i>P</i> =0.593)
Constant of euphoria	-0.99 (3.05)	-0.19 (3.51)	<i>t</i> =0.70 (<i>P</i> =0.491)
Constant of adverse effects	-0.82 (2.18)	1.09 (2.10)	<i>t</i> =2.53 (<i>P</i> =0.016)

Asterisks, test of the null hypotheses that mean VAR parameters were zero (**P*<0.05; ***P*<0.01; ****P*<0.001). *t*-Tests, univariate comparisons of substance groups

^a Whole model test of difference was significant [MANOVA *F*(10,22)=2.38, *P*=0.044]

^b Wilcoxon test was used because of non-normal distribution

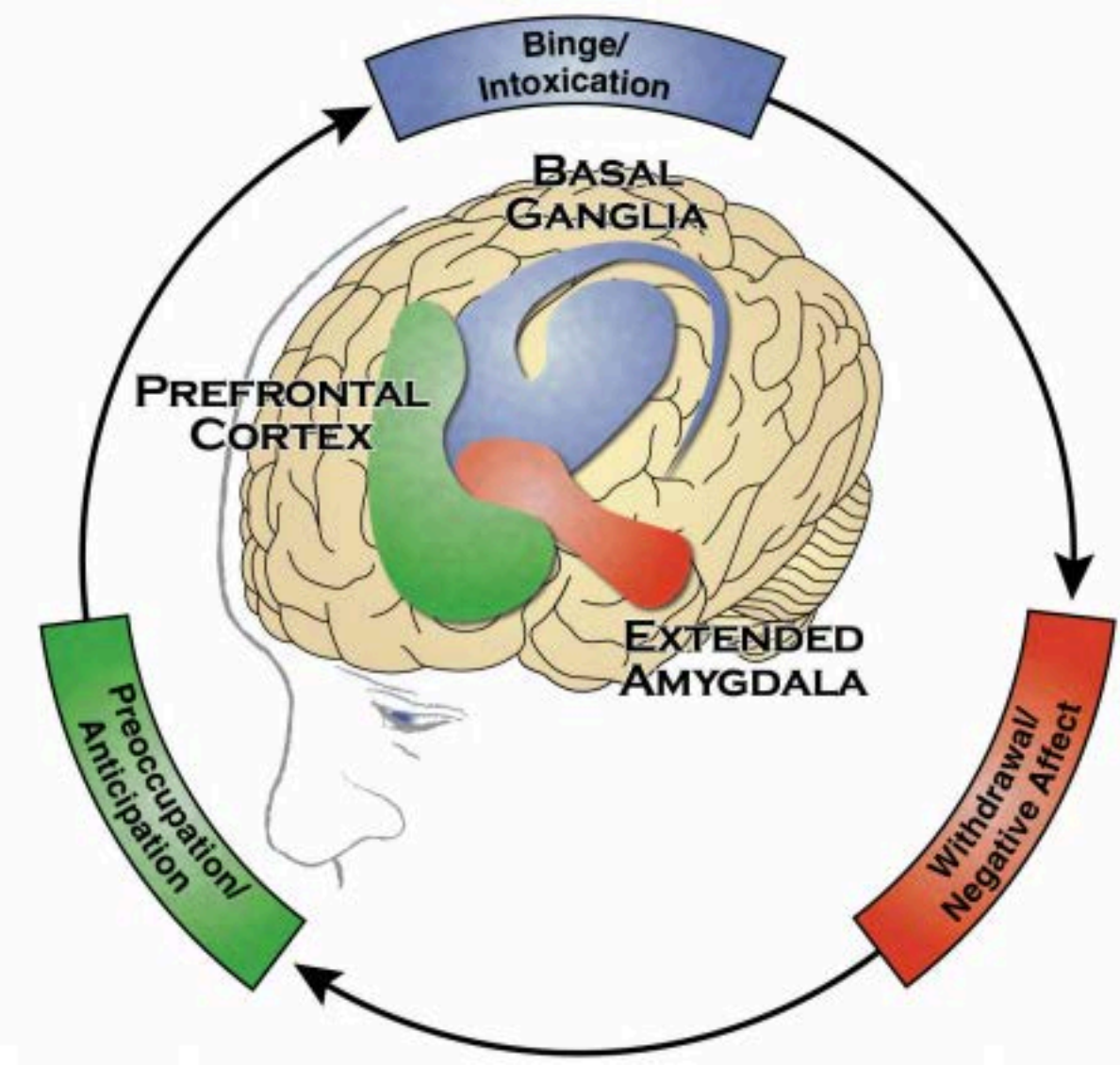


There are many factors that impact America's drug overdose crisis.

www.cdc.gov



Figure 2.3: The Three Stages of the Addiction Cycle and the Brain Regions Associated with Them



DIAGNOSIS OF OPIOID USE DISORDER (OUD)

Diagnostic Criteria for Substance Use Disorders

Using in larger amounts or for longer than intended

Wanting to cut down or stop using, but not managing to

Spending a lot of time to get, use, or recover from use

Craving

Inability to manage commitments due to use

Continuing to use, even when it causes problems in relationships

Giving up important activities because of use

Continuing to use, even when it puts you in danger

Continuing to use, even when physical or psychological problems may be made worse by use

Increasing tolerance

Withdrawal symptoms

Notes: Fewer than 2 symptoms = no disorder; 2-3 = mild disorder; 4-5 = moderate disorder; 6 or more = severe disorder.

Source: American Psychiatric Association, (2013).³⁰



SUICIDE AND OPIOIDS

- 44,965 suicides in the US in 2016
 - 50% firearm
 - 15% drug overdose
 - 4.3% opioid (10 year 2 fold increase)
- Problems with classification of “intentional” versus “unintentional”



SUICIDE RISK IN THOSE WITH OUD

- Suicide risk in those with OUD is 87:100,000 (6 times general population)
- Substance use disorder involving opioids assoc. with 40-60% increase in SI
- Regular use of opioids 75% more likely to make suicide plans
- Regular use of opioids 50% more likely to attempt suicide



SUICIDE RISK IN THOSE WITH CHRONIC PAIN

Petrosky et al.

- Retrospective analysis of National Violent Death Reporting System data
- N = 123,181
 - 8.8% had evidence of chronic pain (increased from 7.4% to 10.2% over 10 year period)
 - 53.6% decedents completed via firearm
 - 16.2% decedents completed via opioid overdose



SUICIDE RISK IN THOSE WITH CHRONIC PAIN

Calati et al.

- Meta-analysis of 31 studies with variable reporting

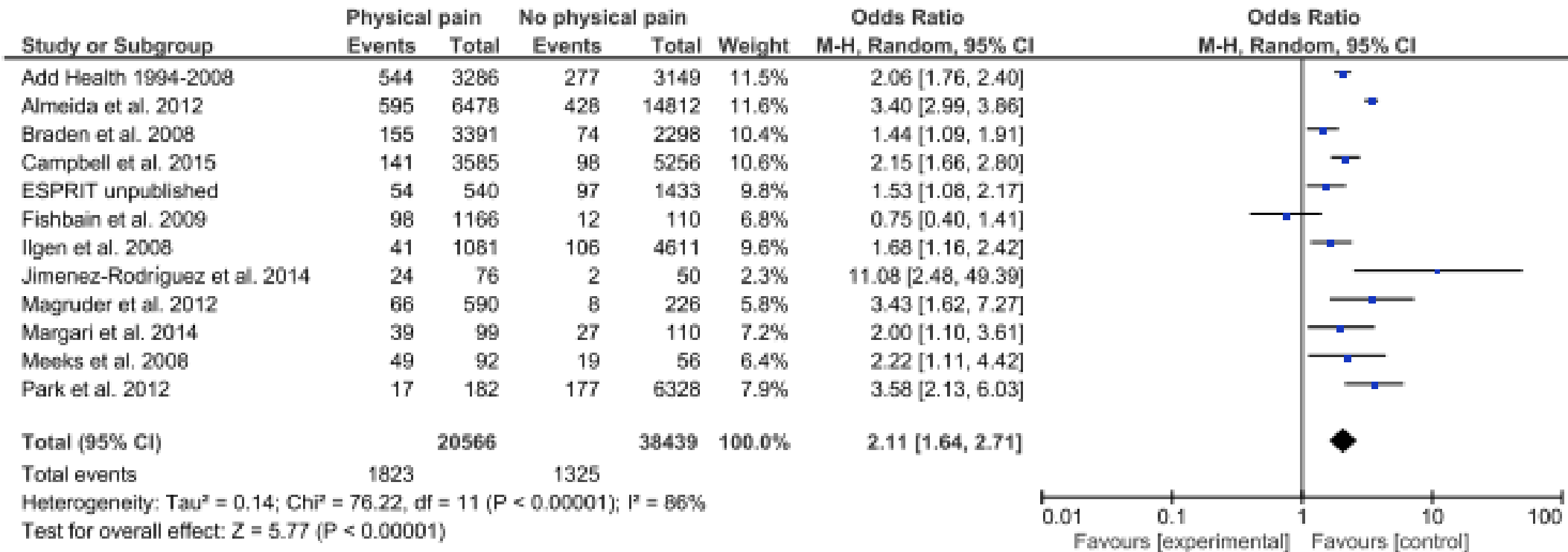


Fig. 3. Forest plot of trials comparing current suicidal ideation rates in individuals with and without physical pain.



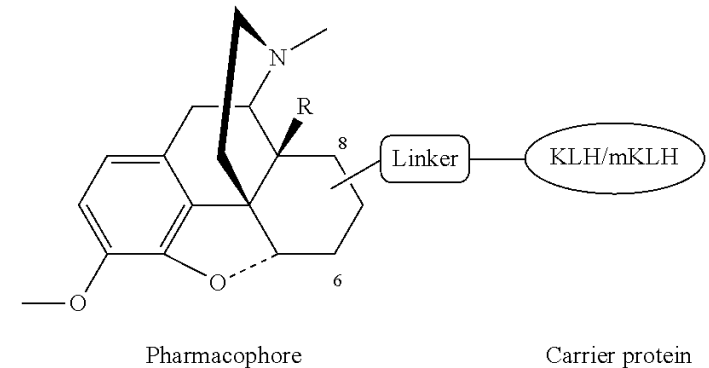
POTENTIAL SOLUTIONS

- Medication Assisted Therapy
 - Buprenorphine containing
 - Methadone
 - Naltrexone (oral and intramuscular)
- Psychotherapy
- Vaccination
- Decreased access
 - Drug take back and enhanced disposal
 - Provider education for judicious prescribing
 - DEA quota reductions
- Vaccination?
- Awareness of warning signs!



OPIOID VACCINE?

- Designed as opioid conjugate vaccines using haptens conjugated to keyhole limpet hemocyanin (KLH)
- Enduring antibodies bind target drugs and alter GPCR binding and CNS distribution
- oxy-MLH (oxycodone and oxymorphone)
- M-KLH (morphine, heroin, 6-MAM)



R = H or OH



CONCLUSIONS

- Death by opioid overdose continue to rise, despite reduced prescribing
- Opioid overdose related deaths are difficult to categorize as intentional vs. unintentional
- Chronic pain may be an independent risk factor for suicide attempt
- Harm reduction from opioids should include suicide risk screening

