MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Management of Opioid Withdrawal and Overdose

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Planning Committee, Disclosures

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Educational Objectives

- At the conclusion of this activity participants should be able to:

1. Gain familiarity with strategies for inpatient and outpatient opioid induction

2. Learn how to use and rate the Clinical Opioid Withdrawal Scale (COWS)

3. Be able to discuss the relative advantages of antagonist vs. agonist treatments, as well as medication-assisted treatments in general, for opioid dependence.

Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

Accreditation Statement

- American Academy of Addiction Psychiatry (AAAP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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Opioid

- Illicit opioids: Heroin (diacetyl morphine)
- Short-acting prescription opioids: Hydromorphine (Dilaudid), Hydrocodone (Vicodin), Codeine, Meperidine (Demerol)
- Long-acting prescription opioids: Oxycodone (Oxycontin), Morphine (MS Contin), Methadone (Dolophine), Fentanyl (Duragesic)

Opioid Analgesics

Short-Acting Opioids	Dosing Frequency (Time/Day)
Hydromorphone Dilaudid	4
Hydrocodone (Vicodin), Codeine	4-6
Meperidine (Demerol) not for chronic pain	6/8
Long Acting Opiods	**Durations (hrs)**
Buprenorphine (Subutex, Suboxone)	8
Codeine (Codeine Contin)	12
Oxycodone (Oxycontin)	12
Morphine (Avinza, MS Contin)	12
Methadone (Dolophine)	12
Fentanyl (Duragesic)	72

American College of Physicians. Available at: http://www.acpinternist.org/archives/2008/01/extra/pain_card.pdf. Accessed March 14, 2011.

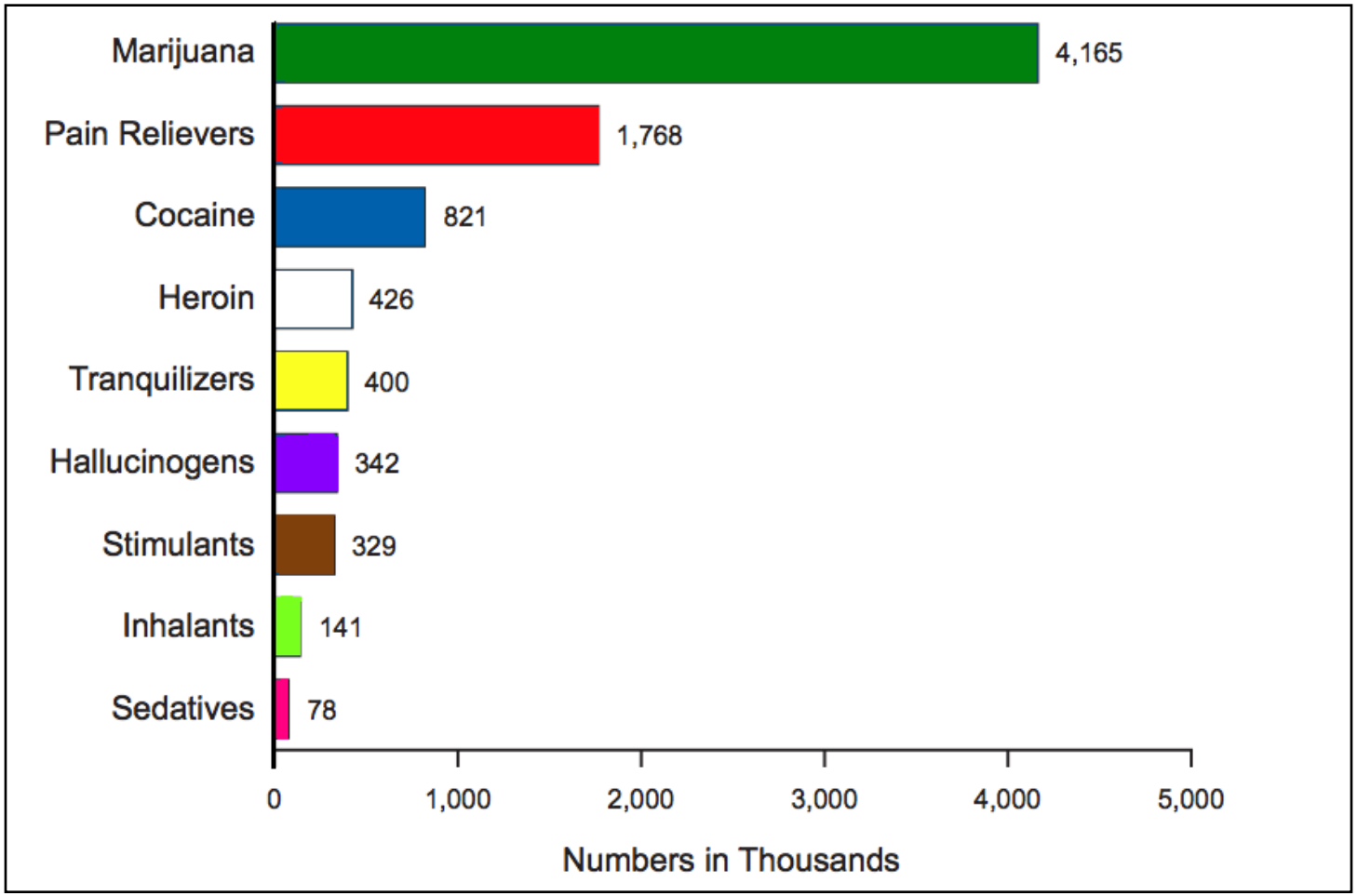
Narcotic Addiction: A Public Health Imperative

- Up to 1 million heroin users in need of treatment and nearly 2 million untreated prescription opioid addicts in the U.S. (NSDUH 2011)
- In past two decades, non-medical use and abuse of opioids has risen dramatically
- Prescription opioid abuse: more than 3 times prevalence of heroin dependence
- By 2006, number of new initiates to prescription opioid abuse exceeded those for marijuana and cocaine (NSDUH, SAMHSA)
- HCV prevalence among injecting heroin addicts: 75-95%
- Mortality: 2% (overdose deaths) - 3.5% (all causes) per year

Epidemiology of Prescription Opioid Abuse in the United States

- 5.2 million Americans (2.1% of U.S. pop.) used prescription opioids non-medically in past month (USDUH 2011)
- Prevalence: 30.4% chronic pain patients in a large (N=239) general practice reported taking extra narcotic doses (Rosser et al., 2011)
- Most common sources for misused opioids: free from friend or relative (60%), followed by obtaining prescriptions from one physician (17%) (NSDUH 2011)
- Prescription opioids are gateway drug: 17.1% of substance abusers cite pain medication as being the first substance they abused (NSDUH 2009)
- Efforts to more aggressively manage pain have resulted in sharp rises in prescribing and misuse of high-potency opioids such as hydrocodone and oxycodone

Illicit Drug Dependence or Abuse in the Past Year Among Persons Aged 12+

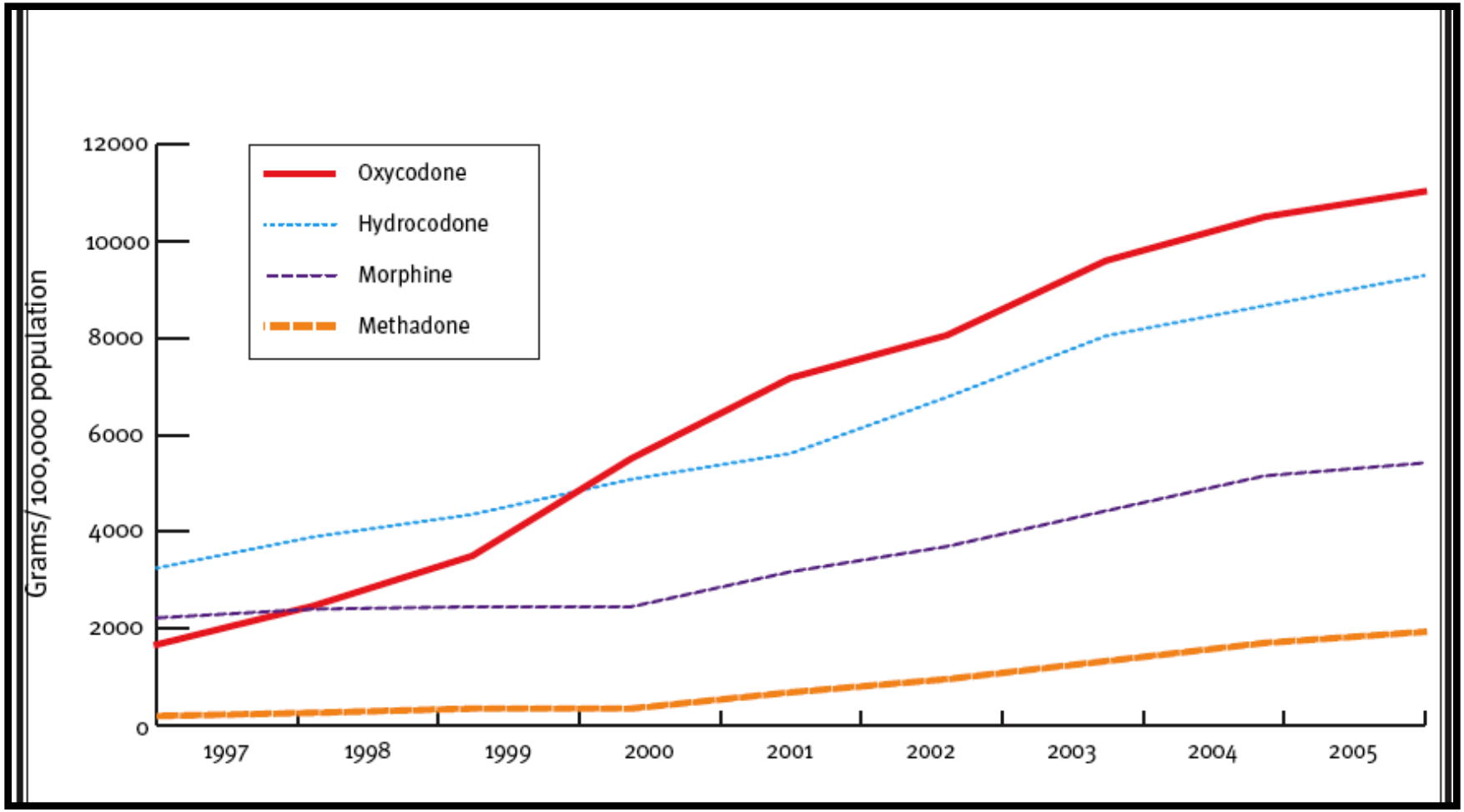


NSDUH, SAMHSA 2011

Opioid Prescribing Trends in the United States

- Events in late 1990s led to increased opioid prescribing: (1) state medical boards liberalized rules for prescribing for non-cancer pain (Manchikanti et al., 2010), (2) FDA approval of high-potency Oxycontin.
- Reimbursement for medical care linked to number of encounters; does not reward risk vs. benefit analyses (Gallagher and Rosenthal 2008)
- From 1997 to 2007, retail sales of oxycodone increased 866% and 1293% for methadone (Manchikanti et al., 2010)
- Physician offices: significant increase in visit rate for high-potency opioids (hydrocodone, oxycodone) (Mendelson et al., 2008).
- MD offices and EDs are important channels for abused opioids.

Prescribed Therapeutic Opioids in the U.S.



Manchikanti et al. 2010

Sources for Misused Opioids

- Sources for abused prescription opioids -- Most frequent: free from friend or relative (60%), Other common source: single physician (17%) (NSDUH 2005)
- Numerous active street markets involve patients, Medicaid recipients, pharmacies (Inciardi et al. 2007)
- Physician offices: significant increase in visit rate for high-potency opioids (hydrocodone, oxycodone) (Mendelson et al., 2008).
- MD offices and EDs are important channels for abused opioids

Management of Opioid Detoxificaton

Signs of Physical Dependence to Opioids

- **Tolerance:** Effectiveness of drug diminishes over time, with regular daily or chronic use
- **Withdrawal:** Rebound hyperactivity of noradrenergic system. Clinically significant opioid withdrawal requires daily use of an adequate amount of an opioid for 2-3 weeks

Signs and Symptoms of Opioid Withdrawal

Early-Moderate

- Anxiety
- Craving
- Dysphoria
- Mydriasis
- Perspiration
- Piloerection
- Restlessness
- Rhinorrhea
- Yawning

Moderate-Advanced

- Abdominal cramps
- Hot or cold flashes
- Increased pulse and BP
- Insomnia
- Low-grade fever
- Muscle and bone pain
- Muscle spasms
- Mydriasis
- Nausea and vomiting

Time Frame for Opioid Withdrawal Onset

Drug	Onset of Withdrawal (hours)	Peak Effects (hours)	Most Symptoms are Over
Heroin	8-12	36-72	7-10 days
Morphine	8-12	36-72	7-10 days
Oxycodone	8-12	36-72	7-10 days
Hydromorphone	4-5	36-72	7-10 days
Fentanyl	3-5	8-12	4-5 days
Methadone	36-72	96-144	14-21 days

Treatments for Opioid Dependence

- **Residential and drug-free approach**: Detoxification is usually followed by referral to psychosocial services without pharmacologic support, but detox. also permits XR-NTX induction.
- **Agonist maintenance**: Buprenorphine/naloxone prescribed in office setting or methadone in MMT
- **Antagonist maintenance**: Oral naltrexone or monthly IM injections of extended-release naltrexone

Goals of Detoxification

- 1. Eliminate acute physiological dependence from chronic opioid use
- 2. Diminish the pain and discomfort of opioid withdrawal
- 3. Provide a safe environment for remaining abstinent during acute withdrawal
- 4. Identify and treat any concurrent medical problems
- 5. Refer patient for treatment to prevent relapse and to address family, work, and legal problems

Medication-assisted Withdrawal

- Two pharmacological strategies for detoxification:
  - (1) Agonist approach: methadone is associated with highest retention rate (80% at 6 months); buprenorphine allows for office-based treatment and retains 60% at 6 months
  - (2) Antagonist treatment: oral or injection naltrexone (XR-NTX) is incompatible with illicit opioid use; does not produce any tolerance or withdrawal

Strategies for Treating Opioid Withdrawal

- **Opioid Agonist Substitution and Taper:**
  - Methadone
  - Buprenorphine
  - Other short-acting prescription opioids
- **Methadone:** orally effective; long-acting opioid produces milder (but protracted) withdrawal syndrome
- **Buprenorphine:** approved in 2002 for detoxification and maintenance; its use as a detoxification agent is increasing

Agonist-based Opioid Detoxification

- Urine toxicology should be done to confirm presence of opioids. Heroin (as morphine) detected up to 48 hrs.
- With illicit opioids, knowledge of exact doses used is usually not available. Wait for withdrawal symptoms to appear.
- Begin with 10-20 mg methadone (relieves withdrawal but safe if habit is low) or 8-mg buprenorphine
- Observe for drowsiness or depressed respiration. Dose can be repeated in 12 hours.
- Total 24-hr dose of methadone should not exceed 40 mg
- On Day 2, repeat dose needed to stabilize patient on Day 1
- Inpatient detox usually 5-7 days; outpatient can be longer

Detoxification and Antagonist Induction

- **Ancillary medications** allow withdrawal symptoms (e.g. myalgias, insomnia) to resolve sooner
- **Combining naltrexone with clonidine**: alpha-2 agonist mitigates precipitated opioid withdrawal
- **Advantages:** reduction in detox time, ability to transition to abstinence with fewer lingering symptoms; no tolerance or withdrawal
- **Disadvantages:** poorer patient acceptance, compared with other techniques; need for intensive monitoring

Ancillary Medications: Non-Opioid Detoxification Agents

- **Alpha-2 agonists** (clonidine, guanfacine, lofexidine)
  - Reduce sympathetic hyperactivity by feedback inhibition of presynaptic neurons
- **Benzodiazepine**s (e.g. clonazepam)
  - For insomnia, anxiety, muscle spasm
- **NSAIDs** (ketorolac, acetominophen, ibuprofen)
  - For muscle and bone pain
- **Anti-emetics** (ondansetron, prochlorperazine)
- **Anti-diarrheal agents** (e.g. loperamine)
- **Hypnotic agents** (zolpidem, trazodone)

Naltrexone

- Approved by FDA in 1984 (oral) and 2010 (long-acting injectable Vivitrol)
- Blocks opioids without agonist effects; incompatible with ongoing illicit opioid abuse. No tolerance or withdrawal develops.
- Oral form taken daily (50 mg) vs. monthly (380 mg) IM injection;
- Serum level of 2 ng/ml provides effective blockade against 25 mg IV heroin effects
- Only 15.8 % of treatment facilities in U.S. report using naltrexone. (SAMHSA, 2009)

SAMHSA. National Survey of Substance Abuse Treatment Services. Data on Substance Abuse Treatment Facilities. 2009. Rockville MD: US Department of Health and Human Services; DHHS publication SMA 05–4112.

Barriers to Antagonist Treatment

- Induction onto naltrexone requires abstinence for 5-7 days from heroin, 7-10 days from methadone.
- **A single day of buprenorphine as part of oral naltrexone-assisted detoxification can shorten the abstinence requirement to 12-24 hours.**
- Adherence has historically been poor with oral naltrexone.
- **Injection naltrexone avoids the need for daily adherence and improves retention.**

Naltrexone-assisted Opioid Detoxification

- *Day 1* – Ancillary meds: clonidine, clonazepam, compazine, zolpidem, trazodone
- *Day 2* – Buprenorphine 4 mg BID
- *Day 3* – Washout Day
- *Day 4* – Naltrexone 3 mg
- *Day 5* – Naltrexone 6 mg
- *Day 6* – Naltrexone 25 mg
- *Day 7* – Naltrexone 50 mg, followed by 380 mg IM (Vivitrol)
  - Alpha-2 adrenergic agents (clonidine), benzodiazepines, and sleeping agents can ameliorate withdrawal symptoms
  - Approximately 70% of patients complete inpatient induction and accept long-acting naltrexone (NTX-XR)

Sigmon, Bisaga, Nunes et al., 2012

Safety Concerns with Naltrexone

- It is expected that 50% of patients will test the blockade. Sporadic testing 1-3 times early in course of treatment should lead to extinction.
- Repeated consecutive testing (blocked use) later in treatment heralds unblocked use; requires more frequent visits, increased therapy, monitored ingestion of oral naltrexone, etc.
- Naltrexone protects against overdose, but discontinuation poses risk because of lost tolerance.
- Consider transition onto agonist to decrease risk of overdose if patient is unable to comply with naltrexone or to stop using.

Anesthesia-assisted Opioid Detoxification

- Patient interest reflects desire for pain-free detox.
- Uses naltrexone, propofol anesthesia, ondansetron, octreotide (anti-diarrhea), clonidine, and benzodiazepines
- Heavy sedation with midazolam is alternative to general anesthesia
- Technique carries potentially serious morbidity and mortality to achieve opioid detoxification, but safer and less expensive methods are available (Collins et al., 2005, Kleber 1998)
- Withdrawal symptoms persist for days or even weeks after the procedure (Collins et al., 2005, Scherbaum et al., 1998)
- Little benefit but significant adverse effects (e.g. pulmonary edema, diabetic ketoacidosis, (Collins et al., 2005)

Buprenorphine Taper for Detoxification

- For detoxification from buprenorphine maintenance, taper is often unsuccessful, with no advantage to longer taper. Abstinence at end of taper: 44% (7 days), 30% (28 days) (Ling et al., 2009)
- For treatment of prescription opioid dependence using buprenorphine/naloxone (bup/nx) stabilization, retention and naltrexone ingestion were superior in a 4-week vs. briefer tapers (both P=.04) (Sigmon et al., 2013)

Comer et al. (2002) Psychopharmacology, 159: 351-360

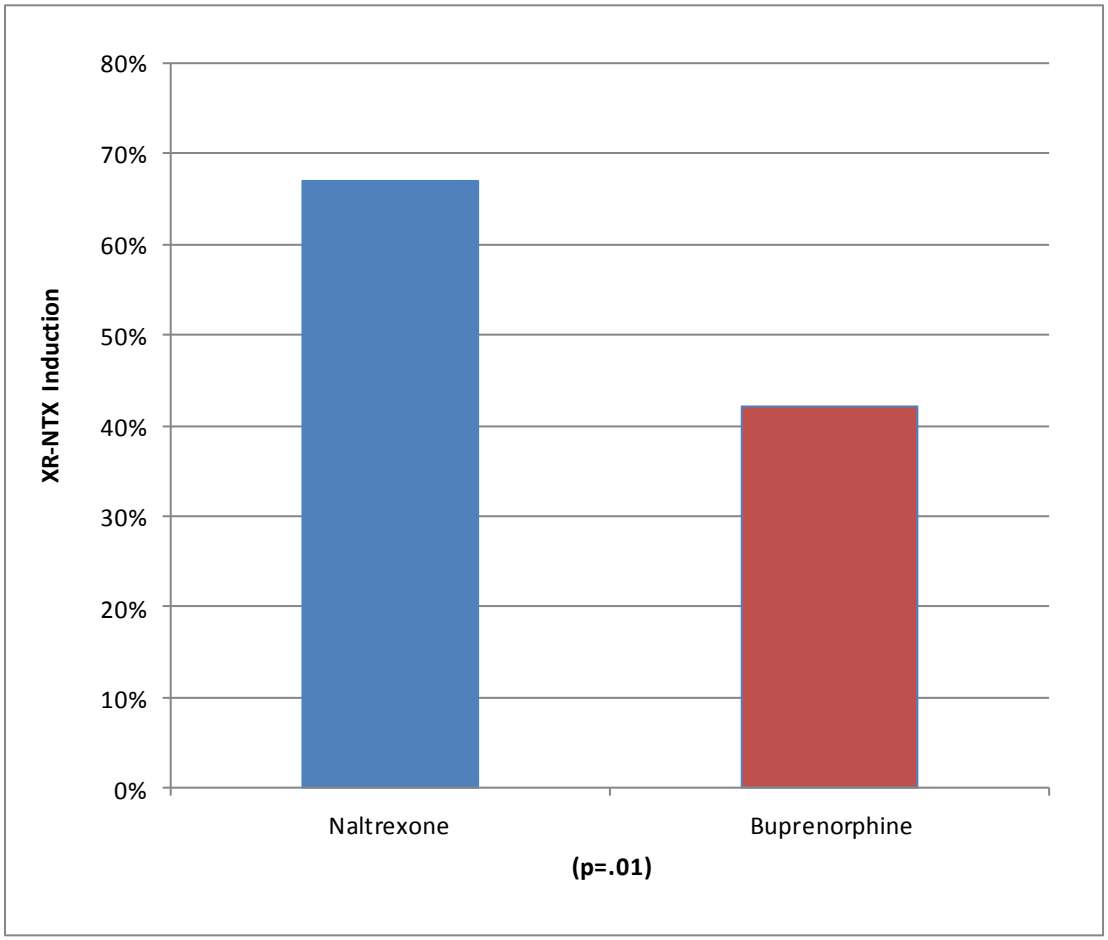
Long-acting Injectable Naltrexone Induction: Randomized Trial of Outpatient Opioid Detoxification with Naltrexone vs. Buprenorphine

- **Sample:** 100 opioid-dependent patients
- **Randomized to one of two outpatient detoxification strategies:**
  - (1) 7-day buprenorphine induction/taper (8 mg to 0 mg)
  - (2) 7-day naltrexone induction (1 mg to 25 mg) + adjunct medications (clonidine, clonazepam, prochlorperazine, zolpidem)
- Single administration of injection naltrexone given on Day 8 (naltrexone group) and on Day 15 (buprenorphine group)
- Aim: Compare injectable naltrexone induction rates between the naltrexone and buprenorphine detoxification arms

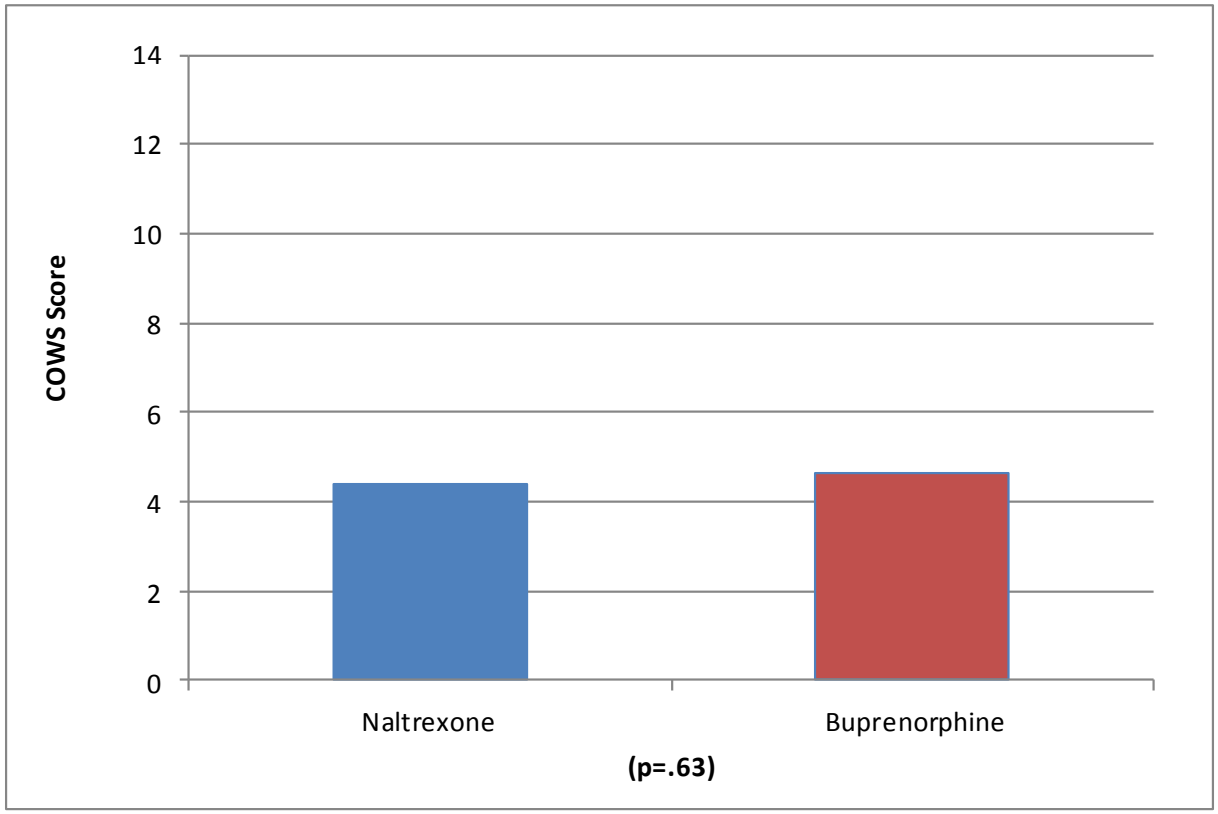
Outpatient Opioid Detoxification: Participant Demographics

	Naltrexone (n=68)	**Buprenorphine (n=38)**	Total (n=106)
Age (mean, SD)	37.3 (12.5)	35.1 (11.1)	36.5 (12.0)
Gender (female)	16.1%	5.2%	12.3%
Ethnicity Caucasian Hispanic African American Asian	61.7% 26.4% 10.2% 1.4%	68.4% 18.4% 10.5% 2.6%	64.1% 23.5% 10.3% 1.8%
Heroin severity of use (mean bags of heroin day)	7.60 (4.68)	6.90 (3.85)	7.38 (4.42)
Rx severity of use (mean mg of morphine/day)	139.22 (78.34)	128.43 (63.97)	134.56 (71.72)
Rx Users	29.4%	34.2%	31.1%
IV Users	13.2%	23.6%	16.0%
IN Users	58.8%	42.1%	52.8%

Injection Naltrexone (XR-NTX) Induction



Withdrawal Symptoms during Detox. By Treatment Group



Summary of Opioid Detoxification

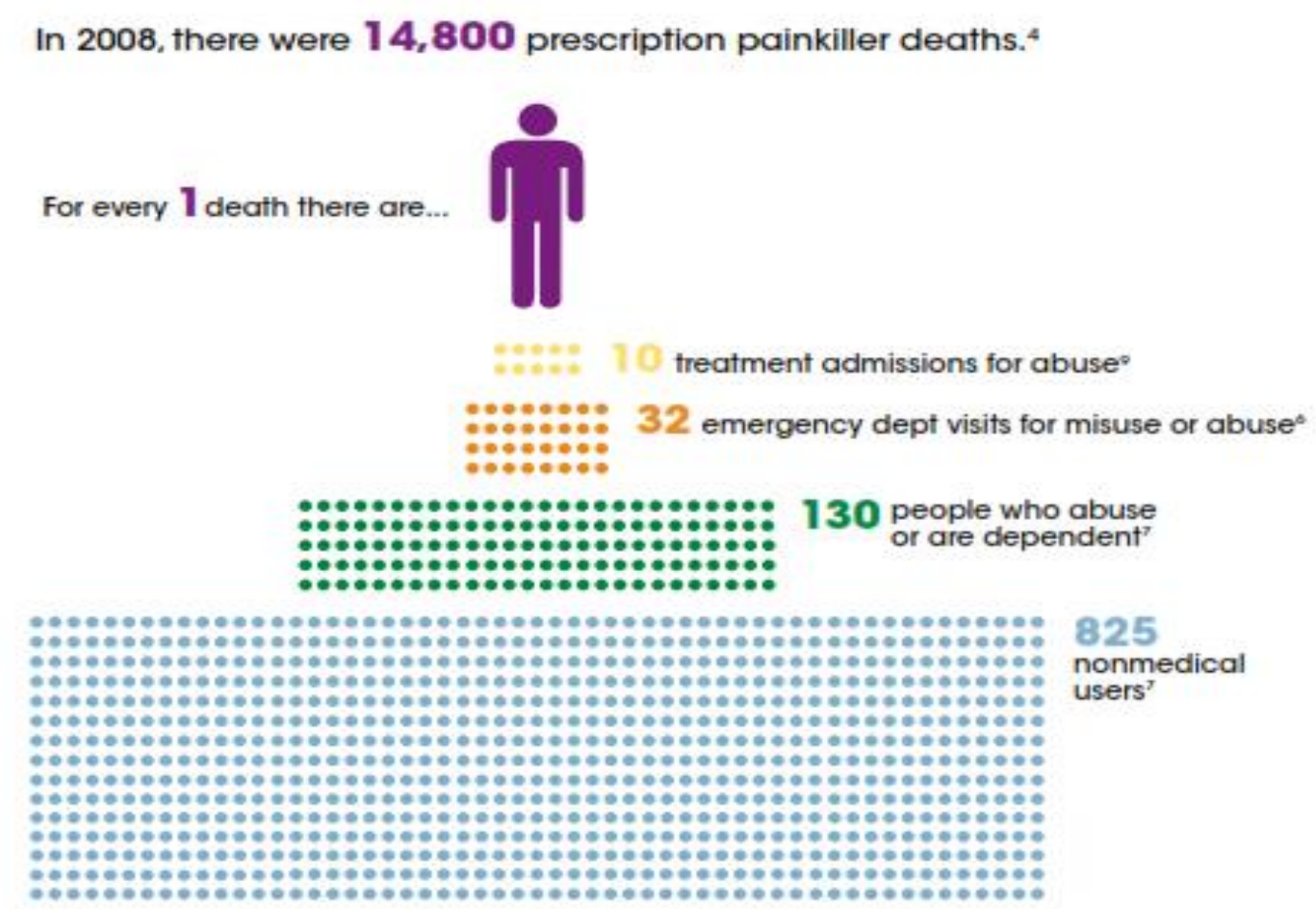
- In early 1900s, detoxification was considered a cure for opioid addiction; in fact, it is only the precursor to abstinence-based treatment.
- Various medications are used for opioid detoxification, including full agonists (e.g. methadone), partial opioid agonists (e.g. buprenorphine), opioid antagonists (e.g. naltrexone), alpha-2 agonists (e.g. clonidine), and adjuvant medications (e.g. clonazepam, ibuprofen) for symptomatic relief
- Within one month of discharge from detox., 80%-90% have relapsed (Smyth et al., 2010, Weiss et al., 2011).
- First weeks after detoxification carry significant risk of overdose and death
- Post- detox. pharmacological assistance with antagonist maintenance is essential: role for long-acting injectable naltrexone (Vivitrol)

Management of Opioid Overdoses

Prescription Opioid Morbidity and Mortality

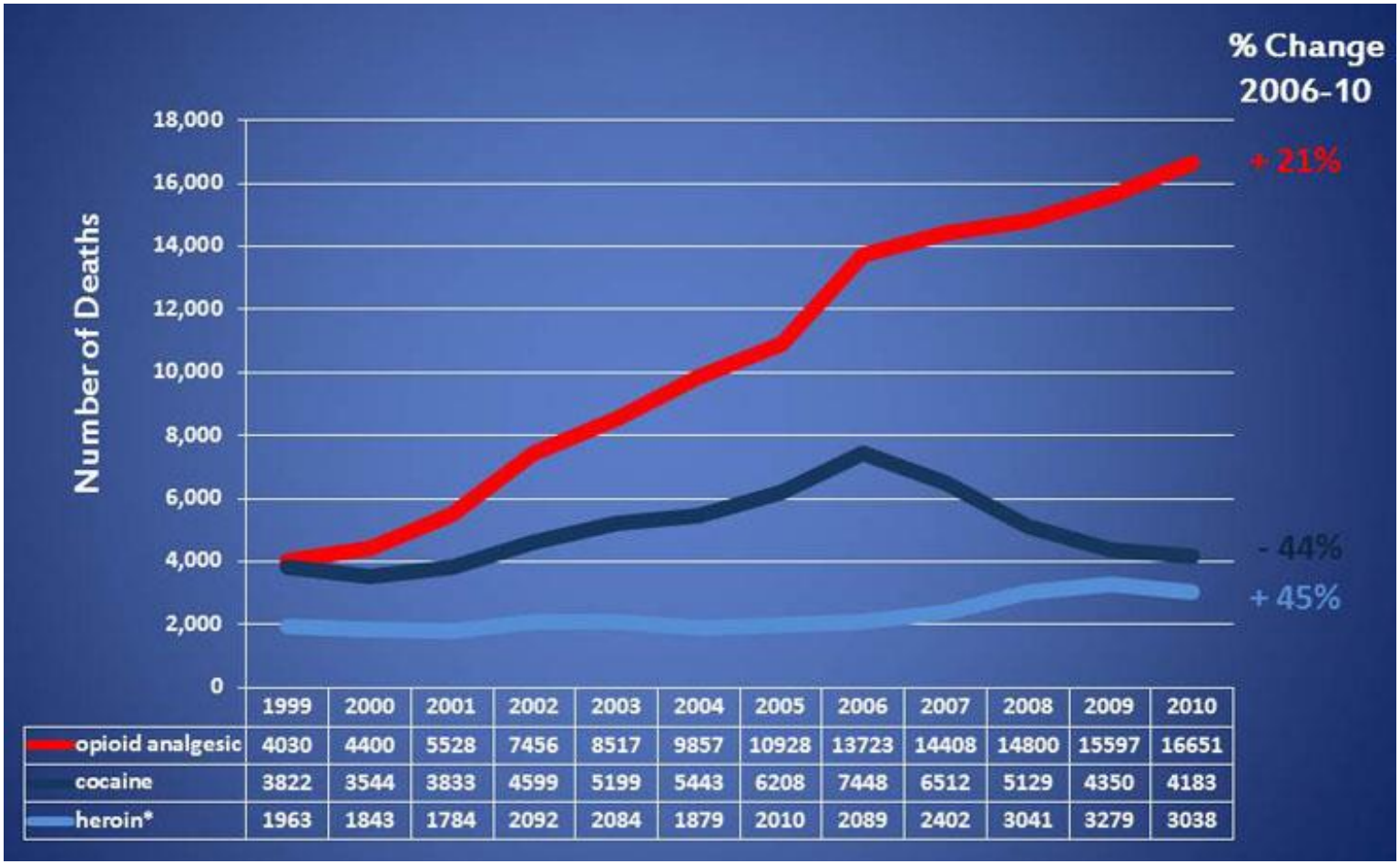
- In parallel with increases in the opioid analgesic use, there has been a dramatic rise in unintentional overdose deaths (CDC 2012).
- Deaths due to opioid analgesics in US (2008): 15,000, surpassing motor vehicle accidents as cause of death in some states (Paulozzi et al., 2008)
- Immunosuppressive effects of opioids may increase morbidity from infectious diseases, autoimmune diseases, and cancer (Pergolizzi et al., 2008)
- In a study of 2112 fatal unintentional prescription opioid overdoses, methadone was associated with highest number of deaths per equi-analgesic dose sold (23.3) (Piercefield et al., 2010)

Prescription Opioid Overdoses



CDC, Policy Impact: Prescription Painkiller Overdoses, November 2011

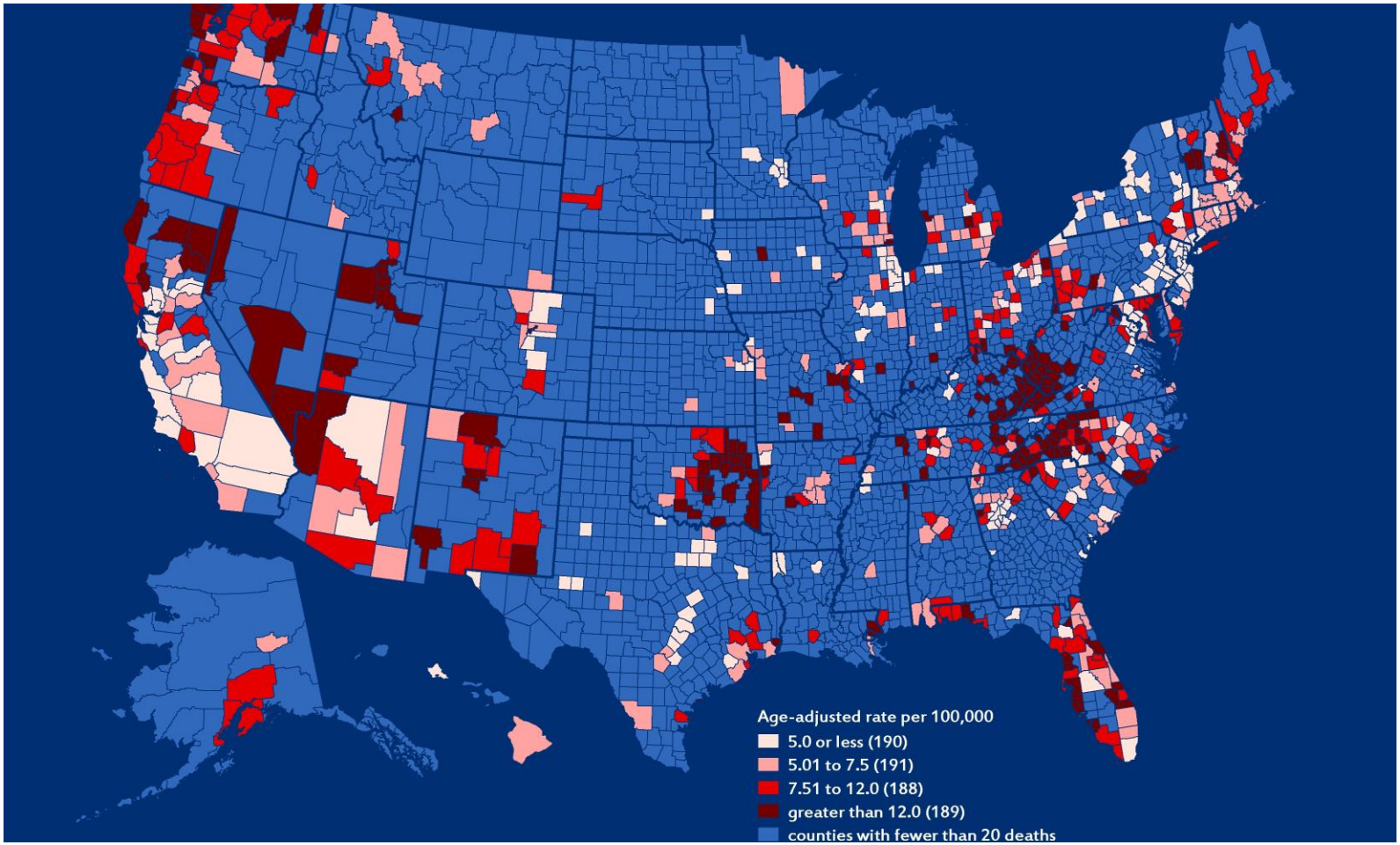
Overdose Deaths in the U.S.,1999-2010



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
opioid analgesic	4030	4400	5528	7456	8517	9857	10928	13723	14408	14800	15597	16651
cocaine	3822	3544	3833	4599	5199	5443	6208	7448	6512	5129	4350	4183
heroin*	1963	1843	1784	2092	2084	1879	2010	2089	2402	3041	3279	3038

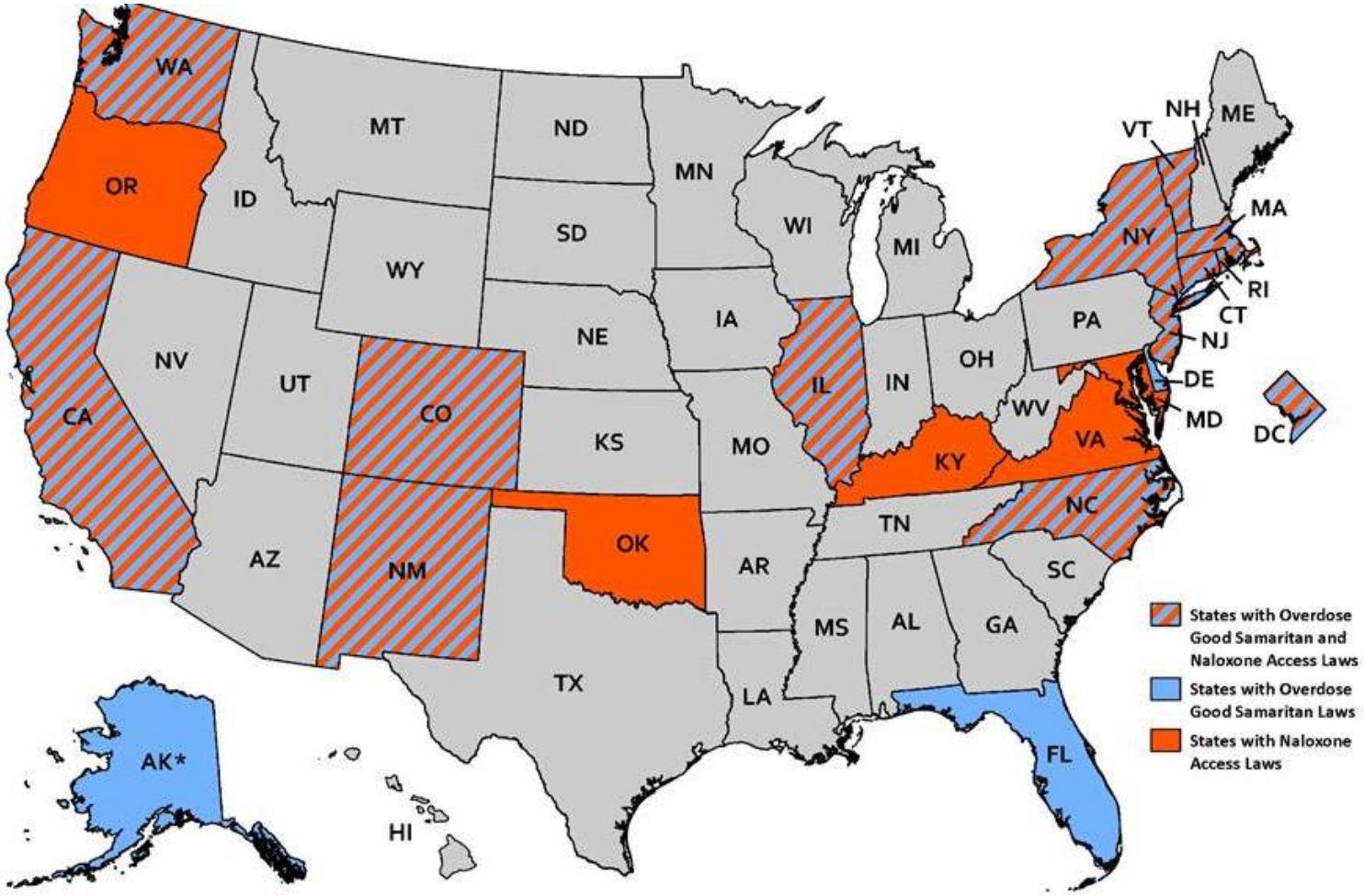
CDC, Number of Deaths from Poisoning, March 2103

Drug Poisoning Deaths Involving Heroin and Other Opioid Drugs, by County, 2006-2010



CDC, 2013

States with Naloxone Access and Overdose Good Samaritan Laws, as of January 2014



NCHRC, 2013

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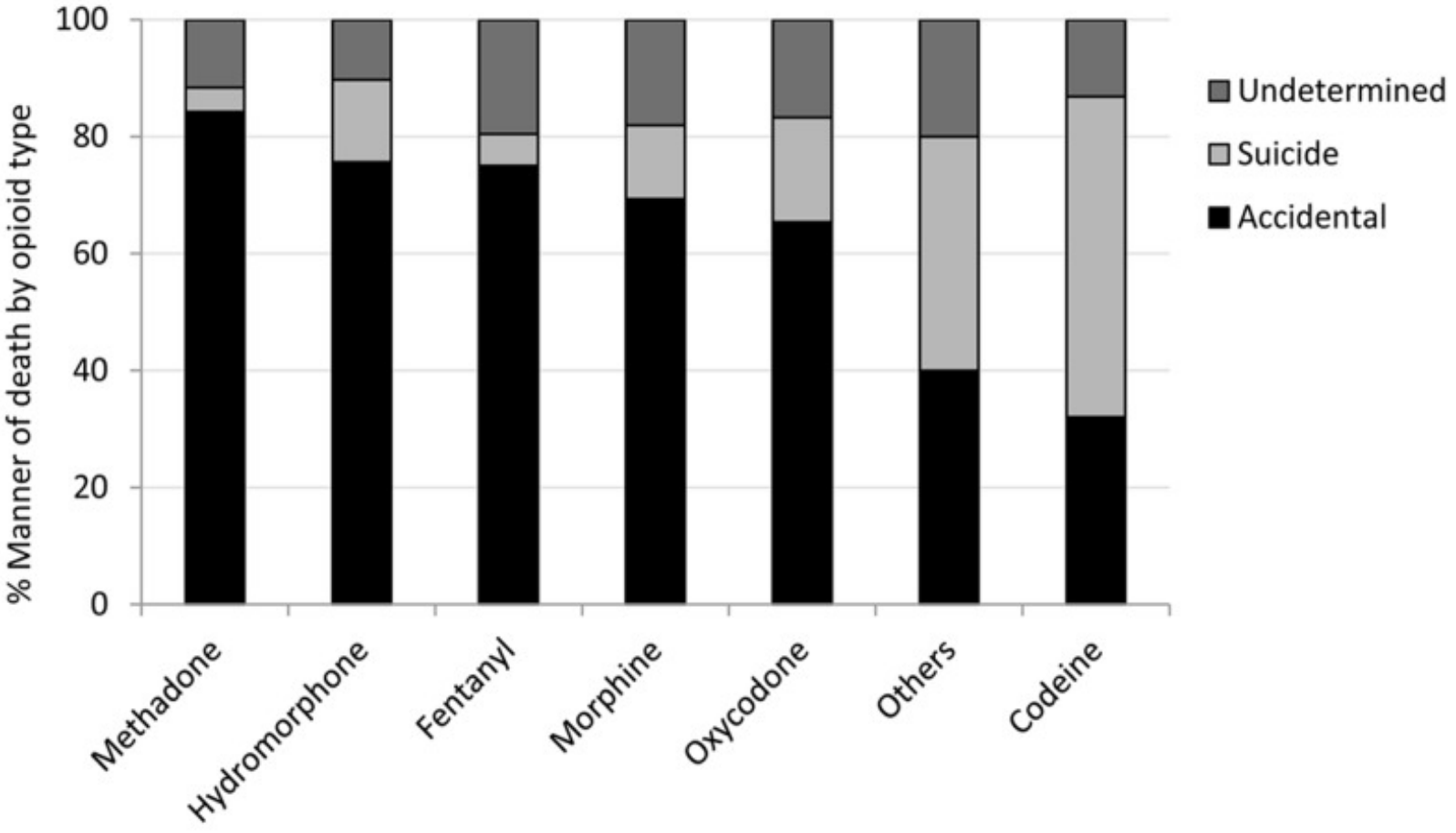
Opioid-Related Deaths in Ontario, 2006-2008 (N=1359)



Madadi et al. 2013

Scope of the Problem

- Drug overdose is a major cause of injury and death worldwide
- Among opioid users worldwide, most common cause of death is drug overdose (Degenhardt et al., 2011)
- Since 2003, opioid analgesics account for more deaths by overdose that cocaine and heroin combined (CDC, MMWR, January 13, 2012/ 61(01): 10-13.)
- In the U.S., single leading leading cause of injury-related mortality in 2008 was poisoning, nearly 90% of which was attributed to legal and illegal drugs (Warner et al., 2011)

Opioid Overdose: Who is at Risk?

- Individuals at risk for overdose include those:
  - with a previous history of overdose (Darke et al., 2007, Wines et al., 2007)
  - recently discharged from detoxification programs (Strang et al., 2003; Wines et al., 2007)
  - initiating or ending opioid maintenance therapy (Degenhardt et al., 2009)
  - recreational users of prescription opioids (Centers for Disease Control and Prevention, CDC Vital Signs, November 2011; Warner et al. 2011)
  - recently released from prison (Seaman et al., 1998; Wakeman et al., 2009)

Overdose: What and Where?

- Among unintentional opioid overdose deaths in NYC 2005-2019 (N=2649), 75% overdosed in a home, 10% in an institution, and the remaining in a public indoor setting or outdoors (Siegler et al., 2013)
- Methadone carries highest risk of accidental opioid overdoses
- Buprenorphine alone is not associated with overdose risk; if injected and/or combined with alcohol or benzodiazepines, fatal overdose can occur
- Sedative drugs and/or alcohol are frequently involved in fatal poisonings with prescription opioids (Hakkinen et al., 2012)

Strategies to Prevent Overdoses

- Education of patients and families of risk of overdose, heightened in the post-detox. period or when opioids are combined with alcohol, benzodiazepines, other sedative-hypnotic drugs (Darke et al., 2006)
- Education of providers on safe opioid prescribing
- Methadone maintenance is most effective proven method of reducing overdose mortality (Sporer 2003)
- Provision of naloxone to injection drug users (Galea et al., 2006)

Naloxone: A Potential Solution

- Naloxone is a potent, short-acting opioid antagonist
- Naloxone is effective in both preventing and reversing opioid agonist effects, including respiratory depression, which is the primary cause of death due to opioid overdose (White and Irvine 1999); approved by FDA in 1971 for overdose treatment..
- Antagonist effects of naloxone are evident within 5 min following administration
- Duration of antagonism at commonly prescribed doses (0.4-0.8 mg)
- It is relatively ineffective orally; typically given IV, IM, SQ, and intranasally (Kerr et al., 2009, Merlin et al., 2010)

Naloxone: the “Pros” I

- UN’s central drug policy-making body, Commission on Narcotic Drugs, approved resolution in March 2012 to promote measures to prevent drug overdose.
- ONDCP Director Gil Kerlikowske endorsed need to train public health and safety personnel to recognize drug overdose and administer life-saving techniques and medications, including naloxone
- “Good Samaritan Laws” have been enacted in several states (e.g. NM, NY), allowing naloxone distribution to “lay savers” and providing “immunity to doctors who administer naloxone to others” (Burris et al., 2009)

Naloxone: the “Pros” II

- Most opioid users (64-97%) report that they have witnessed at least one overdose (Lagu et al., 2006, Tracy et al., 2005), so opportunity for rescue exists.
- Opioid overdoses typically do not occur instantaneously
- Majority of witnessed overdoses occur in presence of a friend (70%), acquaintance (14%), or partner (10%; Strang et al., 2000)

Naloxone: the "Cons"

- **Legal Barriers:**
  - Since naloxone is classified as prescription drug by FDA, question of liability for both prescriber and drug user who uses naloxone on another person
  - Empirical data is lacking on effectiveness of naloxone programs in reducing fatal overdoses, as well as complications of non-fatal overdoses
- **Resistance by Medical Personnel:**
  - In survey (N=327) of health care providers, most (56%) felt training drug users in naloxone would not be effective (Tobin et al., 2005)
  - Among health providers, 37% would not consider prescribing naloxone to at-risk heroin users (Coffin et al., 2003)

Naloxone: the “Cons” II

- **Adverse Events:**
  - Cardiac complications and pulmonary edema have been reported to occur within 10 min after administration to intoxicated patients (Osterwalder 1996)
  - Side effects of administration during opioid overdose are common: confusion (32%), headache (20%), nausea/vomiting (9%), aggression (8%), but serious complications such as seizure (4%) are rare (Buajordet et al., 2004)
  - Because half-life of naloxone is shorter than that of heroin, recurrence of respiratory depression could emerge if victim is left unattended after initial dose of naloxone

Naloxone: the "Cons" III

- **Resistance by Drug Users:**
  - Common reasons cited by drug users for failing to call, or delaying a call, for medical assistance during an overdose: fear of police involvement or feeling they could handle event themselves (Tracy et al., 2005; Worthington et al., 2006)
  - Among those who had received naloxone in the past, 82% reported it was extremely unpleasant (Seal et al., 2003), suggested that previous exposure may be deterrent to naloxone use
  - Yet majority of users (79%) said they would want to receive naloxone if they overdosed, and larger majority (87%) would participate in training to receive naloxone (Seal et al., 2003)

Current Data on Naloxone Distribution Programs

- Of 53.032 individuals who had received take-home naloxone at 48 U.S. programs surveyed, 10,171 overdose reversals were reported (CDC 2012)
- Rates of successful reversal if naloxone is given: 83-96% (Piper et al., 2008, Wagner at al., 2010, Yokell et al., 2011)
- Pilot study conducted at Harm Reduction Coalition in NYC found only 50% of drug users had called 911 during witnessed overdoses; many had attempted ineffectual interventions such as salt water injections (18.6%) or milk administration (11.9%) (Jones et al., 2014, in press)
- Overdose training increased participants' ability to identify opioid overdose ($p<0.05$) and scenarios where naloxone administration was indicated ($p<0.05$)

Conclusions

- Opioid overdose is an increasingly common cause of death, yet could be easily treated with available opioid antagonists
- Individuals recently released from controlled environments (e.g. detox units, prisons) are an especially vulnerable group for both overdose and death
- In most cases, a single administration of naloxone is sufficient to reverse an opioid overdose
- Approaches to minimizing risk of opioid overdose include physician education on prescribing of opioid analgesics and benzodiazepines, prescription of take-home naloxone, Good Samaritan laws, and further research on efficacy of naloxone distribution programs

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