Opioid Dependence and Its Treatment

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Goals for this talk

By the end of this presentation the participant should be able to:

a) describe current rates of illicit opioid use in the United States;

b) name three medications used for the treatment of opioid dependence;

c) identify at least three signs and symptoms of opioid withdrawal.

Disclosures

I have received consulting fees from Indivior and Egalet Pharmaceuticals in the past year, and support from The Oak Group and Pinney Associates for serving on Advisory Boards.

A confession

This is a somewhat U.S. centered talk. At least two reasons for this.

1. I know the local U.S. situation

2. It seems presumptuous to think I could talk about the local features of drug abuse in Taiwan

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(I would also note that the U.S. is often in the vanguard of drug use trends – unfortunately)

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I. Why is the United States so concerned about opioid abuse?

II. Opioid addiction/dependence and withdrawal

III. Treatments available for opioid dependence/addiction

IV. Summary and conclusions

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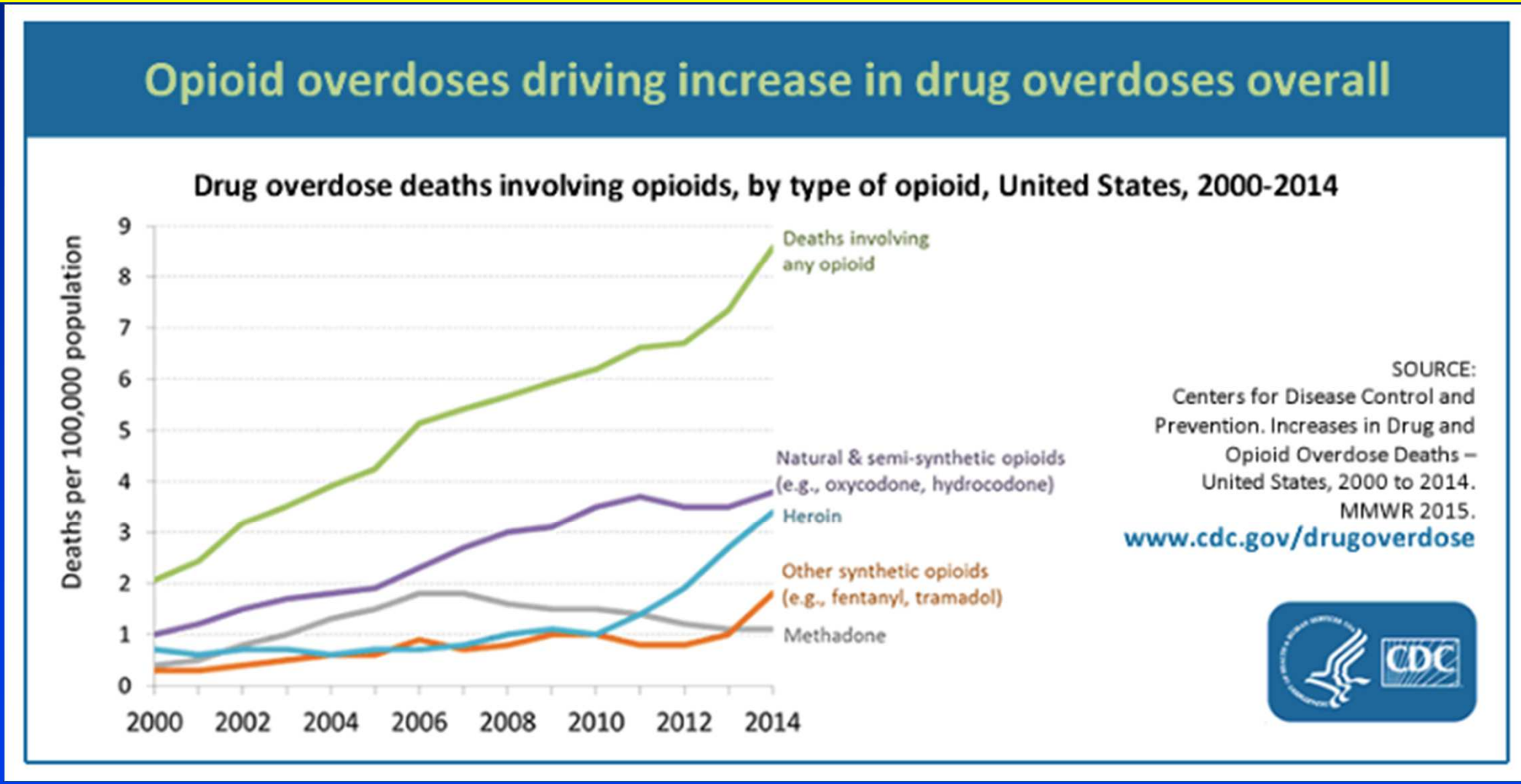
Opioid overdoses



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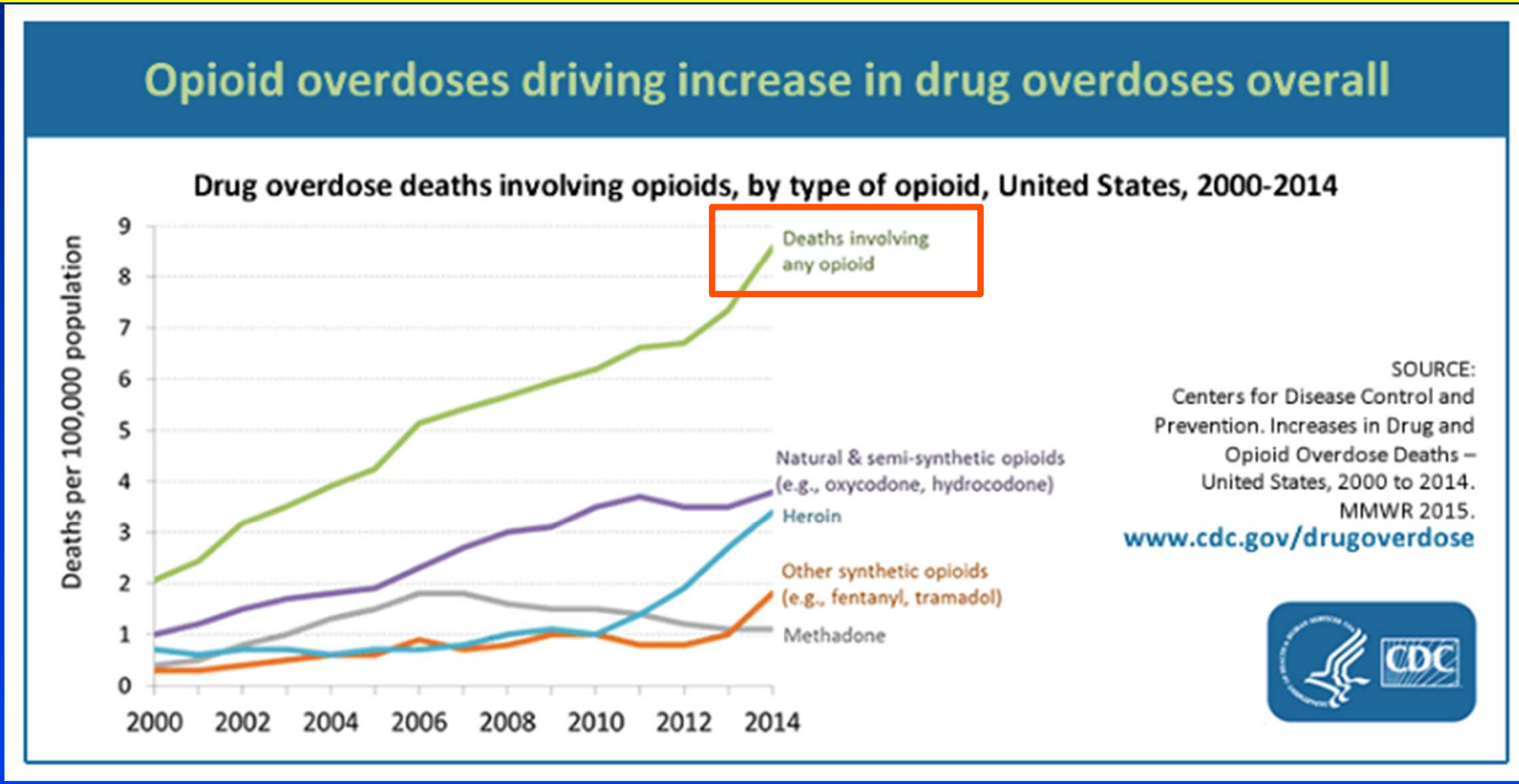

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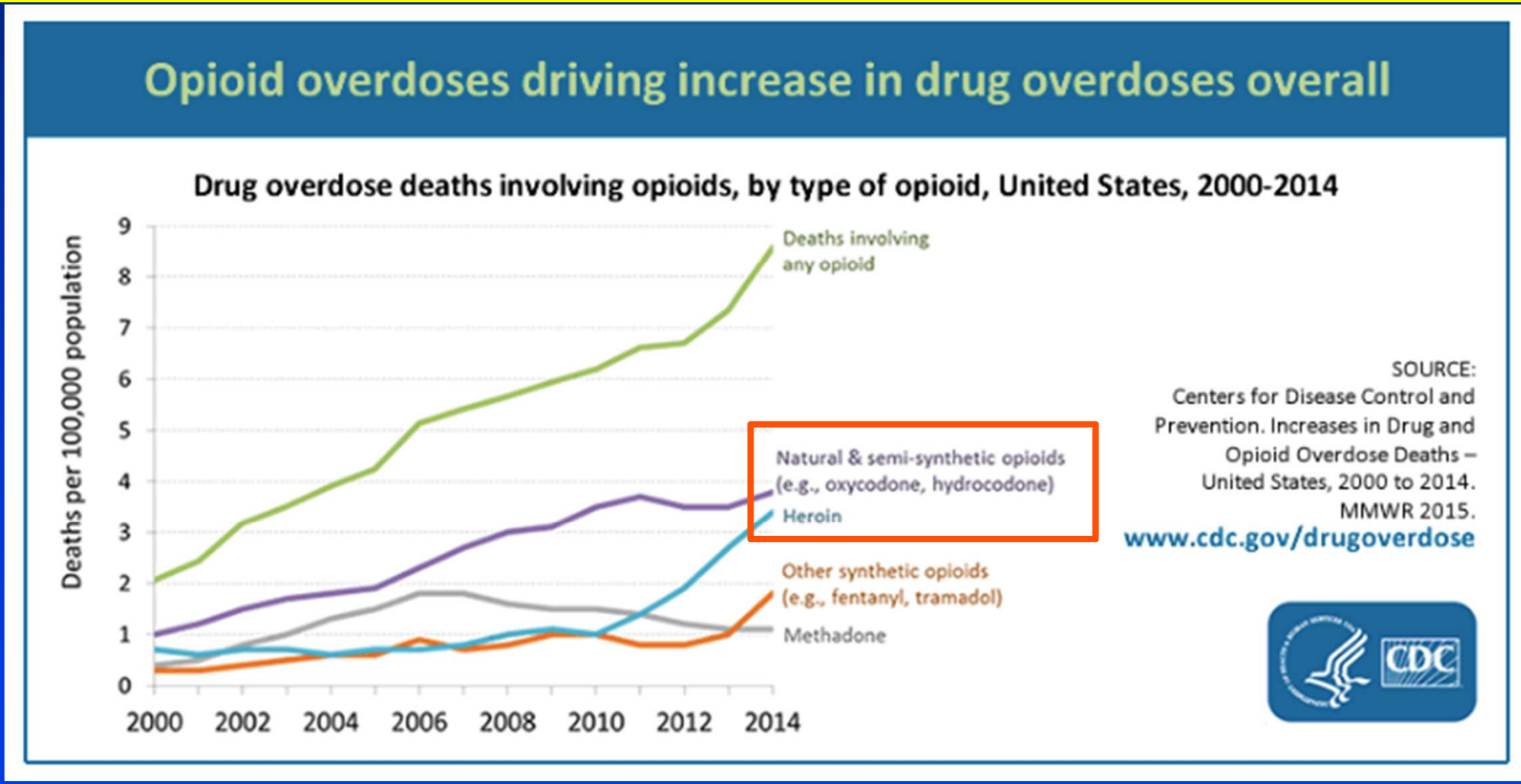

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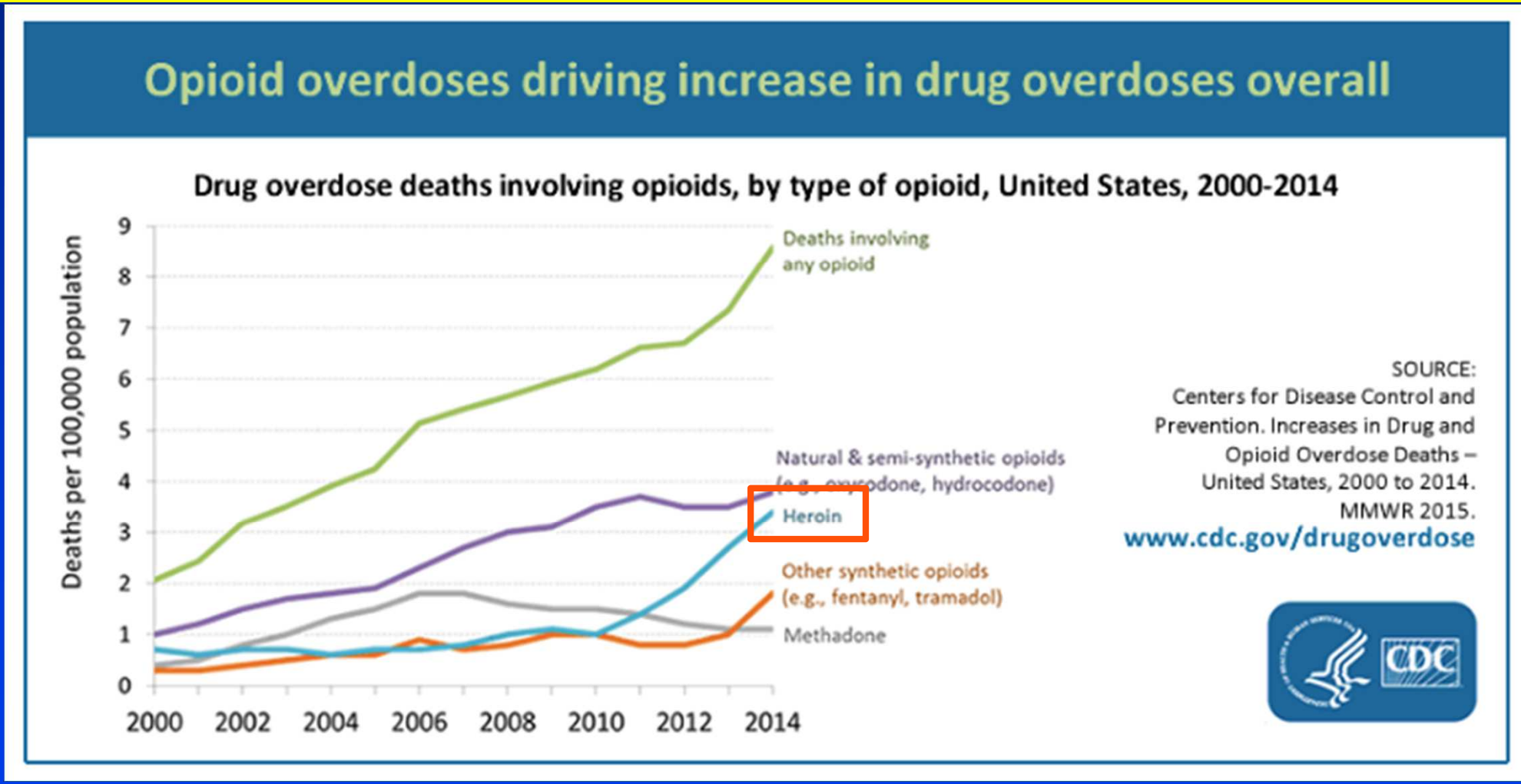

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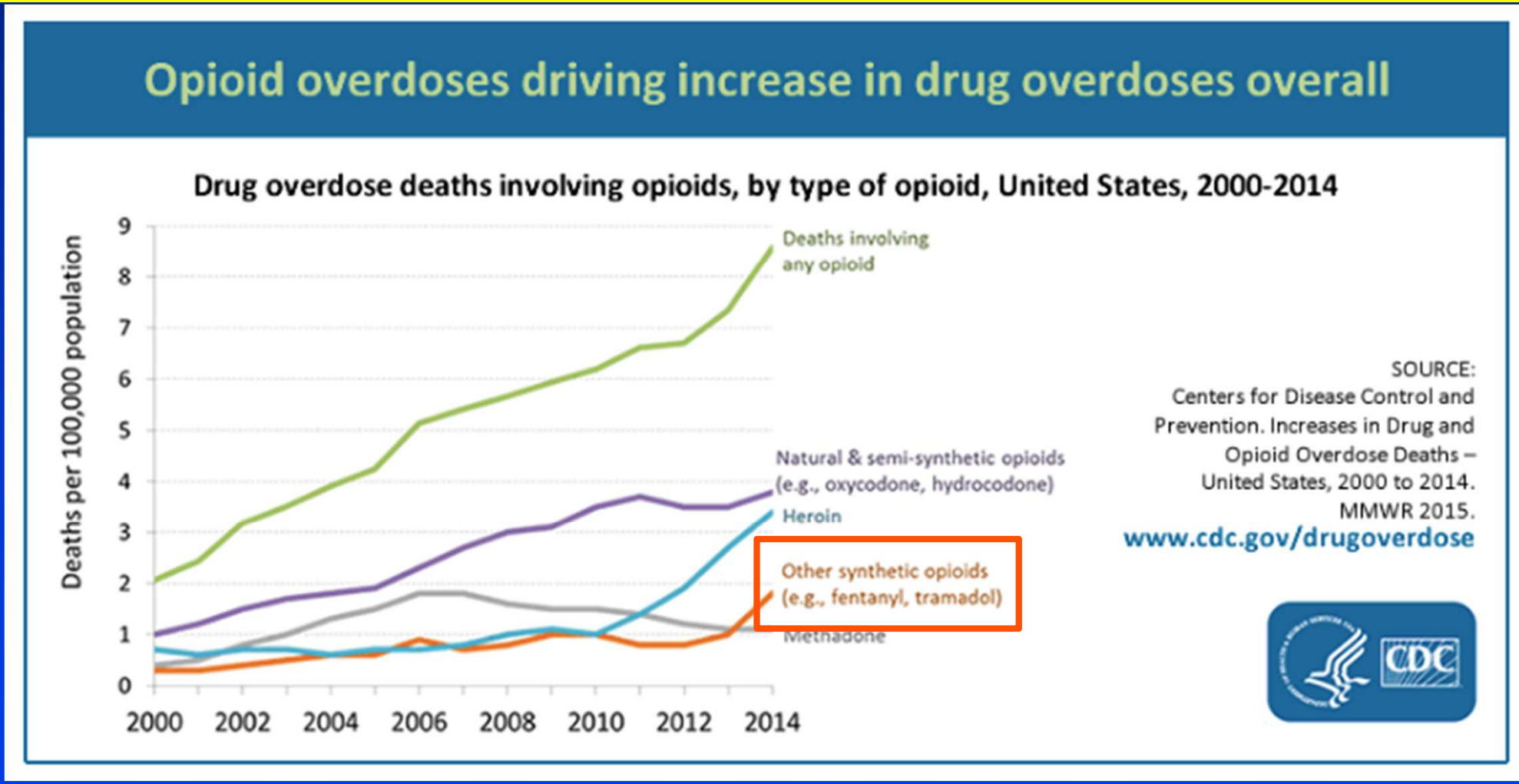

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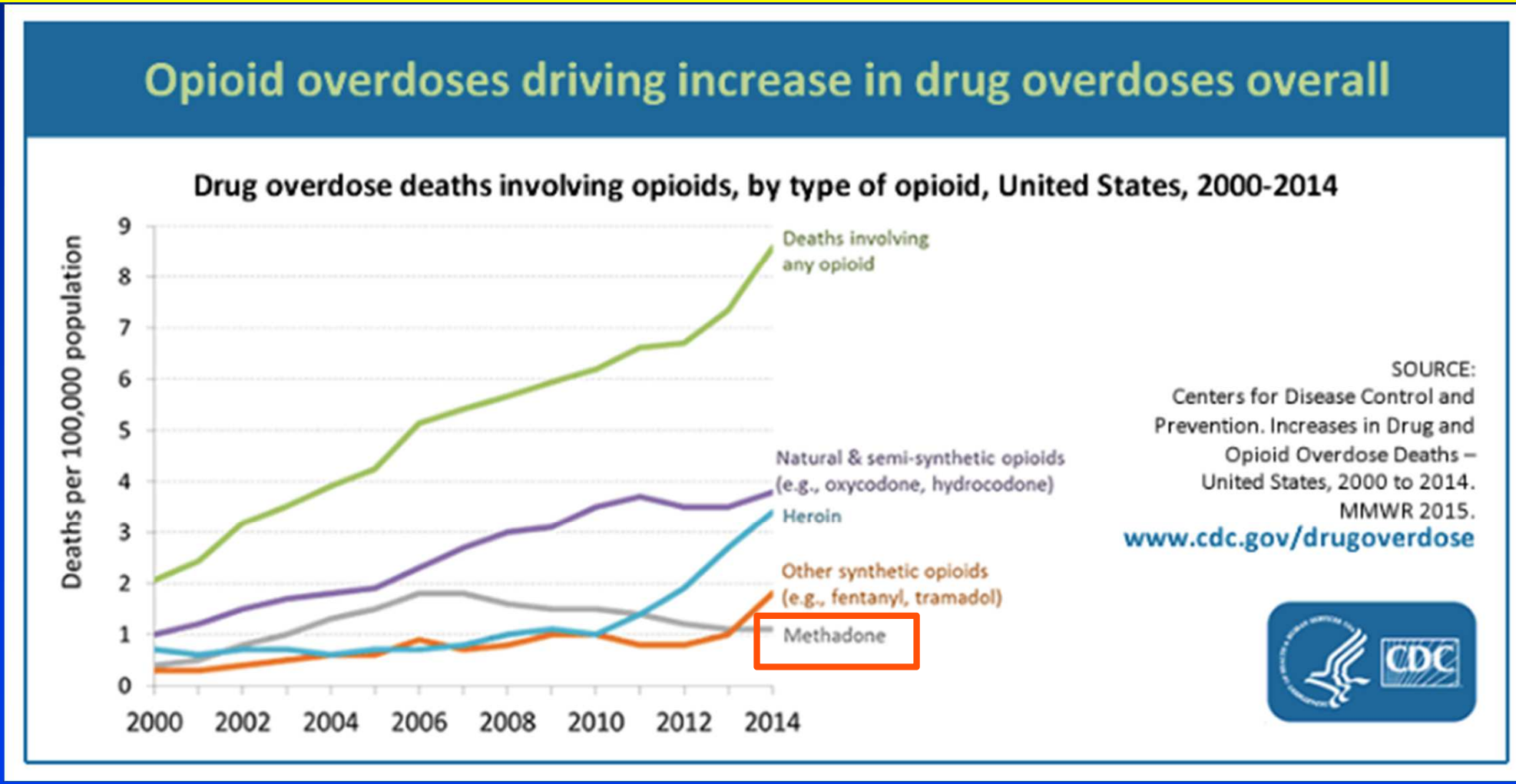

Opioid abuse in the U.S.

U.S. national survey on drug use done annually (“NSDUH” – National Survey on Drug Use and Health)

Particular value is in seeing the change in numbers over years (rather than the absolute number)

Increases are worrisome for health, public policy

Opioid abuse

Prevalence

4,813,000 persons in US reported using heroin at least once in their lifetime (2014 NSDUH) – essentially unchanged from 2013 survey (4.812m)

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A huge relative increase

Opioid abuse

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And past month use of heroin up between 2013 (289,000) and 2014 (435,000)

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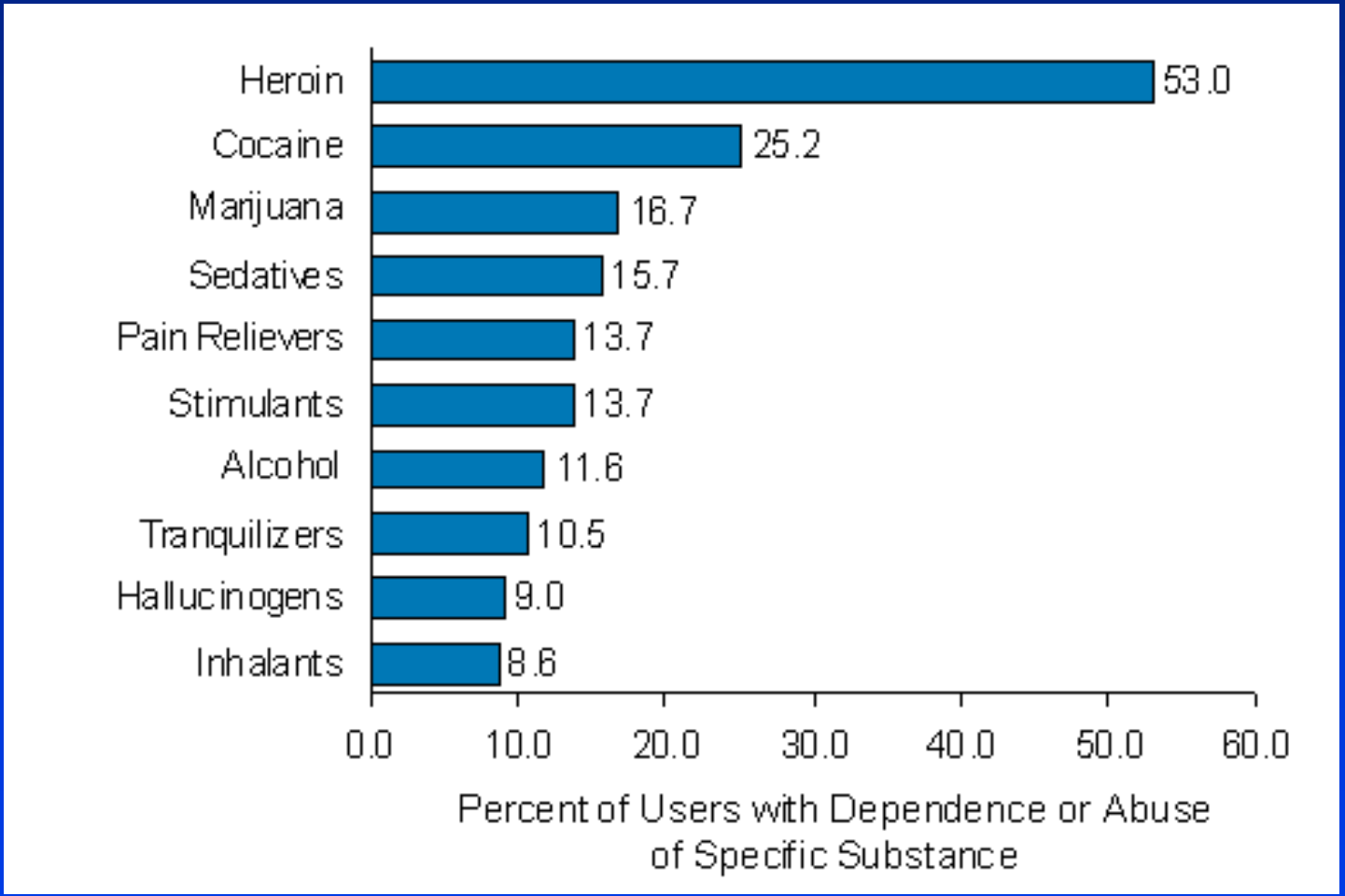
Opioid abuse

This increase in heroin use is worrisome, as heroin seems to be very addictive in those who try it

Past year dependence or abuse by drug class



(NSDUH, 2002)

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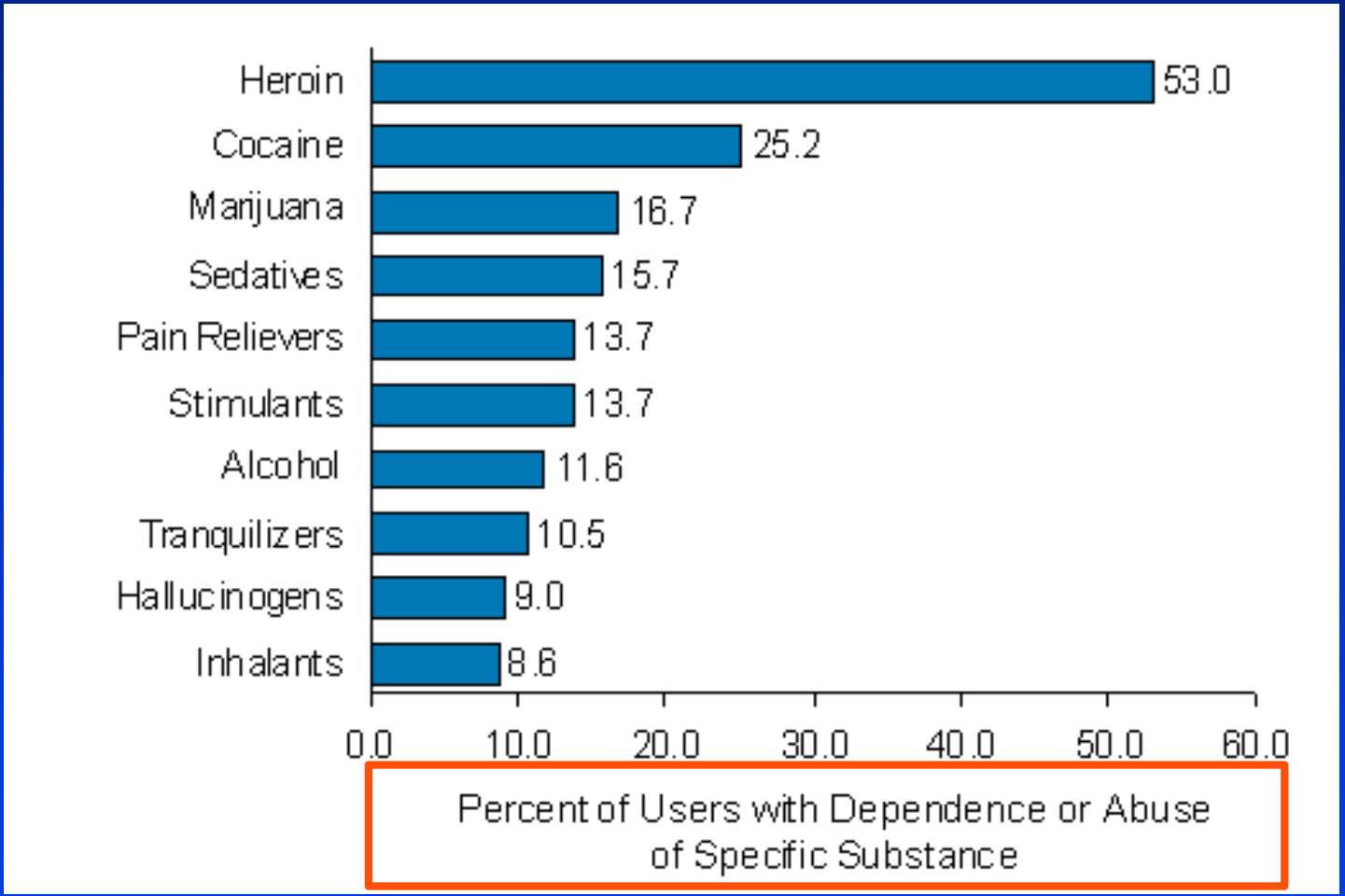

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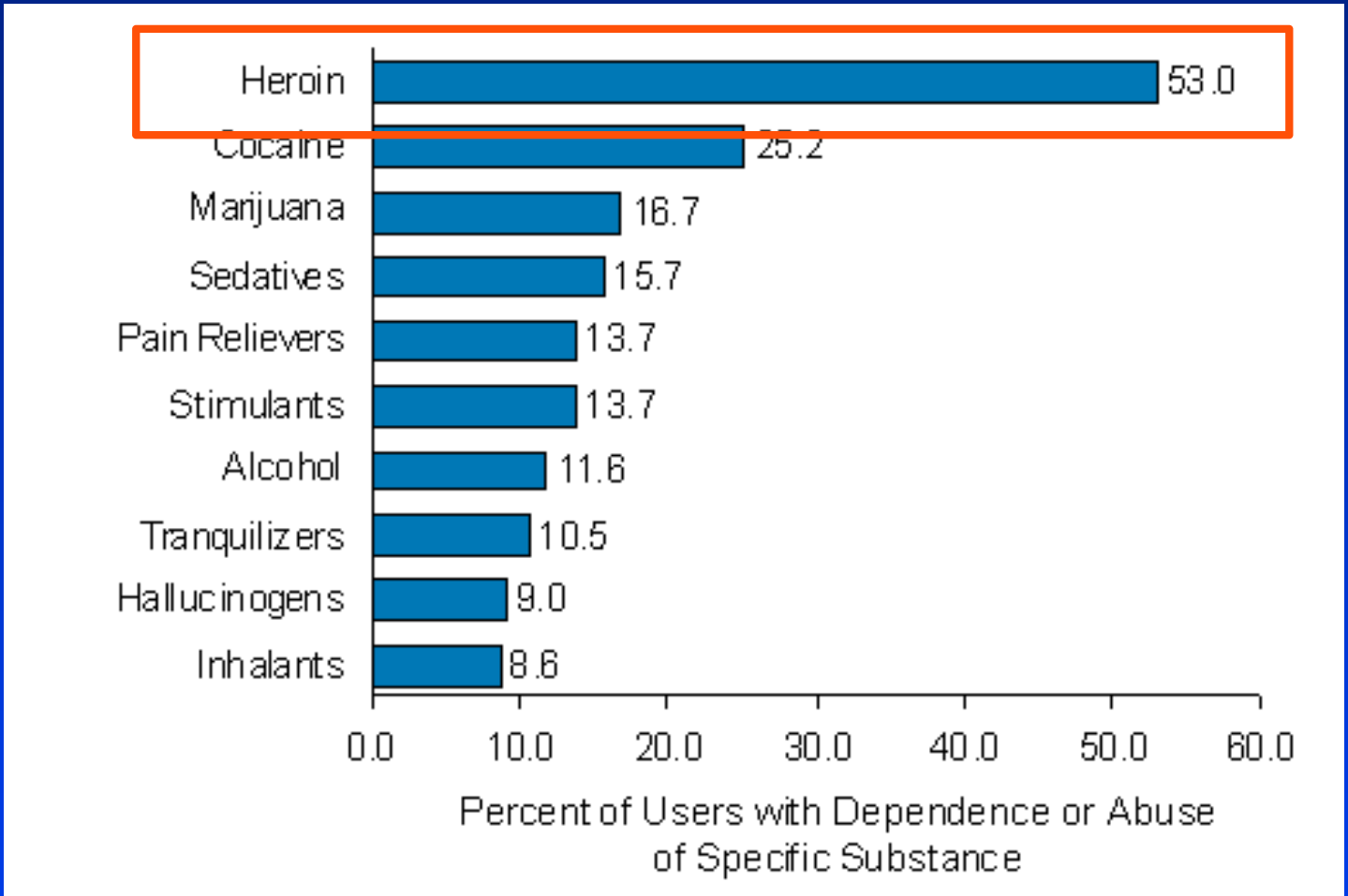

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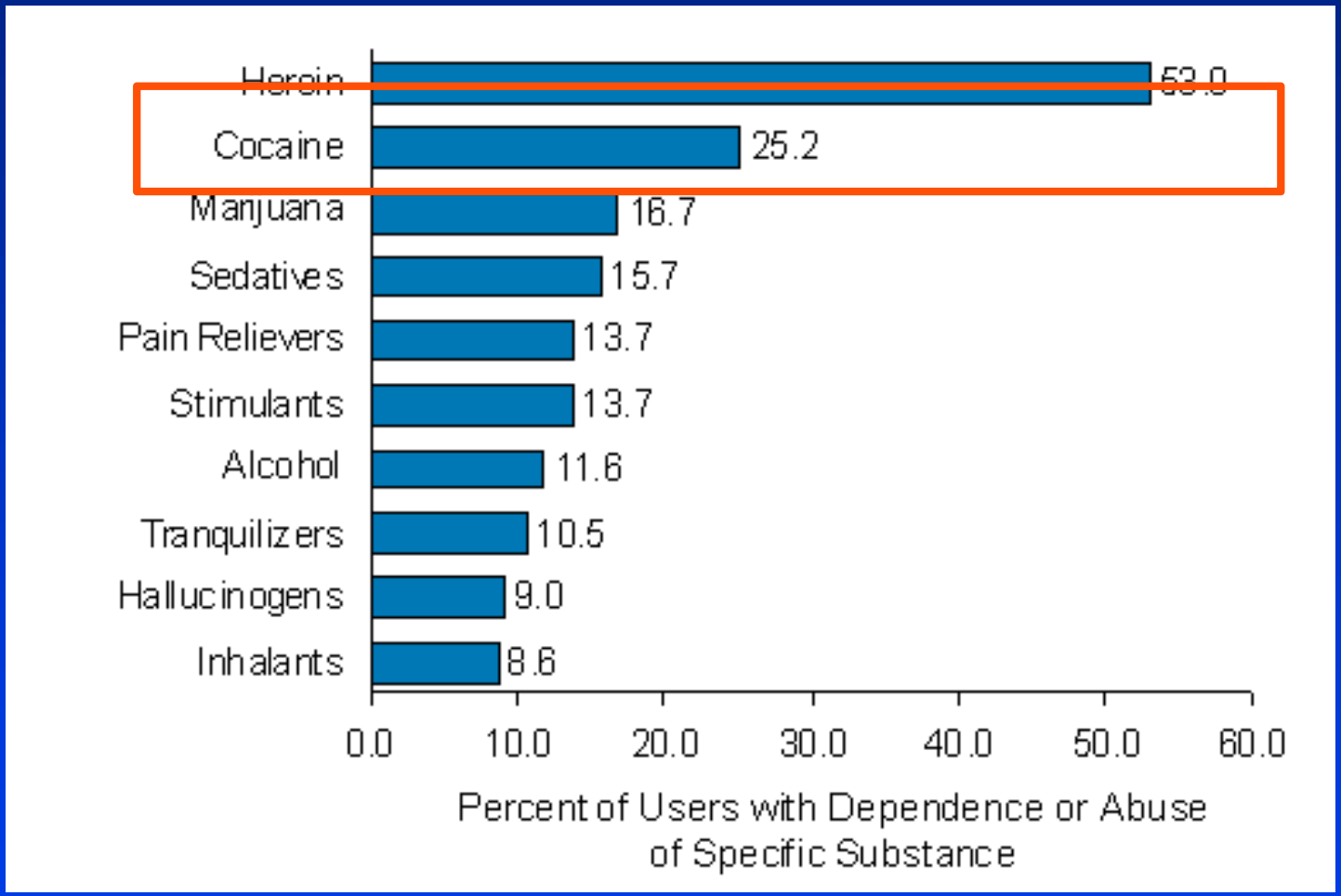


(NSDUH, 2002)

Opioid abuse

Across all drug classes, use of heroin was the drug which was most likely to result in developing abuse or dependence

That is, the NSDUH results suggest that trying heroin is more likely to result in problematic use than trying other classes of abused substances

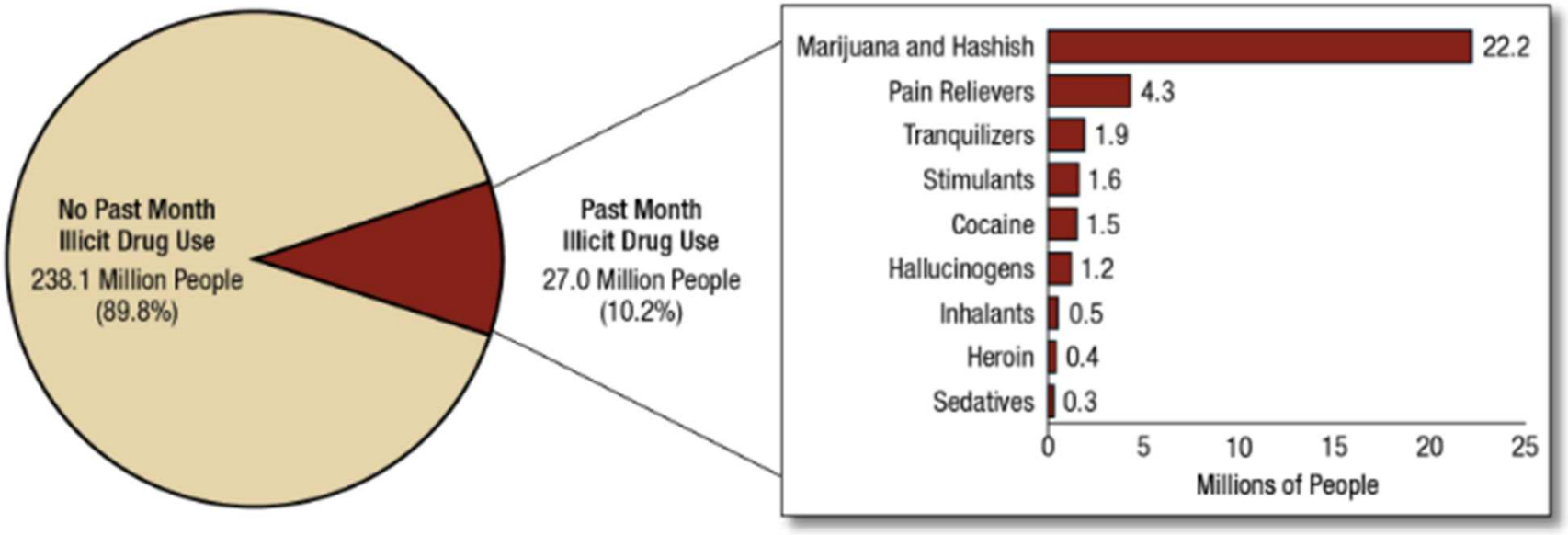
And now we have people migrating from prescription opioids to heroin use

Opioid abuse

However, another problem with respect to opioid use is non-medical use of prescription pain medications

Past month use by drug class

Figure 1. Numbers of Past Month Illicit Drug Users among People Aged 12 or Older: 2014



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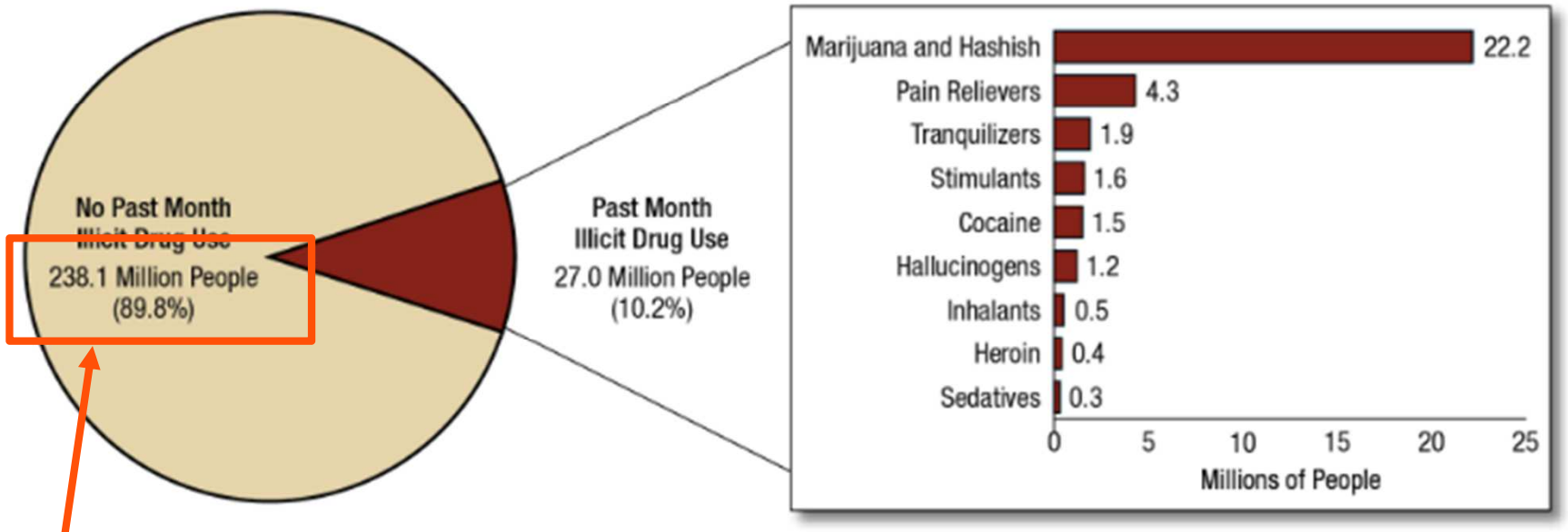

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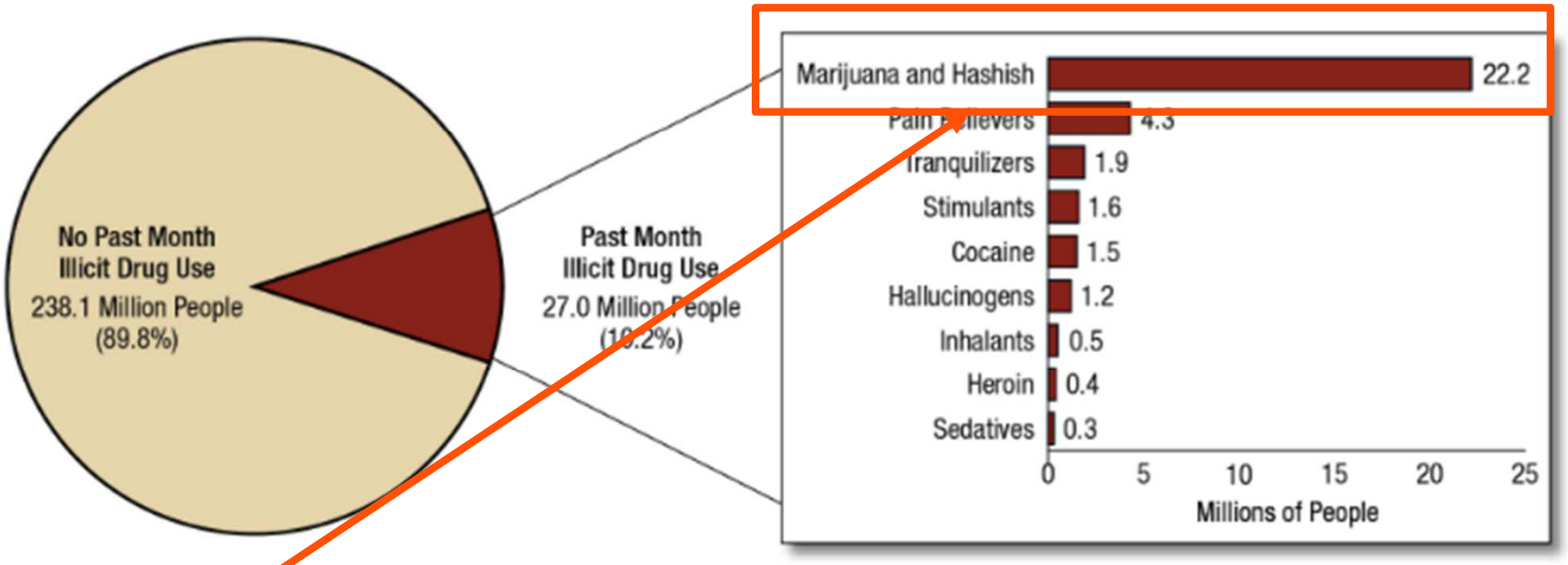

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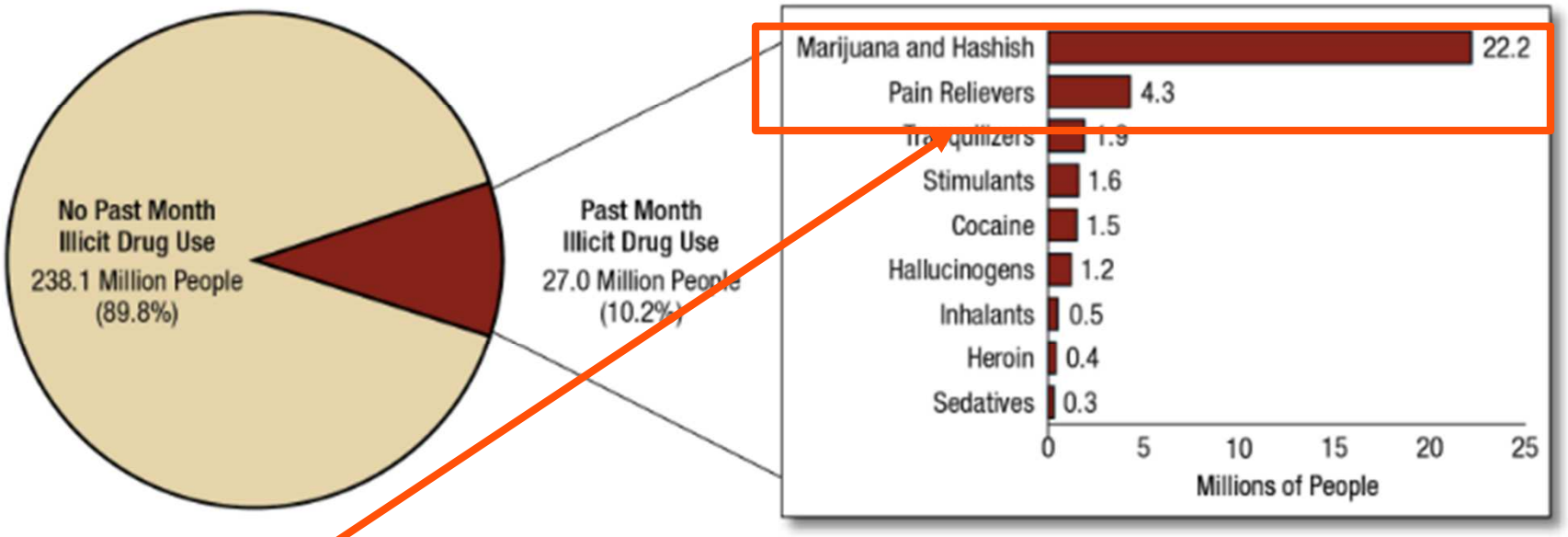

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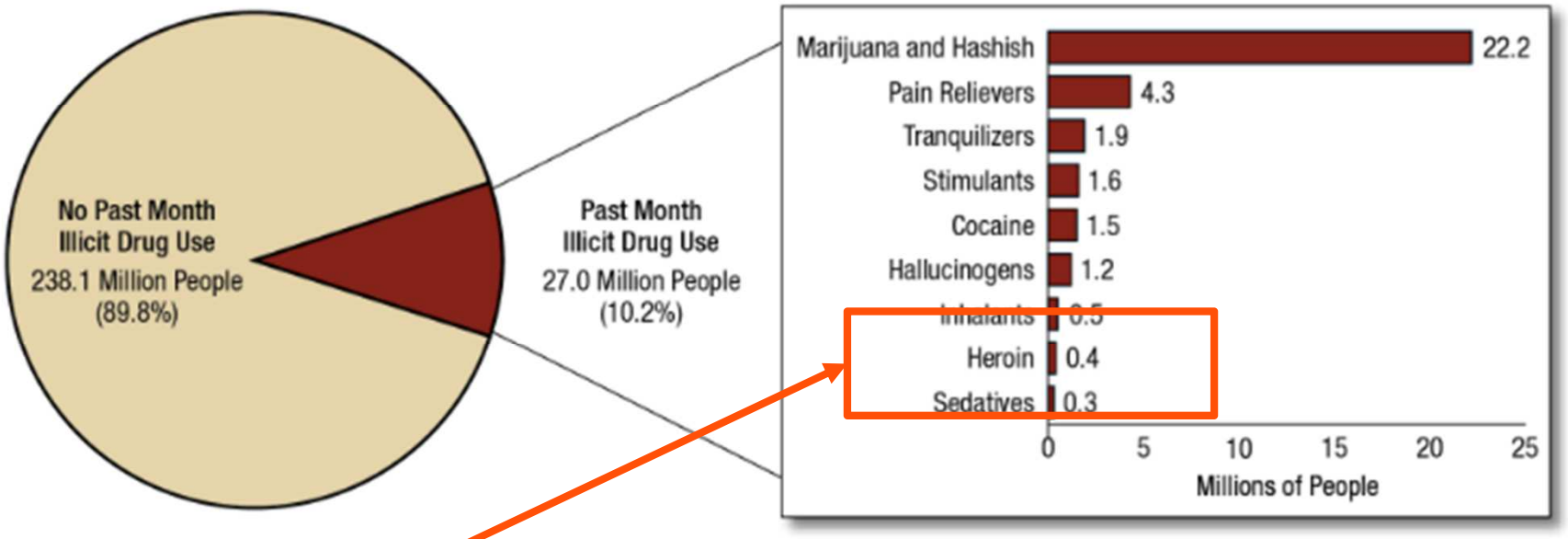


(NSDUH, 2014)

Extent of opioid abuse:
Non-medical use of opioid analgesics

Non-medical use of pain relievers (lifetime):

2000: 19,210,000
2001: 22,133,000
2002: 29,611,000
2003: 31,207,000
2004: 31,768,000
2005: 32,692,000
2006: 33,472,000
2007: 33,060,000
2008: 34,861,000
2009: 35,046,000
2010: 34,776,000
2011: 34,247,000
2012: 37,045,000
2013: 35,473,000
2014: 36,064,000

(NSDUH)

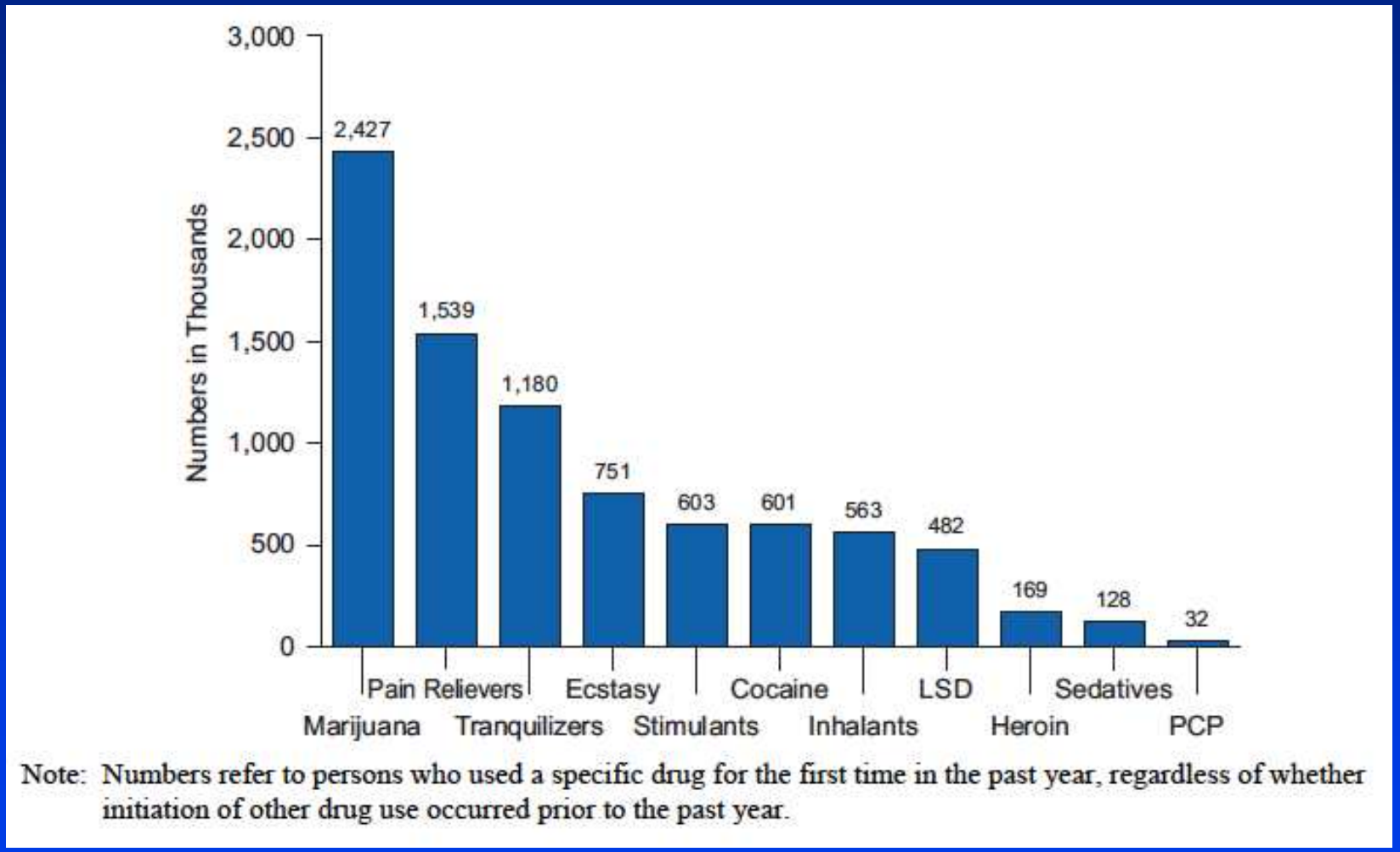
Extent of opioid abuse:
Non-medical use of opioid analgesics

Non-medical use of pain relievers (past month):

2000: 2,782,000
2001: 3,497,000
2002: 4,377,000
2003: 4,693,000
2004: 4,404,000
2005: 4,658,000
2006: 5,220,000
2007: 5,174,000
2008: 4,747,000
2009: 5,257,000
2010: 5,100,000
2011: 4,471,000
2012: 4,862,000
2013: 4,521,000
2014: 4,325,000

(NSDUH)

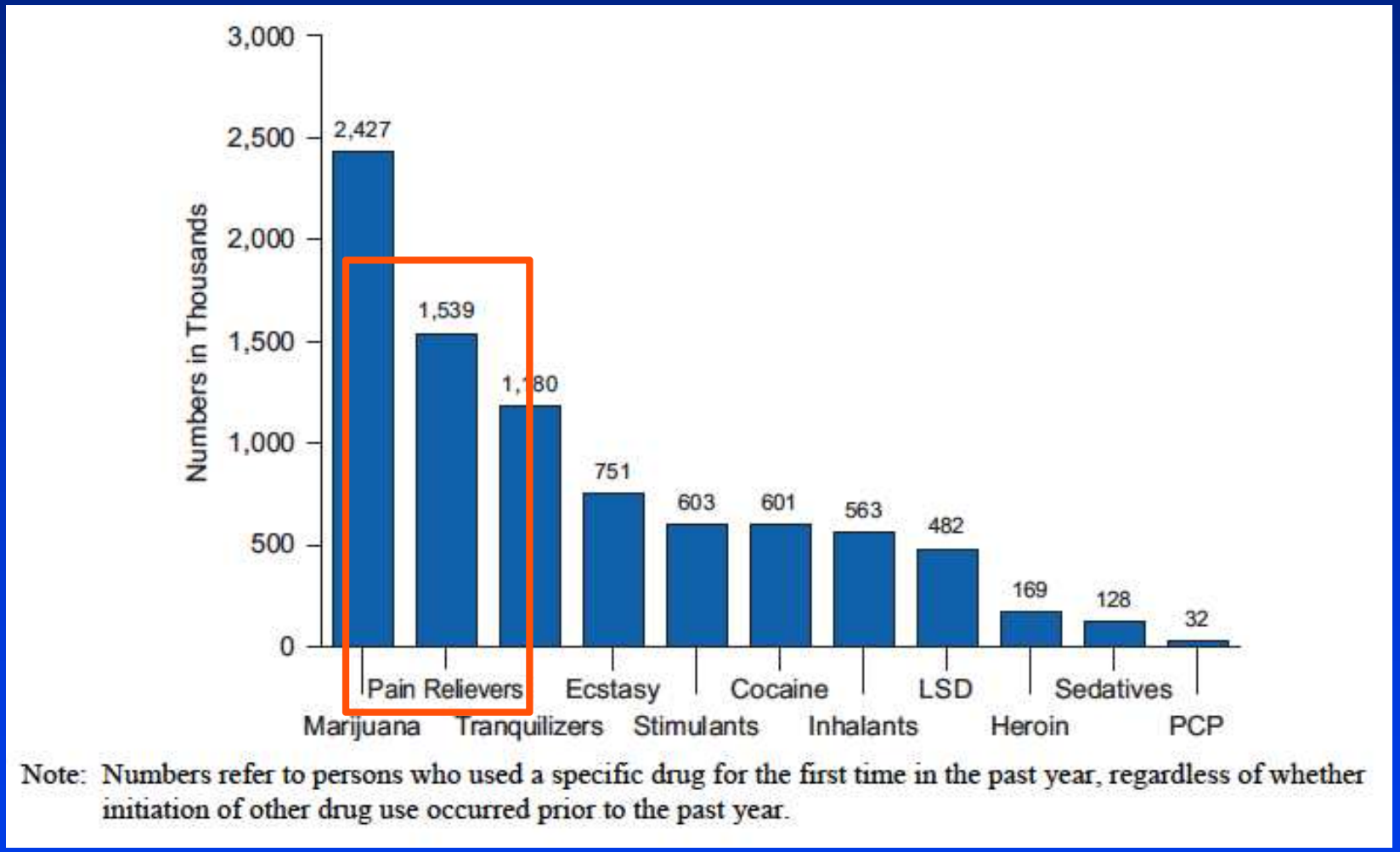
Past year initiates by drug class



Note: Numbers refer to persons who used a specific drug for the first time in the past year, regardless of whether initiation of other drug use occurred prior to the past year.

(NSDUH, 2013)

Past year initiates by drug class



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(NSDUH, 2013)

Epidemiology of opioid abuse

Sources of misused prescription opioids (2012-13 NSDUH)

- Friend or relative for free: 5,713,000
- One doctor: 2,287,000
- Bought from friend or relative: 1,149,000
- Took without asking from friend/relative: 429,000
- Bought from dealer/stranger: 460,000
- More than one doctor: 276,000

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To summarize

While somewhat difficult to pin down, probably at least one milion persons with regular heroin use in the U.S.

The heroin users overlap with the prescription opioid users to some extent, but probably at least another one million persons who regularly misuse prescription opioids (but again, a hard number to pin down – are all truly misusing?)

To summarize

- Appears we are seeing some stabilization/decrease in prescription opioid misuse in the U.S., but most recent epidemiologic report suggests that there may be a worrisome rise in heroin use
- Shifting from prescription opioids to heroin, as prescription opioid use becomes less easy to access

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Opioid addiction and withdrawal

Use

Abuse, Dependence

Substance Use Disorder

Addiction

Withdrawal

Opioid use

Patients can have use of an opioid that is not problematic (and note that it can include physical dependence on an opioid)

Opioid Abuse, Dependence

These were DSM-IV diagnoses; both were dropped in DSM-5

Substance Use Disorder (SUD)

Diagnosis in DSM-5 – is an “Opioid Use Disorder”

Combines DSM-IV criteria for Dependence and Abuse diagnoses; total of eleven items (one new one – craving); only need two for a diagnosis

Opioid addiction

No criteria in DSM for a diagnosis of addiction

ASAM definition (long) of addiction, viewed as a “primary chronic disease of brain reward, motivation, memory and related circuitry…”

Generally used interchangeably with DSM concept of Dependence / Opioid Use Disorder

Opioid withdrawal

- Well characterized syndrome (classic)
- Not diagnostic of pathologic/problematic use
- Varies as a function of type of drug used, dose, pharmacokinetics

Opioid withdrawal

- Dysphoric mood
- Nausea or vomiting
- Muscle aches
- Insomnia
- Diarrhea
- Yawning
- Fever
- Lacrimation or rhinnorhea
- Pupillary dilation, piloerection, or sweating

Opioid withdrawal

- Treat based upon objective signs of withdrawal (signs versus symptoms)
- Opioid withdrawal is not life-threatening to the patient
- However, it can be very unpleasant (to the patient)

Opioid withdrawal

- Usually begins hours after last dose of opioid (e.g., 4-6 hours after last dose of heroin)
- Lasts about 3+ days for heroin
- Protracted abstinence syndrome (?)

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Treatments for opioid dependence

Will focus on typical medications for maintenance treatment of opioid dependence/opioid use disorder (OUD)

Not reviewing pharmacotherapies for withdrawal

Maintenance Medications for Opioid Addiction

- Buprenorphine
- LAAM
- Methadone
- Naltrexone

Buprenorphine

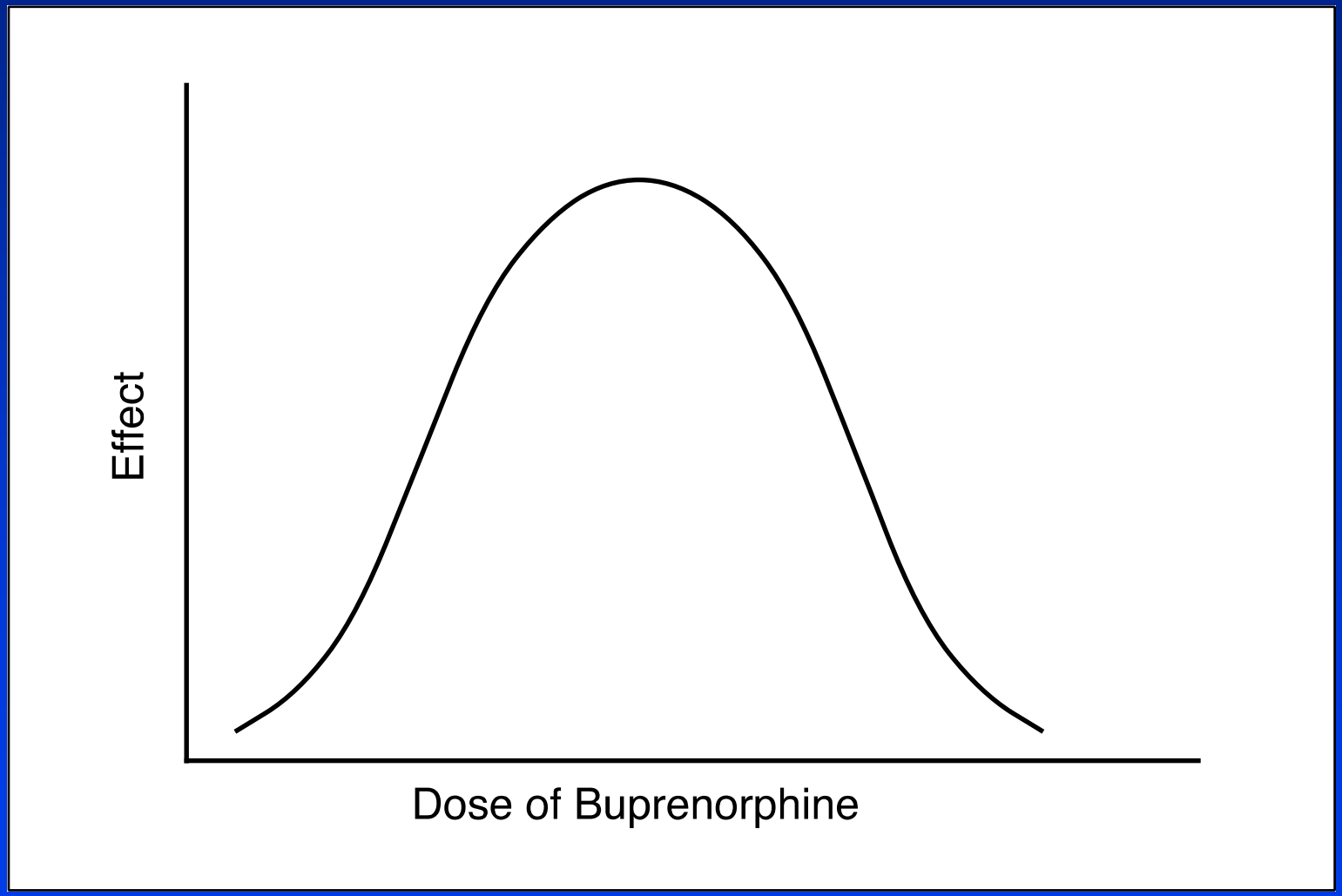
Pharmacology

Opioid mixed agonist-antagonist (partial mu agonist, ORL-1 agonist, kappa antagonist)

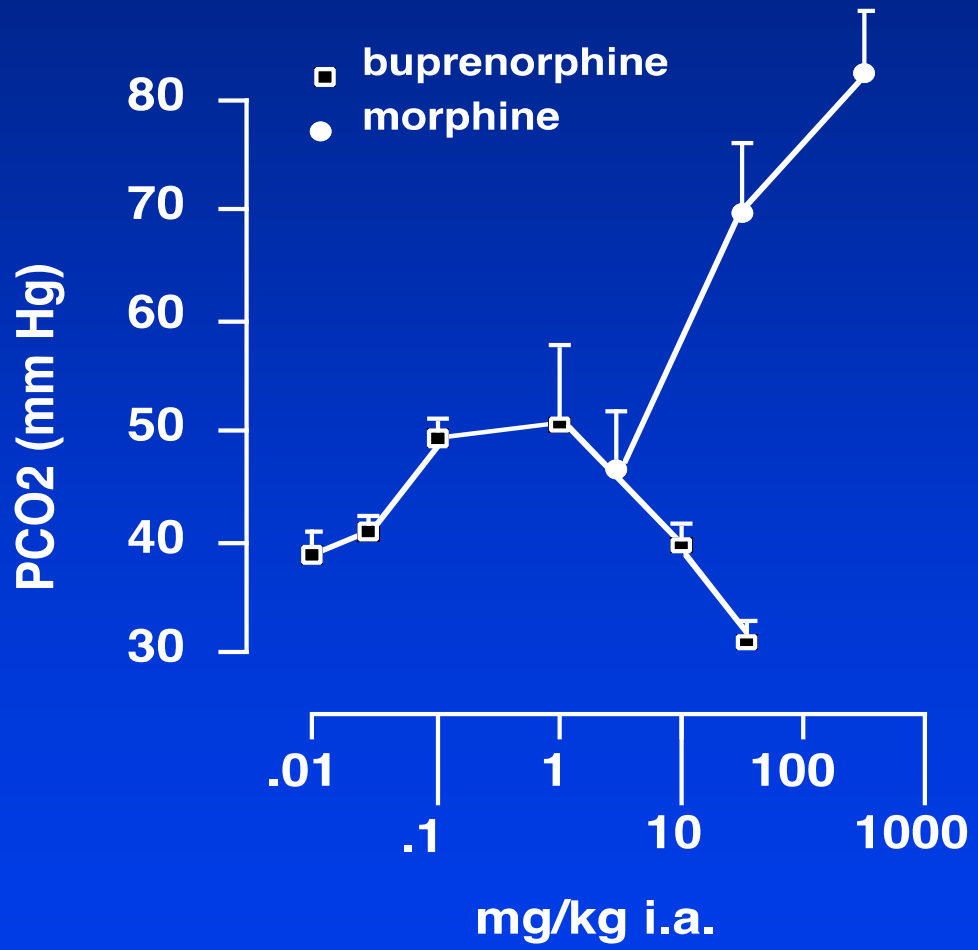
Partial agonism – less maximal effect than full agonist

Bell-shaped dose response curve

Bell-shaped dose response curve



Intra-arterial buprenorphine and PCO2 in male rats



Buprenorphine

Pharmacology

High affinity for mu opioid receptor – competes with other opioids and blocks their effects

Slow dissociation from mu opioid receptor – prolonged therapeutic effect for opioid dependence treatment (contrasts to its relatively short analgesic effects)

Buprenorphine

Pharmacology

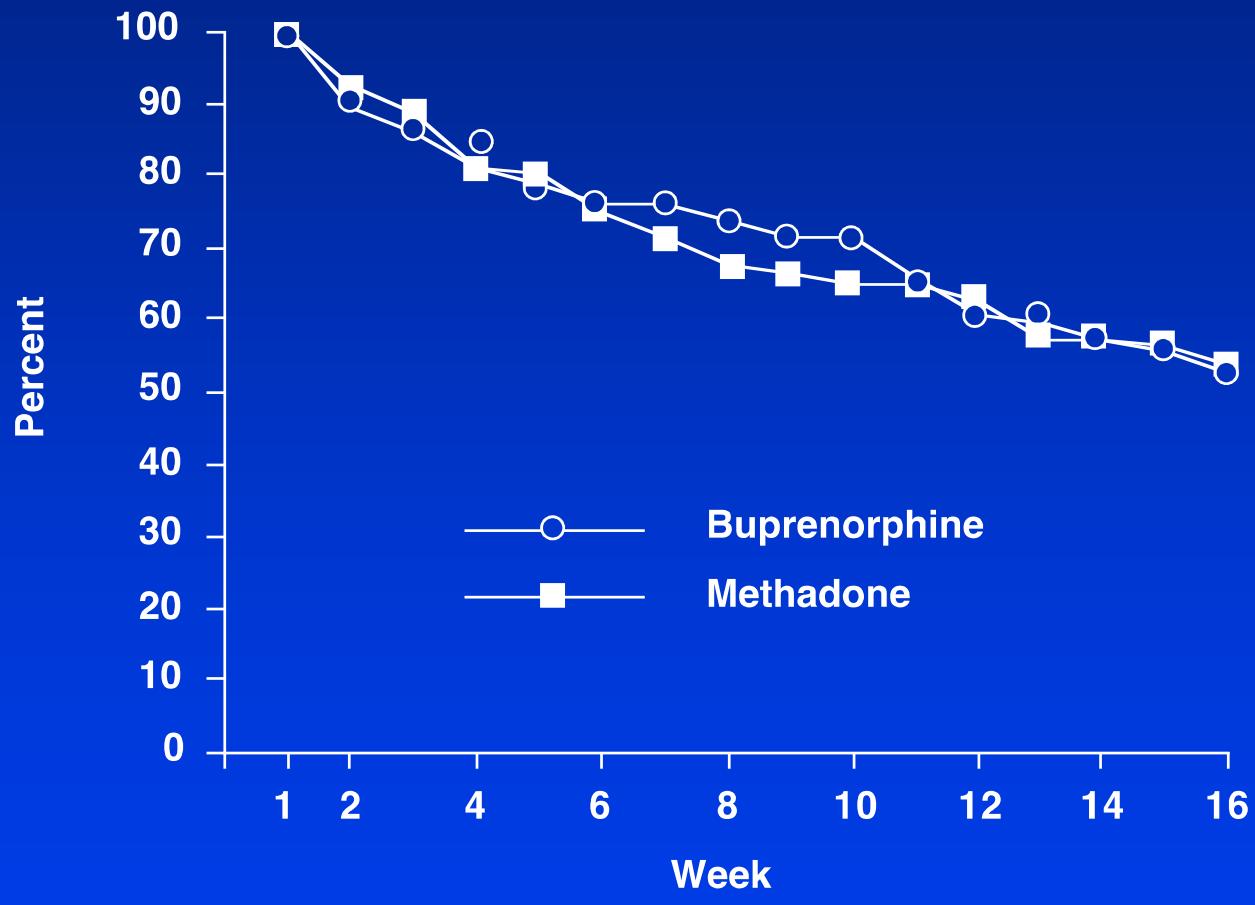
- High percentage of buprenorphine bound to plasma protein
- Metabolized in liver by cytochrome P450 3A4 enzyme system into norbuprenorphine and other metabolites
- Excreted in urine

Buprenorphine

Efficacy for maintenance treatment

Outpatient clinical trials show daily dosing superior to placebo, equally effective as moderate doses of methadone (about 60 mg per day of oral methadone)

Buprenorphine – methadone: treatment retention

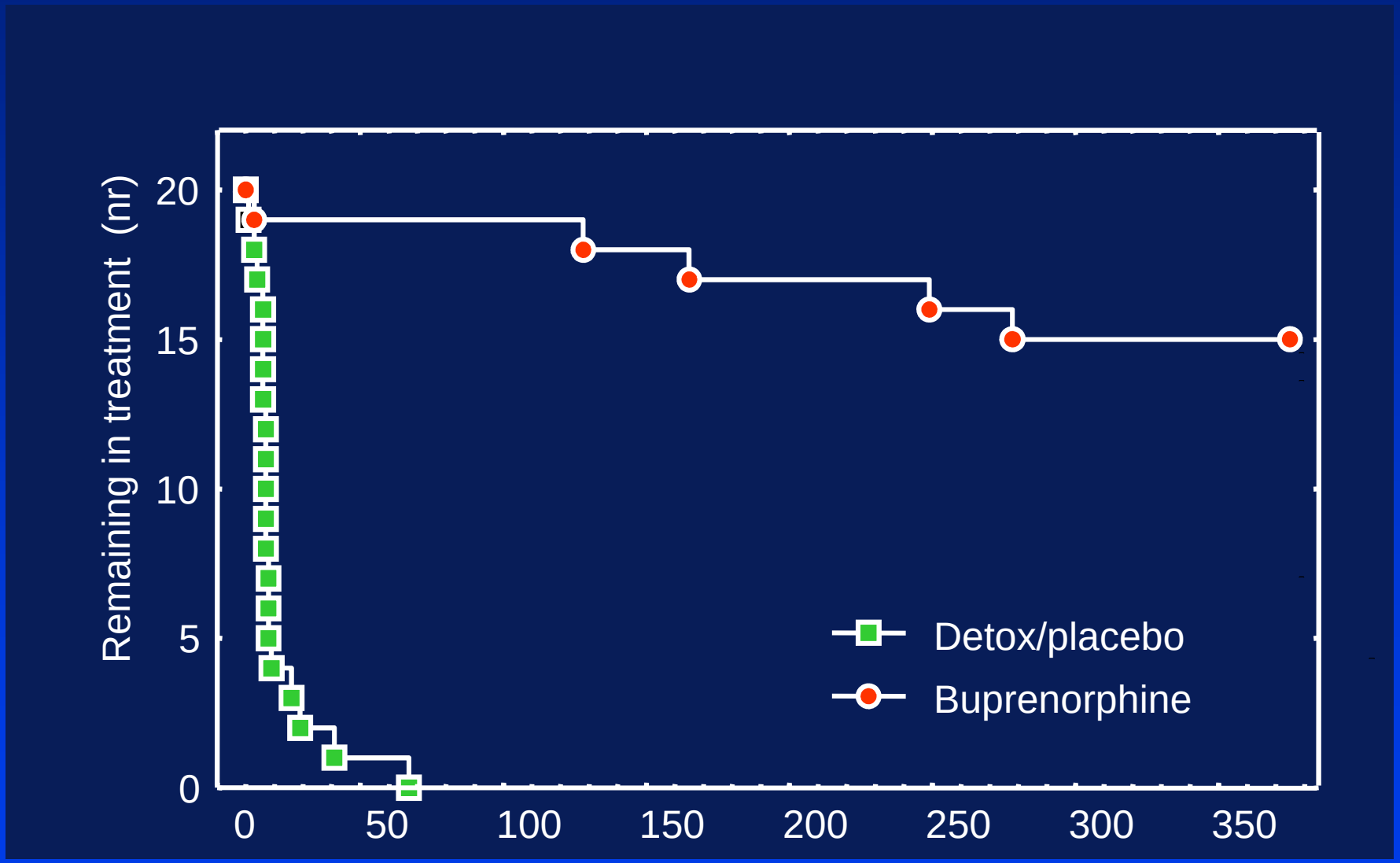


(adapted from Strain et al., 1994)

Buprenorphine Maintenance/Withdrawal

(Kakko et al., 2003)

Buprenorphine Maintenance/Withdrawal: Retention



(Kakko et al., 2003)

Buprenorphine

Safety, side effects

Similar profile as other mu agonist opioids (constipation, increased sweating); no evidence of particular cardiovascular concerns (e.g., QTc prolongation)

Can be abused (dissolve and inject tablets, films)

Buprenorphine

Safety, side effects

Combined naloxone with buprenorphine to decrease parenteral abuse potential (B/N in a 4/1 dose ratio) – naloxone has poor sublingual absorption, but good parenteral bioavailability, so would precipitate withdrawal if table dissolved and injected by an opioid dependent person

Buprenorphine

Buprenorphine effects in dependent volunteers (2001)

Subjects (n=8) maintained on daily oral hydromorphone (40 mg total per day)

Conditions: IM and SL buprenorphine/naloxone (1/0.25, 2/0.5, 4/1, 8/2, 16/4); IM hydromorphone (10 mg); IM naloxone (0.25 mg); IM and SL buprenorphine (8 mg); placebo

Buprenorphine

Buprenorphine effects in dependent volunteers (2001)

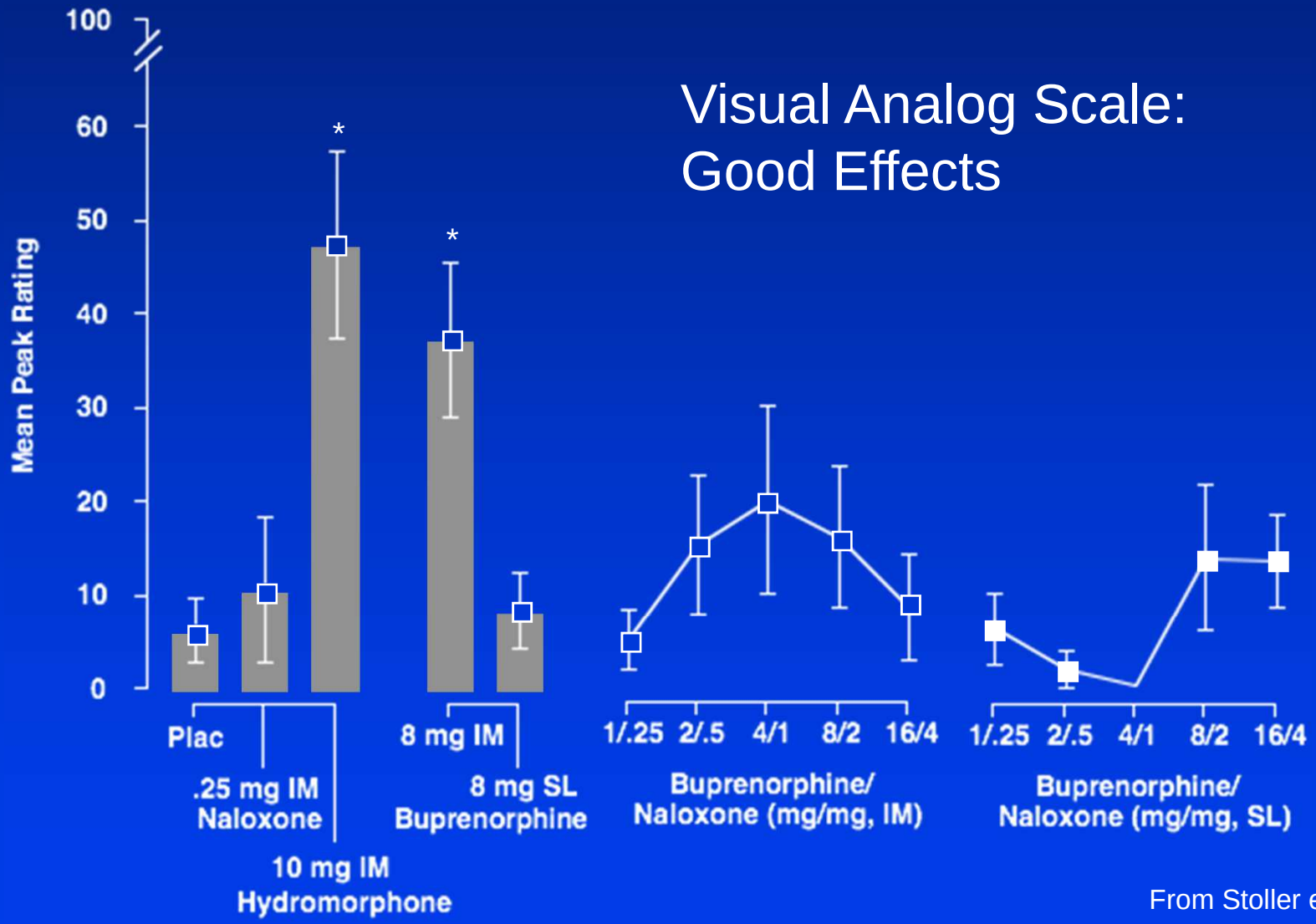
- Challenge sessions 3 hours after dose of hydromorphone
- SL buprenorphine doses were in tablet form (combination of active and placebo tablets to maintain blind)

Buprenorphine

Buprenorphine effects in dependent volunteers (2001)

Goal was to determine if would see precipitated withdrawal with buprenorphine/naloxone IM (from naloxone), but not with same doses of buprenorphine/naloxone when given SL

Buprenorphine/naloxone in opioid dependent volunteers



From Stoller et al., 2001

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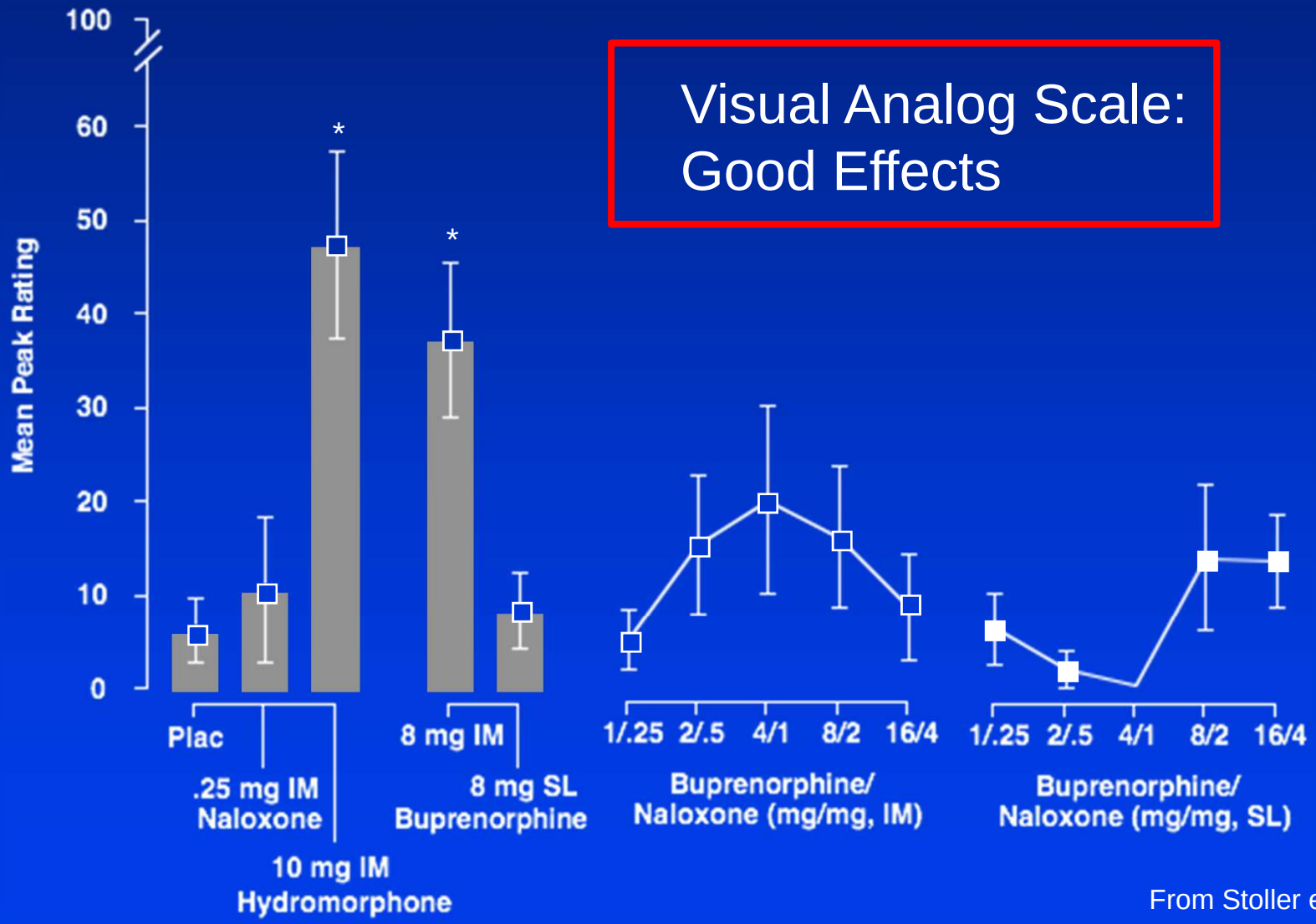

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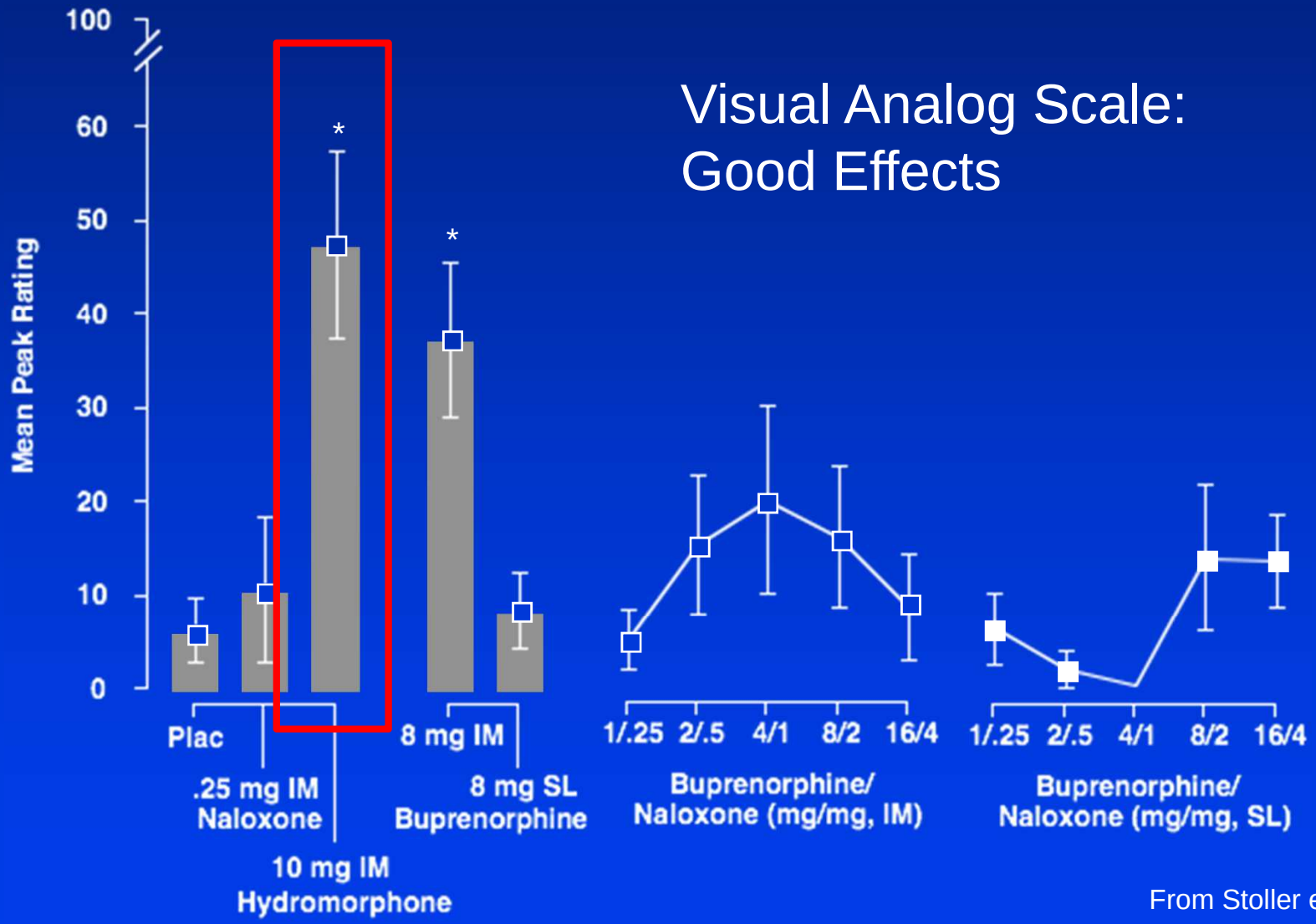

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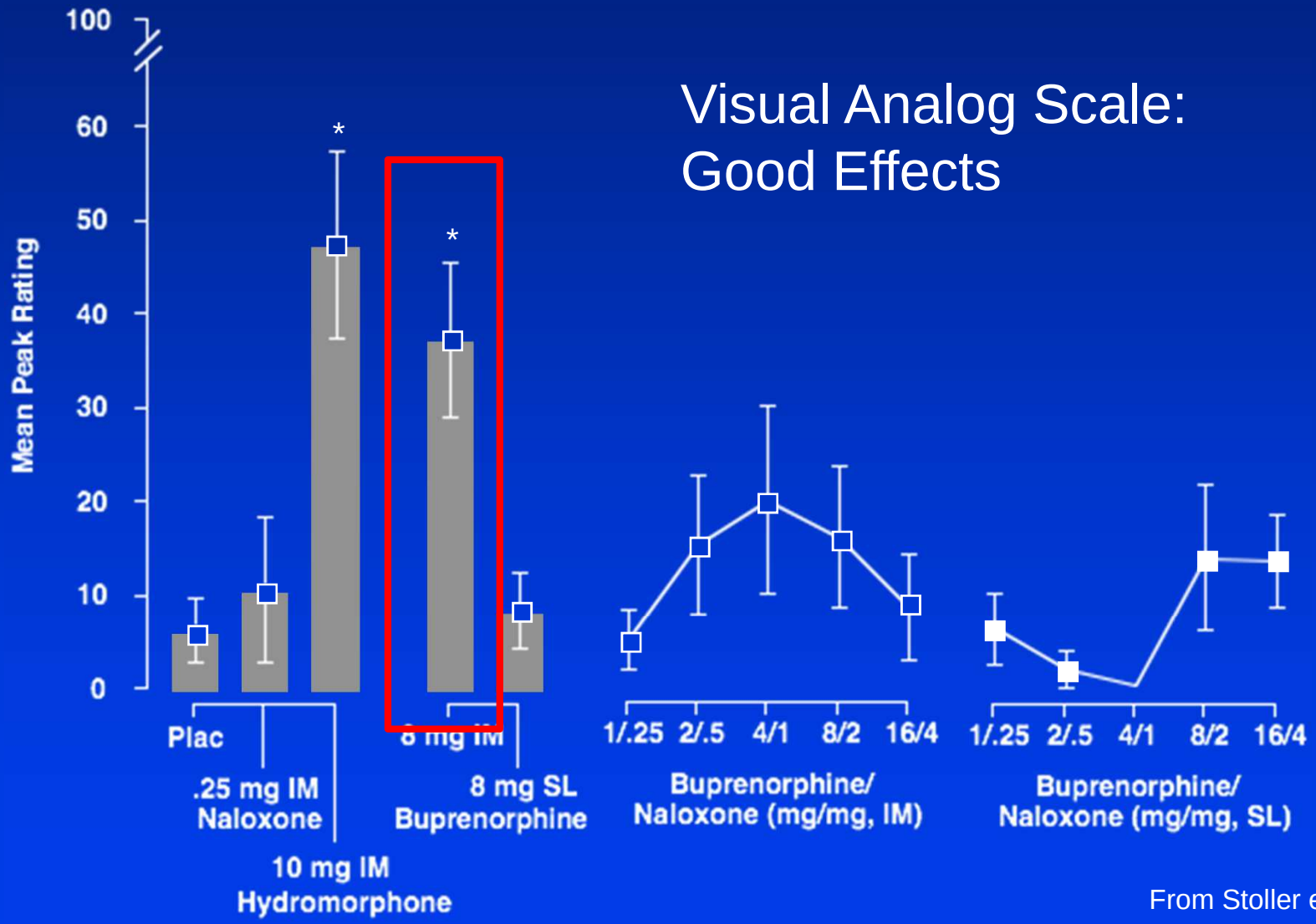

Visual Analog Scale: Good Effects

From Stoller et al., 2001

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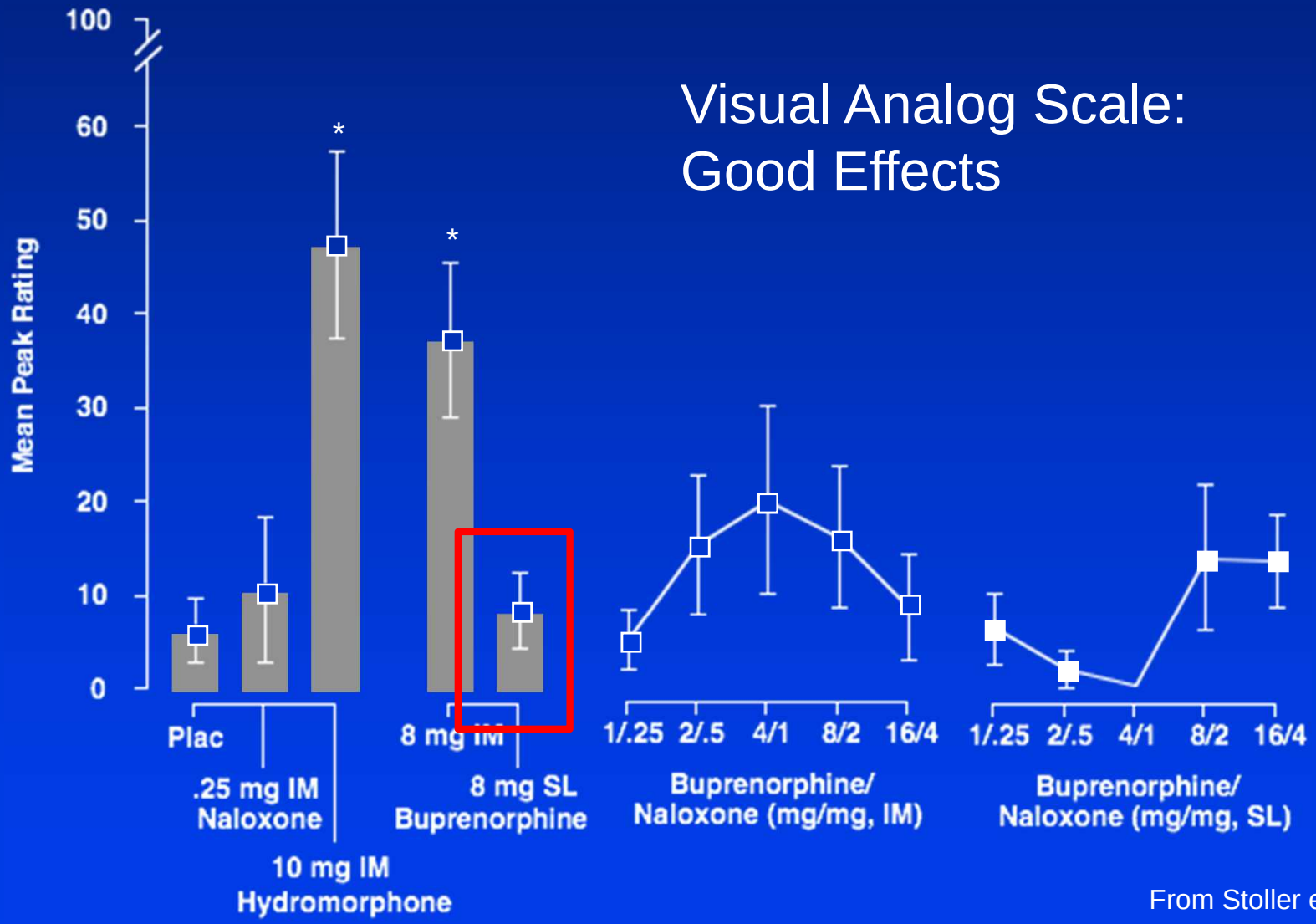

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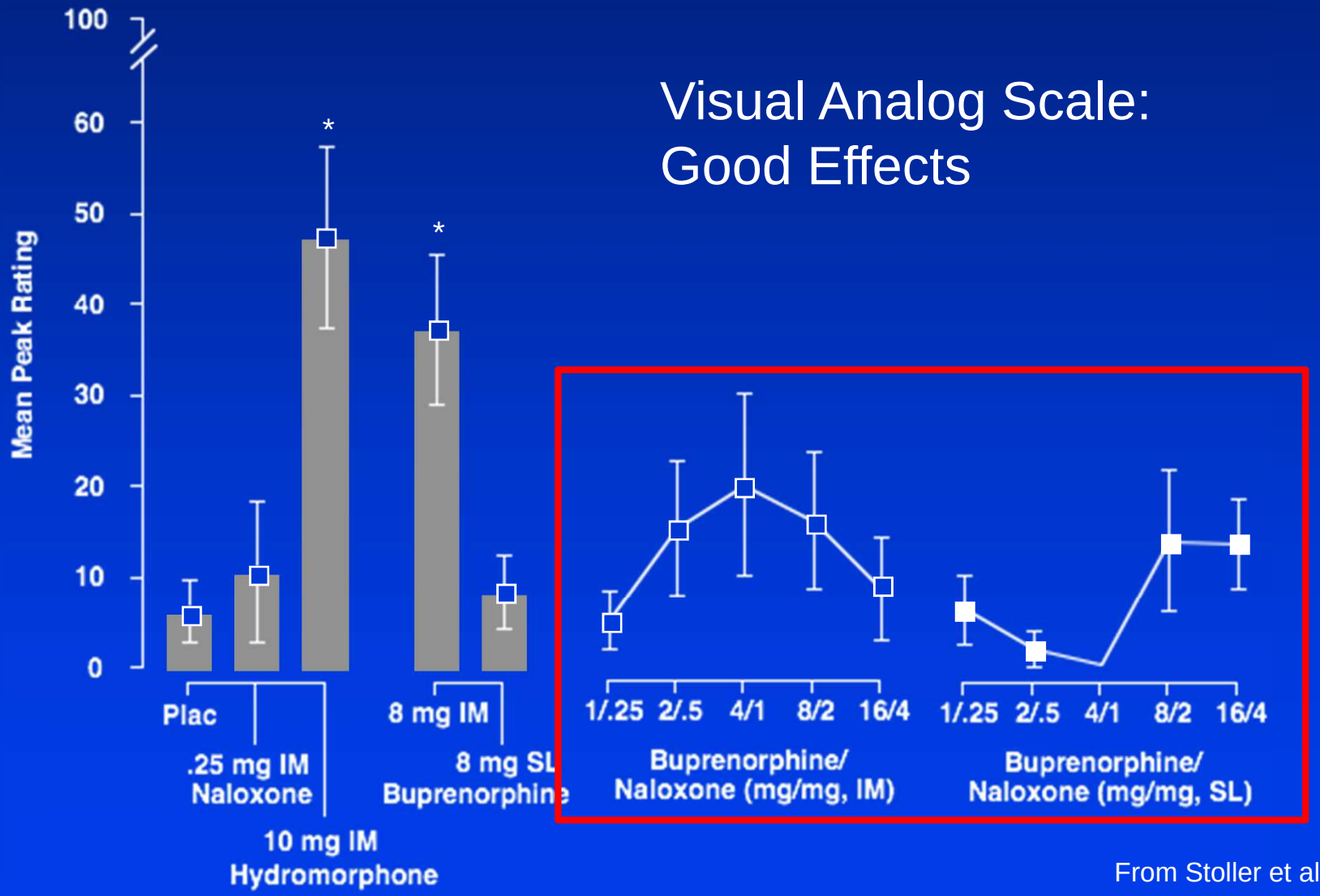

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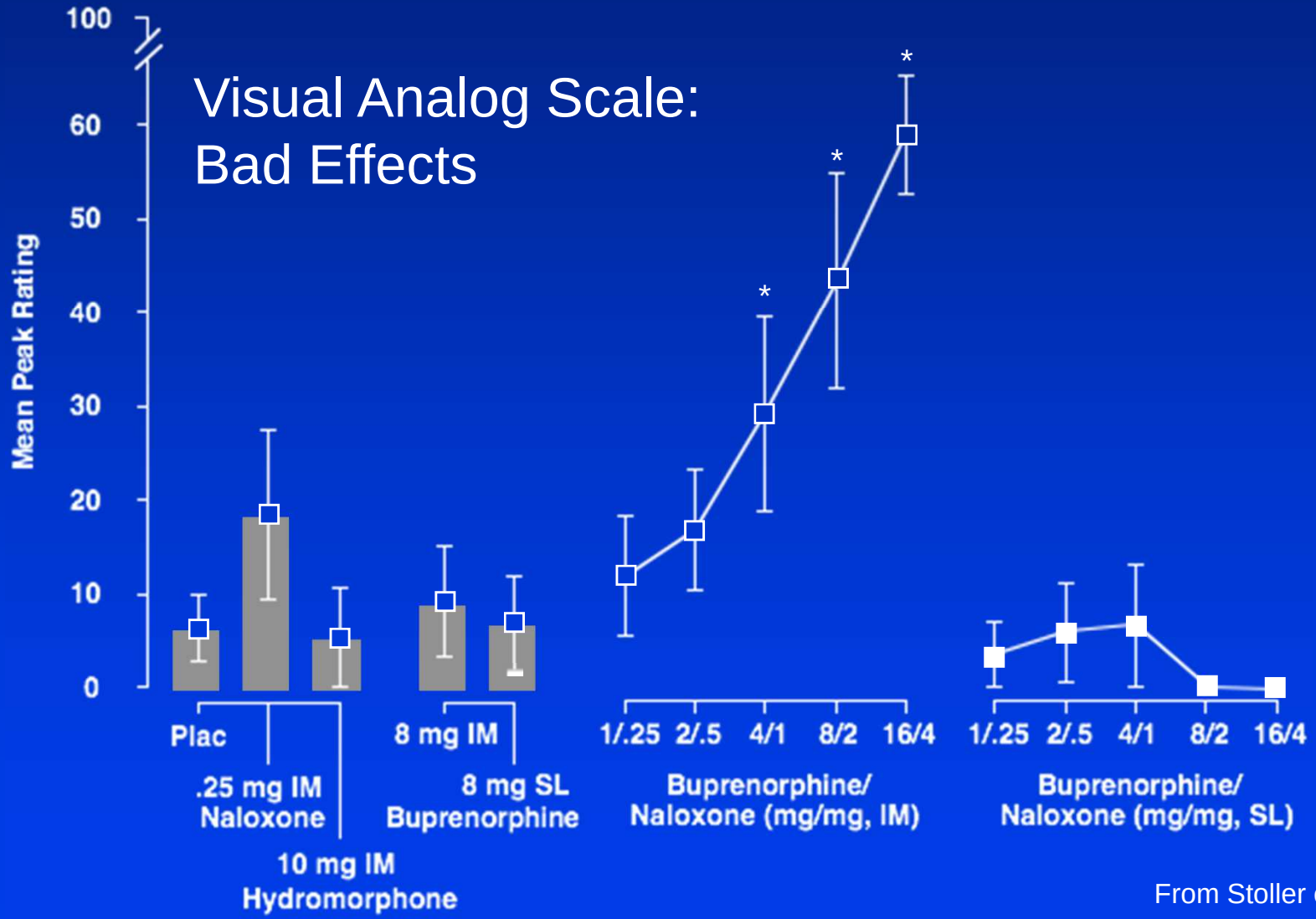

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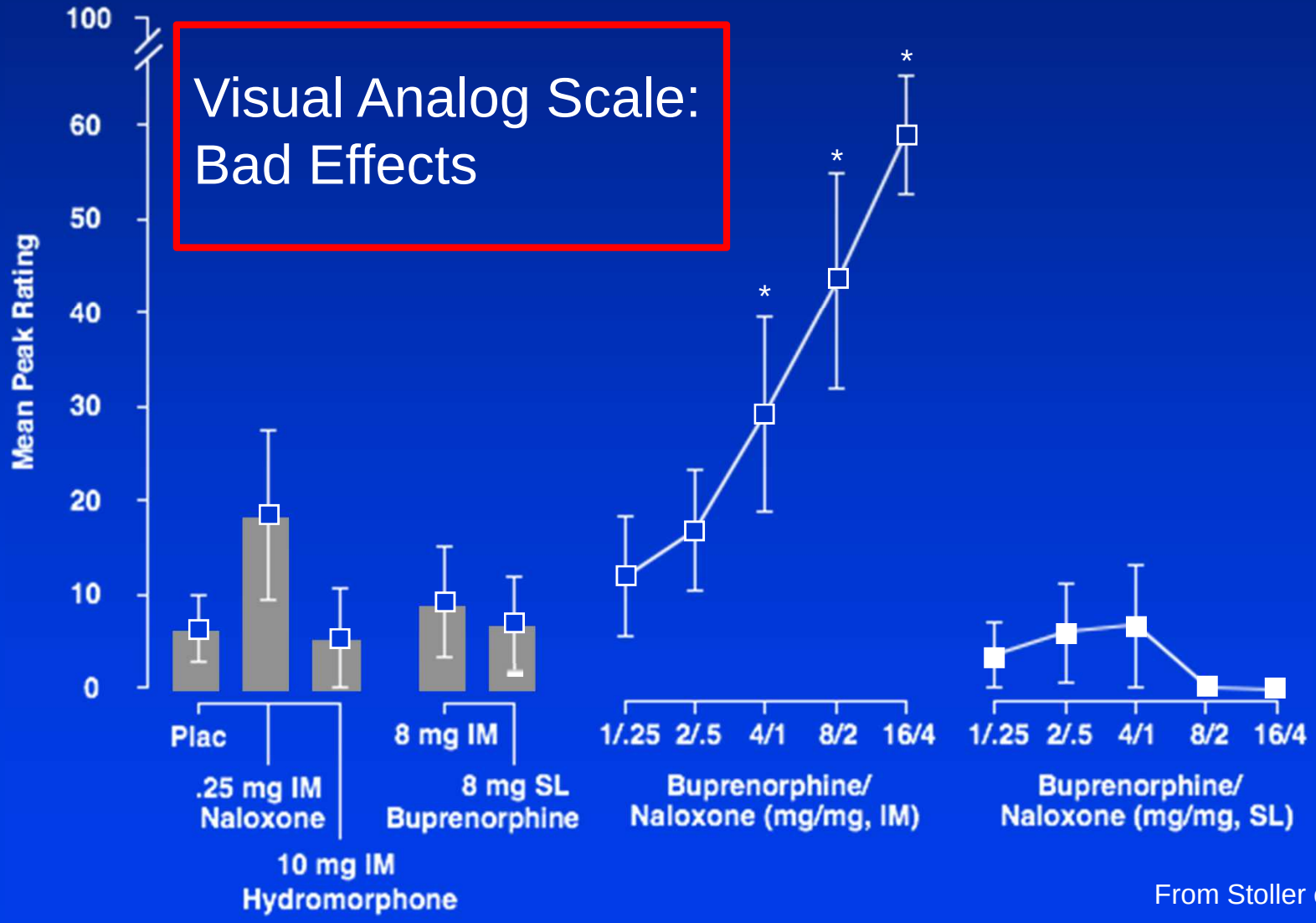

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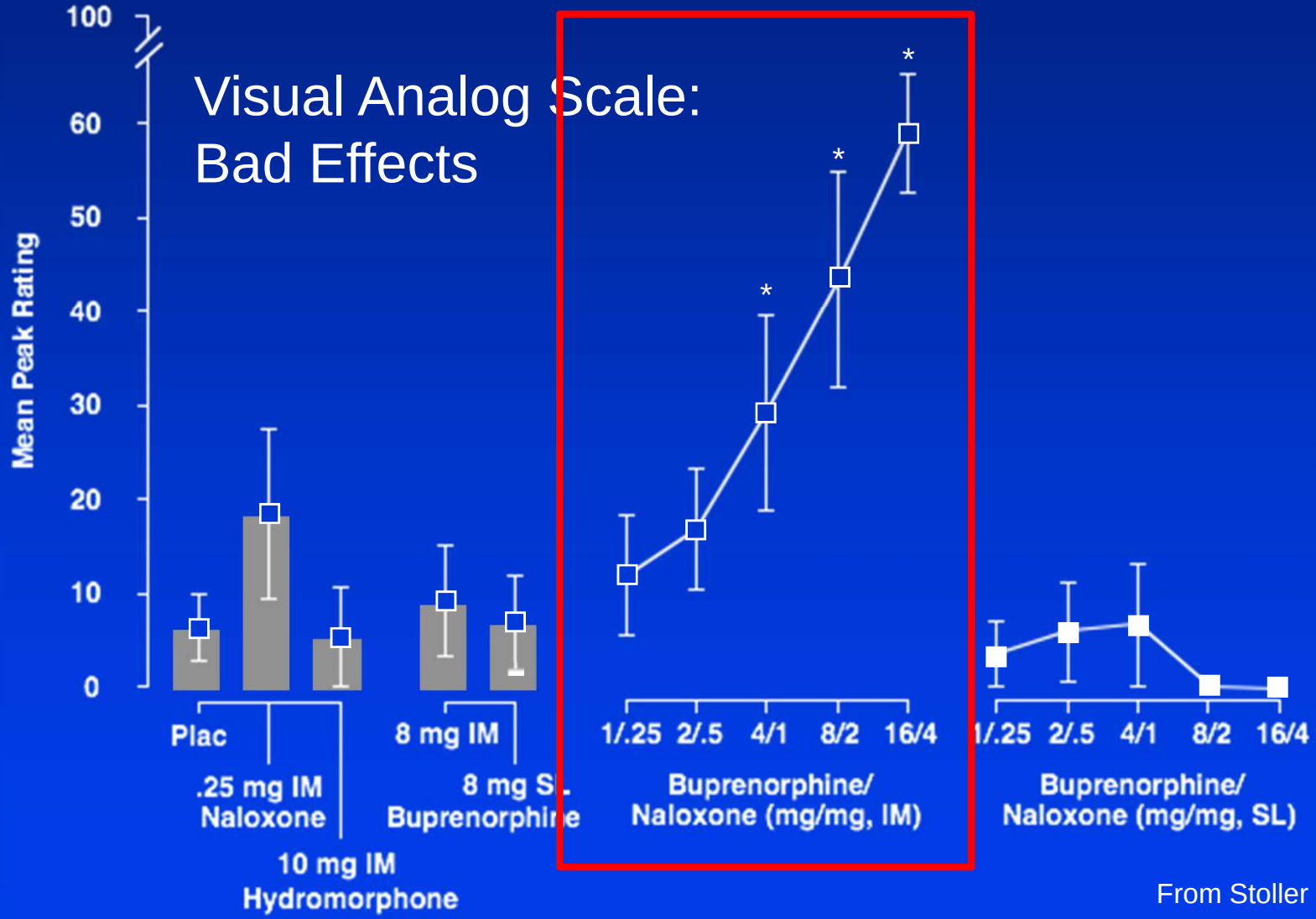

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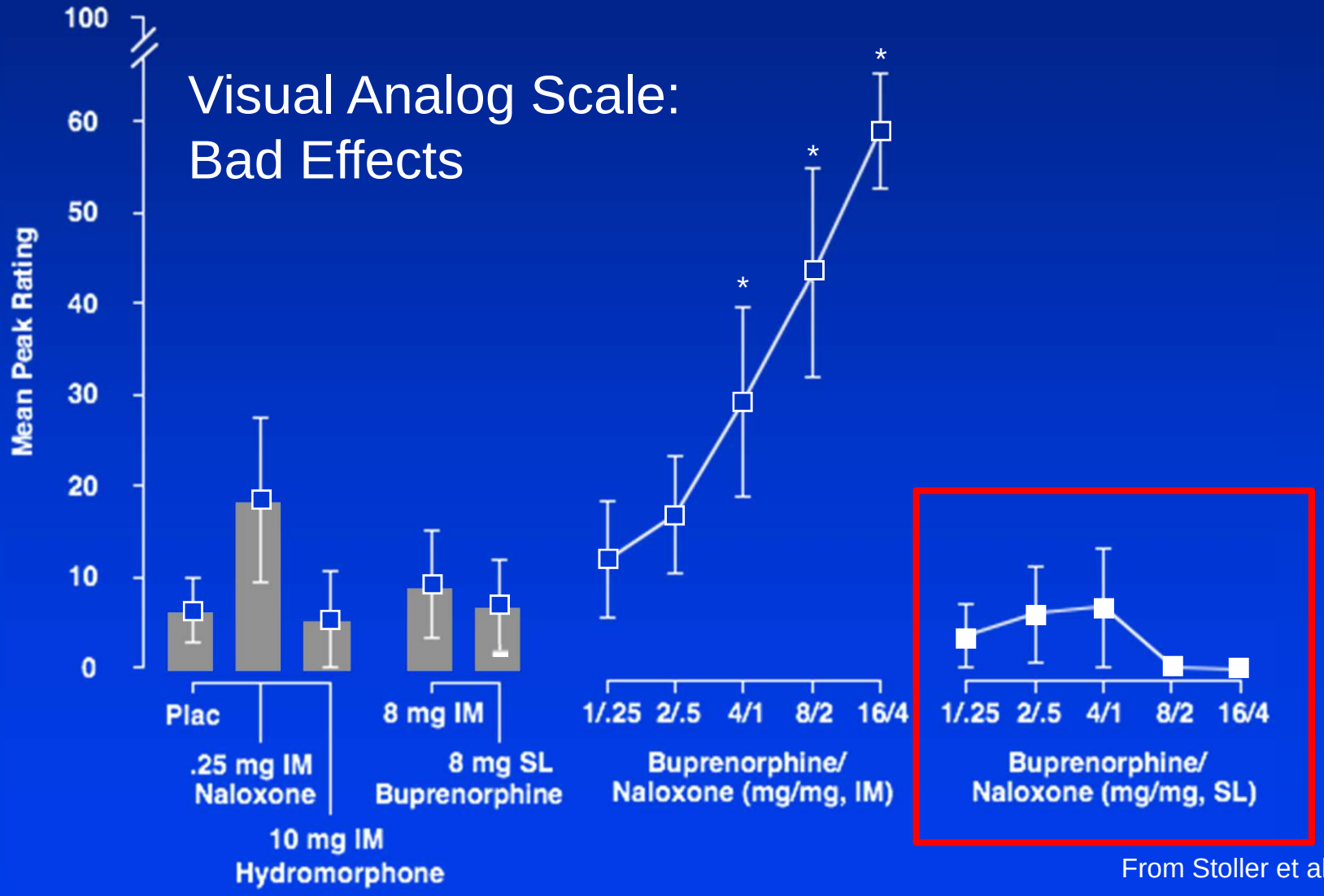


From Stoller et al., 2001

Buprenorphine

Buprenorphine effects in dependent volunteers (2001)

- Study demonstrated hypothesized effects -- that injected buprenorphine/naloxone produced precipitated withdrawal, but no such effects with same doses given SL

Buprenorphine

Safety, side effects

Low risk of respiratory depression with overdose (partial agonist effects)

Label notes to watch LFTs (especially persons with preexisting liver disease), but a large study did not show a problem with this

Buprenorphine

Clinical use

- Marketed in U.S. as sublingual tablets (generic buprenorphine, buprenorphine/naloxone), as a soluble film (Suboxone – buprenorphine/naloxone), and long-acting inserted rod (Probuphine)
- Multiple dose sizes for tablets and film
- Insertion and removal of rods requires special training

Buprenorphine

Clinical use

Daily SL doses generally between 8/2-16/4 mg, can be higher

In the U.S., possible to prescribe from doctor's office setting (need to be qualified, get special DEA number, limit on number of patients treated) – this is different from how methadone is provided (more regulated clinic system)

Maintenance Medications for Opioid Addiction

Buprenorphine

LAAM

Methadone

Naltrexone

LAAM

- l-alpha-actelymethadyl
- Structurally related to methadone
- Duration of action longer than methadone's (allows dosing on MWF basis)
- Was prescribed through Opioid Treatment Programs (aka methadone clinics) for opioid dependence treatment

LAAM

Approved by FDA in 1993, but never many patients treated with it (probably less than 10,000)

Small number of reports of torsades with its use – withdrawn from European market, and manufacturer stopped marketing it in U.S. in 2004 (low sales)

Could be picked up by another company

Maintenance Medications for Opioid Addiction

Buprenorphine

LAAM

Methadone

Naltrexone

Methadone

Pharmacology

- mu agonist opioid
- Good oral bioavailability
- Long duration of action (once daily dosing)
- Suppresses spontaneous opioid withdrawal
- Blocks effects of other opioids (cross tolerance)

Methadone

Efficacy

"Methadone maintenance treatment" (MMT) is combination of medication and non-pharmacological treatments (counseling, group therapy, urine monitoring, contingency interventions); provided in Opioid Treatment Programs (OTPs)

MMT more effective than placebo

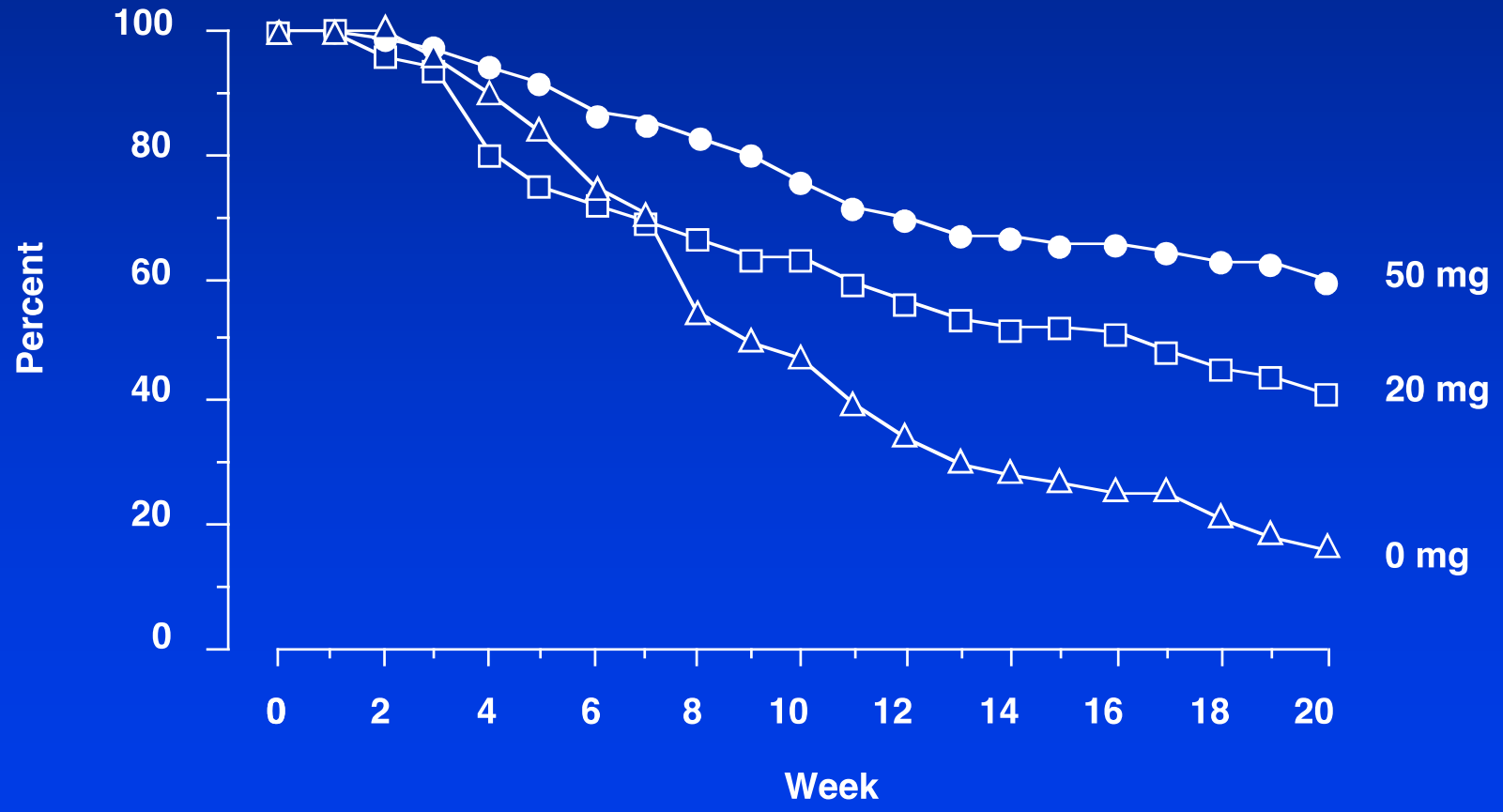
Methadone

Efficacy

Extensively studied, efficacy is dose-related

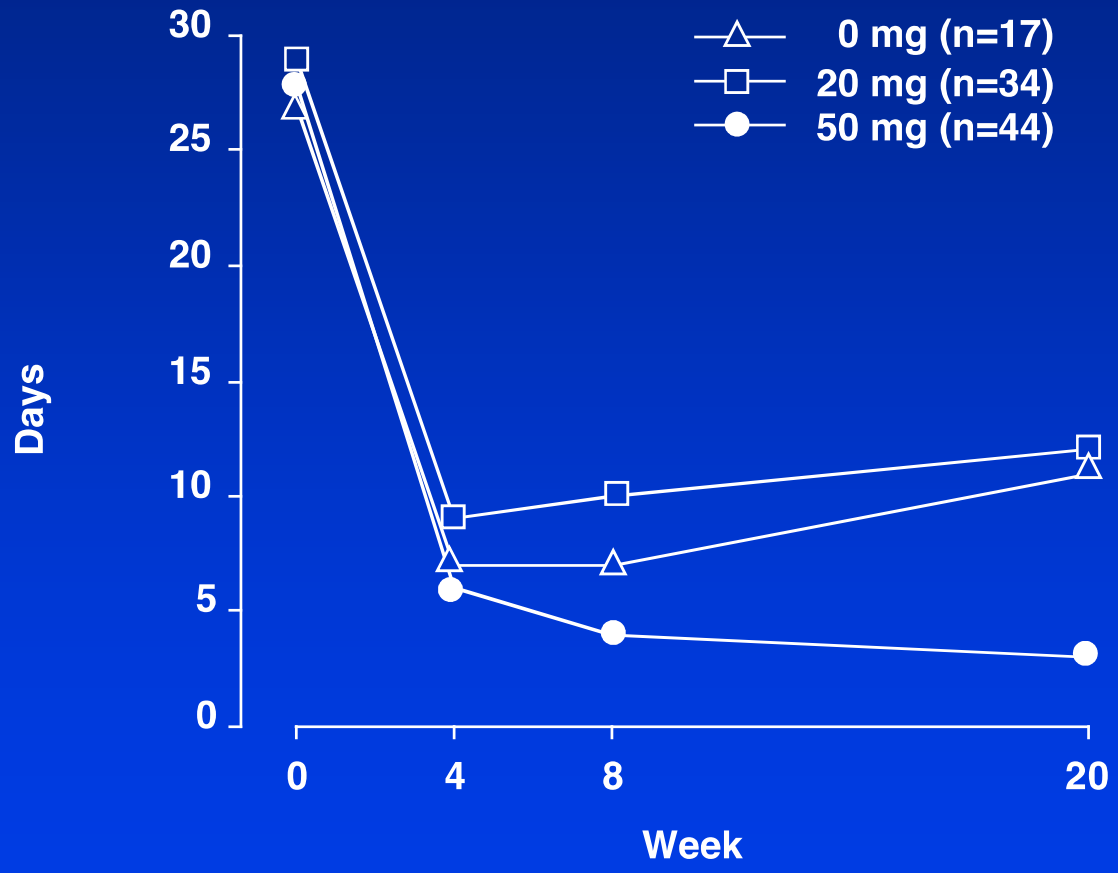
Outcomes examined generally time in treatment (retention) and illicit opioid use (but other pro-social changes noted with methadone treatment)

Methadone Study 1: Treatment retention



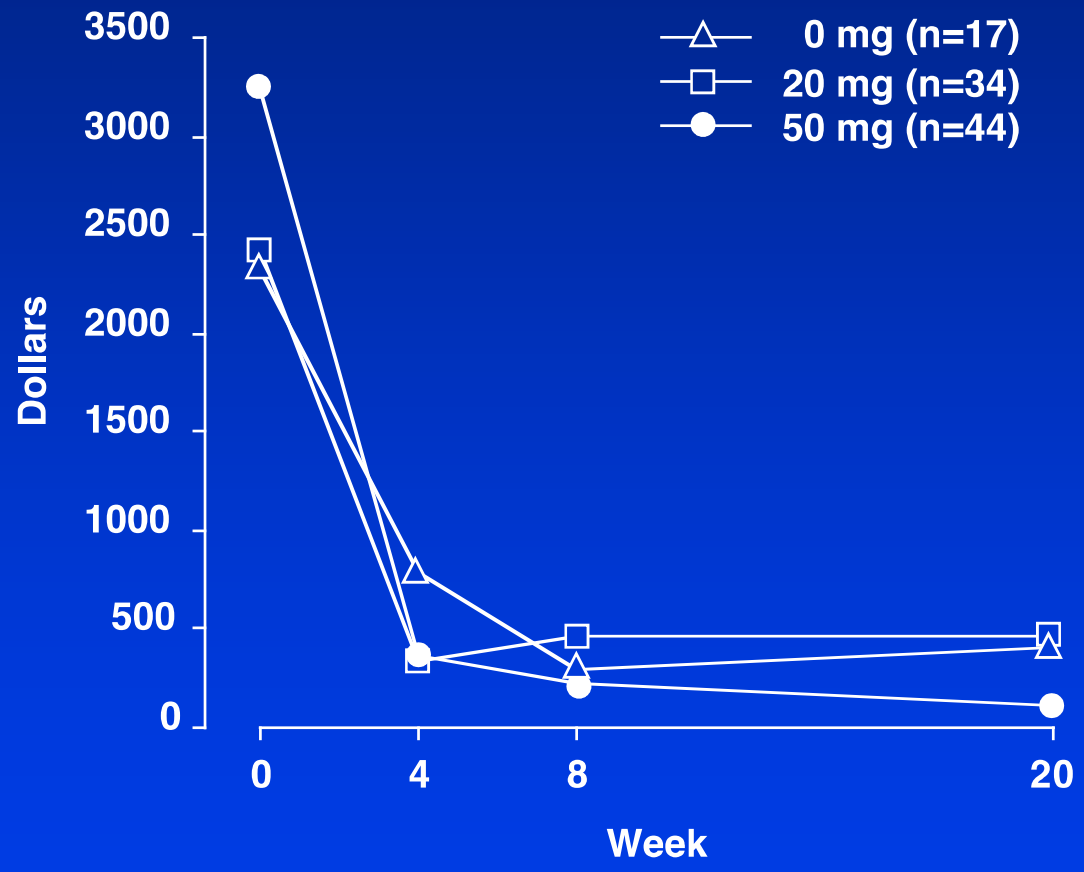
From Strain et al., 1993

Methadone Study 1: Heroin use



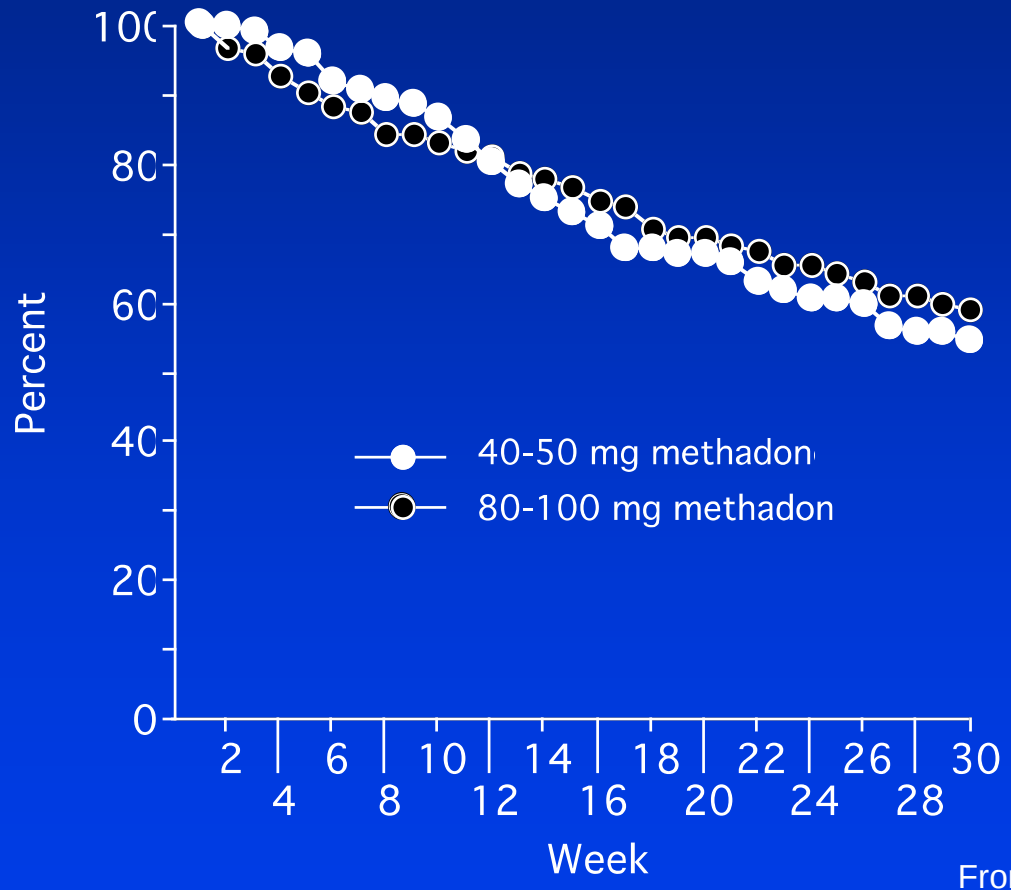
From Strain et al., 1994

Methadone Study 1: Money spent on drugs



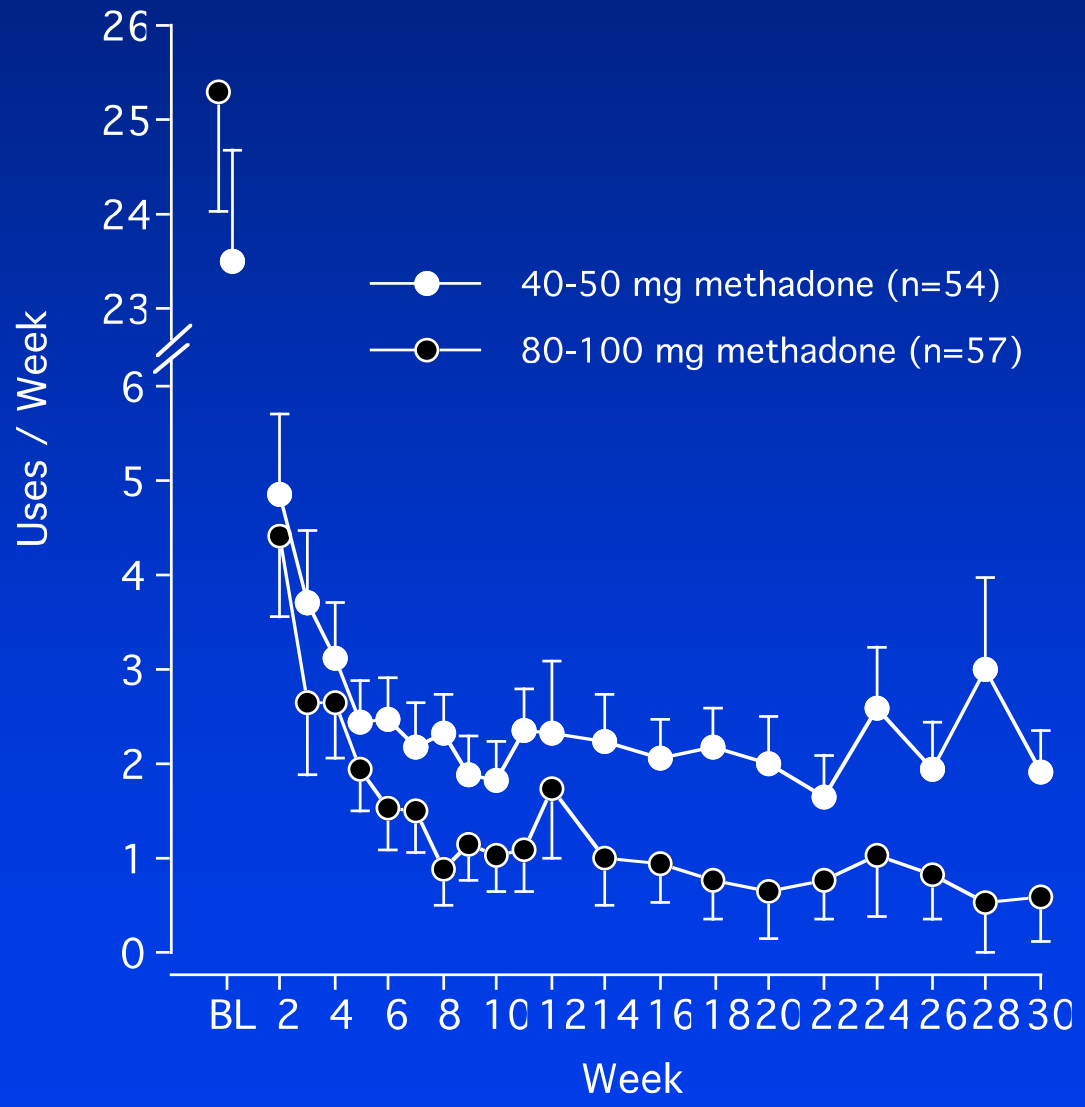
From Strain et al., 1994

Methadone Study 2: Treatment retention



From Strain et al., 1999

Methadone Study 2: Self-reported illicit opioid use



From Strain et al., 1999

Methadone

Safety, side effects

- Generally safe and well-tolerated medication
- Side effects typical for mu agonist opioids (constipation, increased sweating)
- Rare case reports of torsades with very high doses/other risk factors for QTc prolongation

Methadone

Safety, side effects

Risk of respiratory depression if overdose (full mu agonist opioid) – particular concern with take home doses, or if dose is diverted and taken by person with lower level of physical dependence (or not physically dependent)

Methadone

Clinical use

At least 250,000 persons treated with methadone in the U.S. (and similar number in rest of the world)

Used for opioid dependence treatment since mid-1960s (first studied by Dole and Nyswander at Rockefeller University)

Methadone

Clinical use

In U.S., use of methadone for opioid dependence treatment limited to special clinic system (Opioid Treatment Programs, OTPs) – rare for physicians to be allowed to prescribe for addiction treatment outside this system

OTPs historically under significant governmental regulation (and now Joint Commission, CARF)

Methadone

Clinical use

Some U.S. OTPs poorly run in the past (little medical input and supervision, emphasis on medication but inadequate dosing, punitive rules)

Past difficulty in expanding treatment capacity of OTPs (community resistance to opening new clinics)

[This part of reason buprenorphine office-based]

Methadone

Clinical use

- Dosing with methadone usually in an oral solution, supervised by a nurse, occurs once per day
- Patients initially attend clinic daily for dose (6 or 7 days per week)
- Supervised urine collection, random testing
- Counseling (individual, group) on site

Methadone

Clinical use

As stability achieved (no drug use, involved in work or education), patients typically allowed “take home” (TH) doses

THs desired by patients– lessens burden of daily attendance

THs used as a contingency for treatment goals

Methadone

Clinical use

Initial dose usually 30 mg per day

Doses titrated up as clinically indicated (decrease illicit opioid use, craving, opioid withdrawal symptoms), in 10 mg increments every few days

Average doses of 80-100 mg per day, with doses as high as 200 mg per day

Methadone

Clinical use

Final point about methadone treatment: While focus today is on pharmacotherapy, also has been shown that non-pharmacologic treatment enhances outcomes and is dose related

Maintenance Medications for Opioid Addiction

- Buprenorphine
- LAAM
- Methadone
- Naltrexone

Naltrexone

An opioid antagonist (occupies receptor but does not activate receptor)

Blocks effects of other opioids (don’t experience high effect from opioid when taking naltrexone)

Not reinforcing (fundamental difference from buprenorphine, LAAM, and methadone)

Naltrexone

Hope was that reinforcing effects of opioids would extinguish in person maintained on naltrexone

In an opioid dependent person, a dose of naltrexone will precipitate withdrawal (not a good thing), so should not start until patient has been completely withdrawn off opioids (not physically dependent)

Naltrexone

- Dosing can be daily (50 mg po per day) or thrice weekly (MWF, 100/100/150 mg)
- Generally safe and with minimal side effects (label warns to watch LFTs, but this was in study using very high doses)
- When a patient takes it, naltrexone is effective – but, patients often stop taking it

Naltrexone

Generally limited use for treatment of opioid dependence (special situations, such as physicians and other professionals mandated to use as part of licensing)

Extended release form of naltrexone also available (dosed once per month by injection)

Maintenance Medications for Opioid Addiction

- Buprenorphine
- LAAM
- Methadone
- Naltrexone
- Other options on horizon?

Maintenance Medications for Opioid Addiction

Other options/potential medications

- Heroin
- Hydromorphone
- Tramadol
- Other forms of buprenorphine (especially long acting injectables)

Outline for this talk

I. Why is the United States so concerned about opioid abuse?

II. Opioid addiction/dependence and withdrawal

III. Treatments available for opioid dependence/addiction

IV. Summary and conclusions

Summary

Rising rate of opioid misuse seen in the U.S. in recent years, primarily driven by prescription misuse – may be now stabilizing or even decreasing

Medications available that are effective and safe (especially methadone and buprenorphine)

While focus on medications today, non-pharmacological treatment also very valuable

Acknowledgements

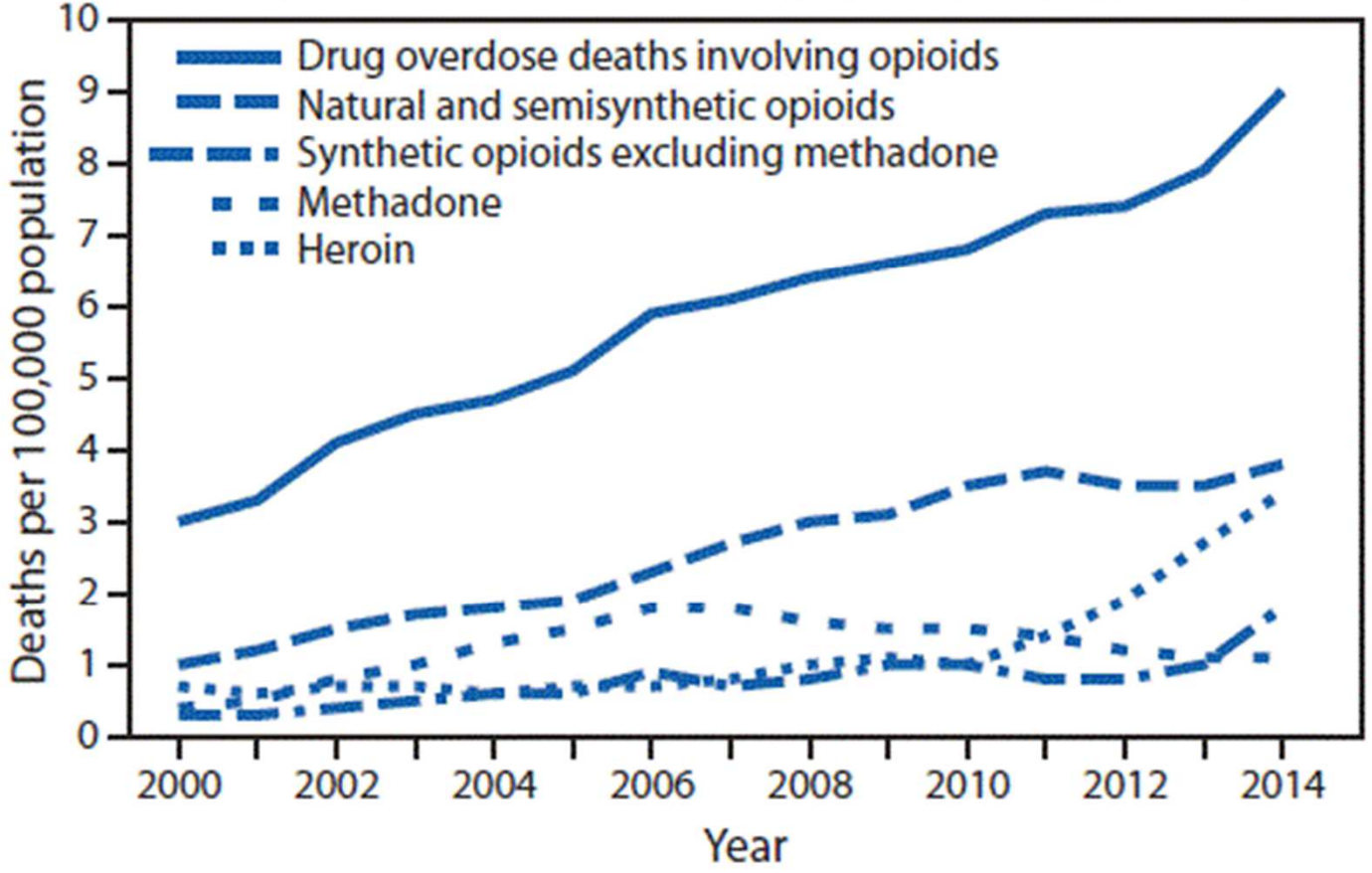
Support of NIDA

Patients and staff at the Behavioral Pharmacology Research Unit at Johns Hopkins University School of Medicine

Thank you.

Opioid overdoses

FIGURE 2. Drug overdose deaths* involving opioids,[†,§] by type of opioid[¶] — United States, 2000–2014



Source: National Vital Statistics System, Mortality file.

From MMWR, January 2016