

Developing an Ideal Analgesic: The Need Now is Greater Than Ever

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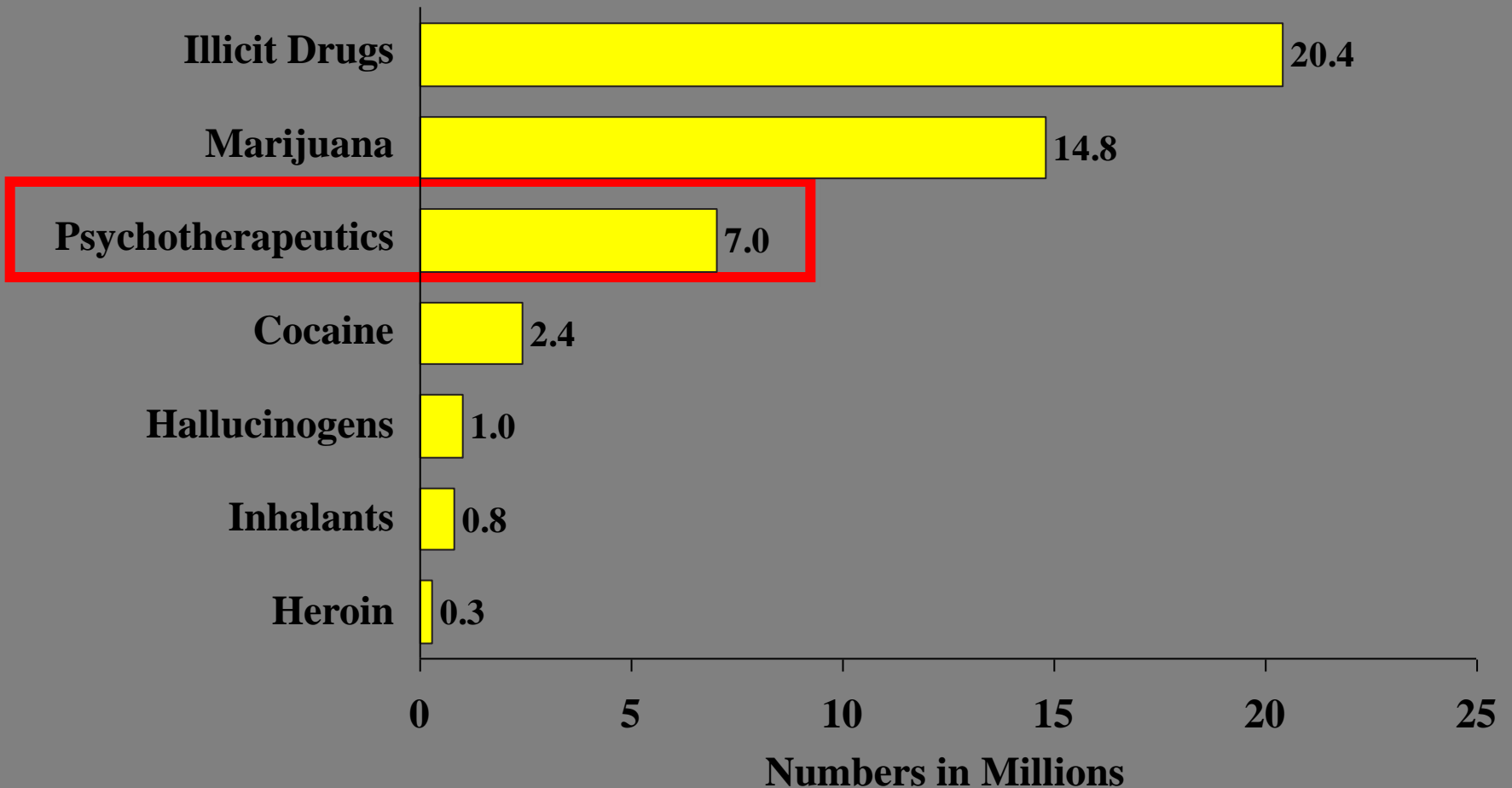
Characteristics of an Ideal Analgesic

- An ideal analgesic would be:
 - Orally active
 - Universally efficacious
 - Non-abusable
 - Non-dependence producing
 - Lacking in tolerance development to the analgesic effects
 - Lacking intolerable side effects or serious adverse events
 - Lacking in drug-drug interaction activity
 - Affordable to the average consumer

Opiate Prescribing in the US

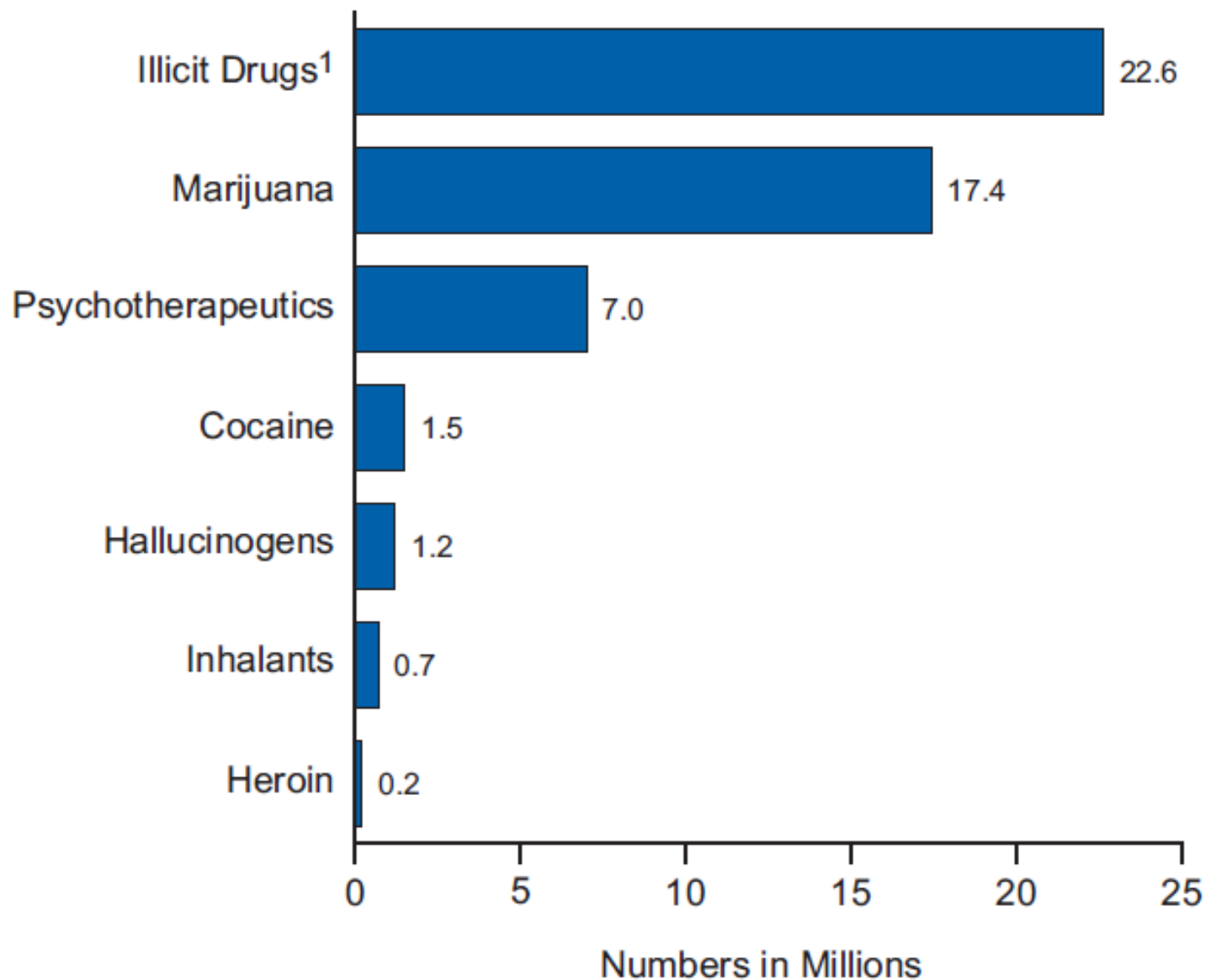
- In 1997 there were 174 million prescriptions filled for an opiate analgesic with an average amount of 74 mg/person
- In 2007 there were 257 million opiate prescriptions filled with an average of 369 mg/person
- Assuming 10 mg per day opiate equivalent dose that's a months supply of opiates for every person in the US over 12 years old

Past Month Use of Specific Illicit Drugs among Persons Aged 12 or Older: 2006



Source: SAMHSA, 2006 National Survey on Drug Use and Health

Past Month Use: NSDUH 2010



2007 Monitoring the Future Study

Prevalence of Past Year Drug Use Among 12th graders

Drug	Prev.	Drug	Prev.
Marijuana/Hashish	31.7	MDMA (Ecstasy)	4.5
Prescription drugs*	15.4	Ritalin*	3.8
Vicodin*	9.6	Inhalants	3.7
Amphetamines*	7.5	LSD	2.1
Sedatives*	6.2	Crack	1.9
Tranquilizers*	6.2	Methamphetamine	1.7
Cough Medicine*	5.8	"Ice"	1.6
Hallucinogens	5.4	Steroids	1.4
Cocaine (any form)	5.2	Ketamine	1.3
OxyContin*	5.2	Rohypnol	1.0
Cocaine Powder	4.5	Heroin	0.9

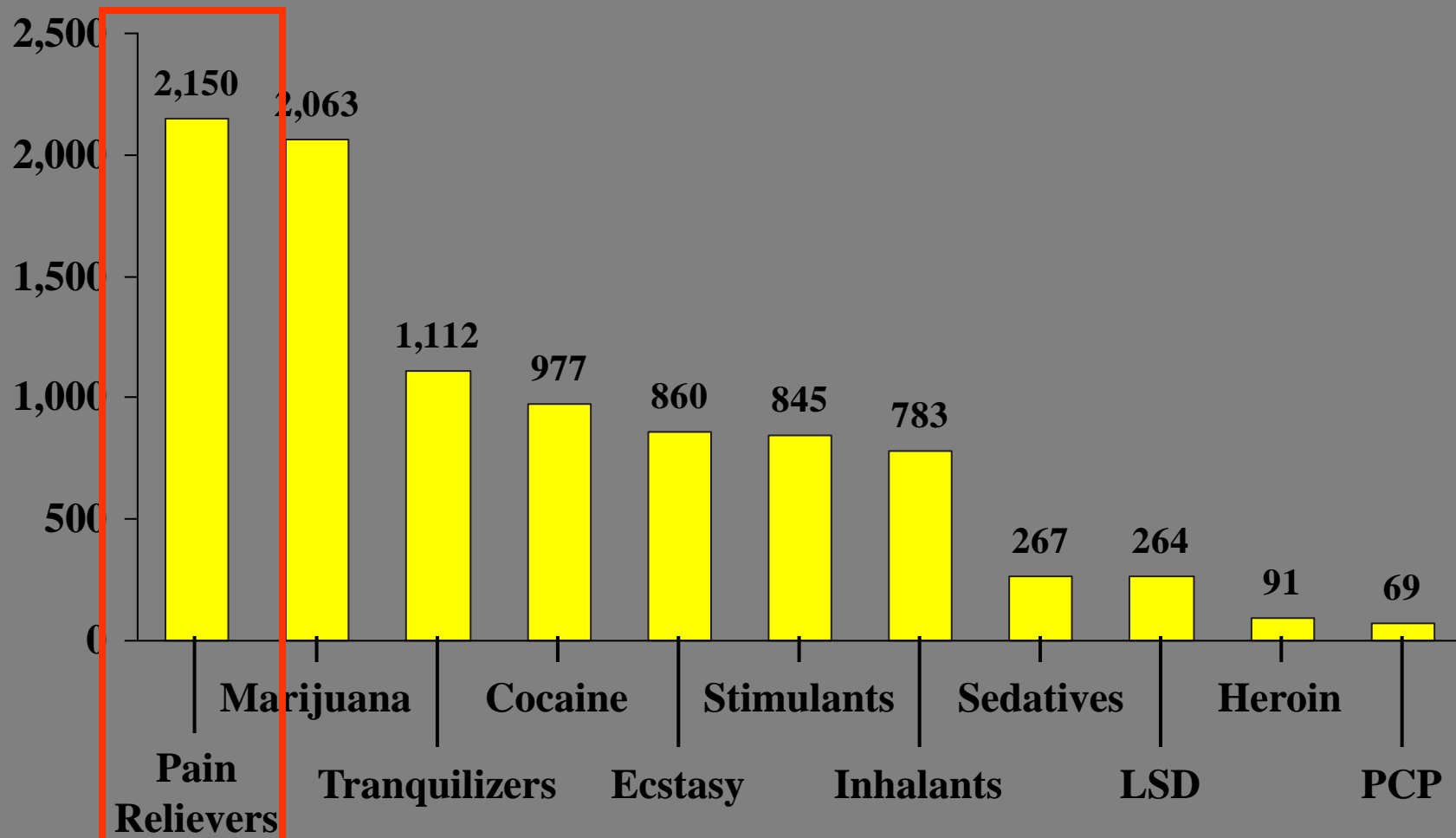
* Nonmedical use

Source: University of Michigan, 2007 Monitoring the Future Study

**Prescription Opioids have
become a Major Concern**

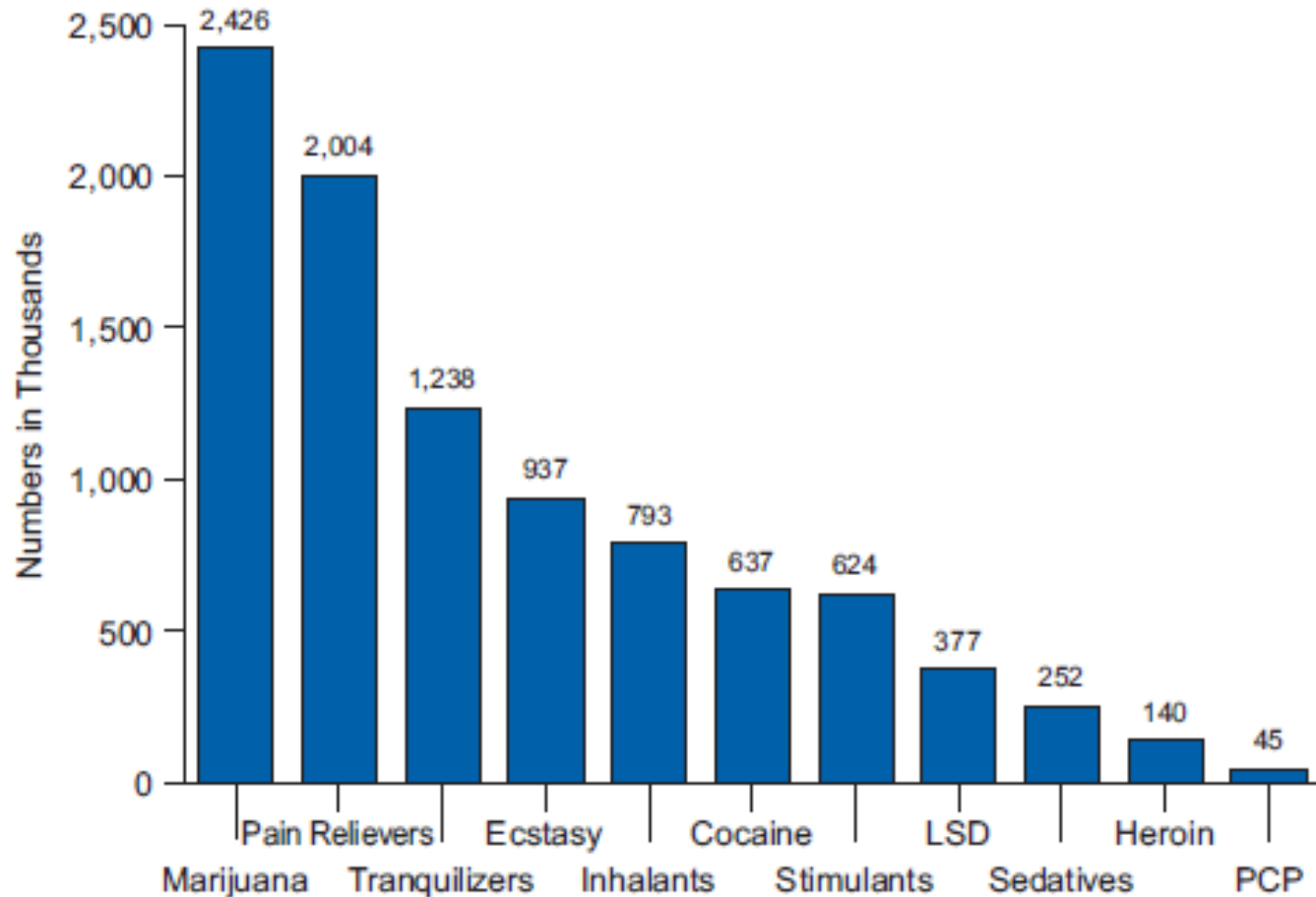
How many? Past Year Initiates for Specific Illicit Drugs, Ages 12+, 2006

Numbers in Thousands



Source: SAMHSA, 2006 National Survey on Drug Use and Health

Past year Initiates: NSDUH 2010



Why Has the Abuse of Prescription Drugs Been Increasing?

- 1) Increasing numbers of prescriptions (greater availability)**
- 2) Attention by the media and advertising (television and newspaper)**
- 3) Easier access through family and friends**
- 4) Improper knowledge and monitoring (addiction may go unrecognized)**

Heroin Versus Prescription Opiate Dependence Treatment in TEDS

TEDS admissions for primary *heroin* abuse were at 14 to 15 percent of all admissions from 1995 through 2005. Heroin represented 93 percent of all primary opiate admissions in 1995, but fell to 79 percent in 2005.

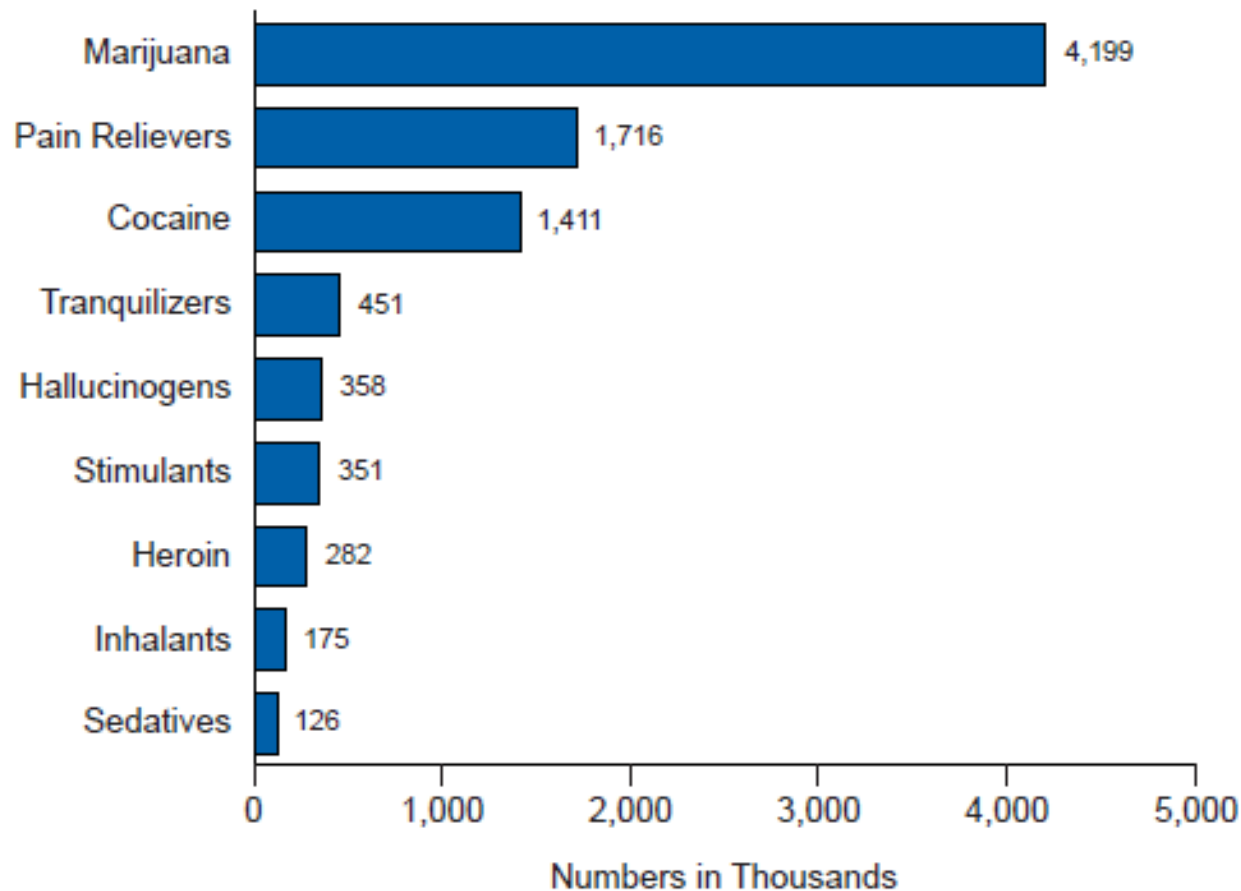
The proportion of TEDS admissions for abuse of *opiates other than heroin*¹ increased from 1 percent in 1995 to 4 percent in 2005. Opiates other than heroin represented 7 percent of all primary opiate admissions in 1995, but rose to 21 percent in 2005.

TEDS Opiate Admissions 1999-2009

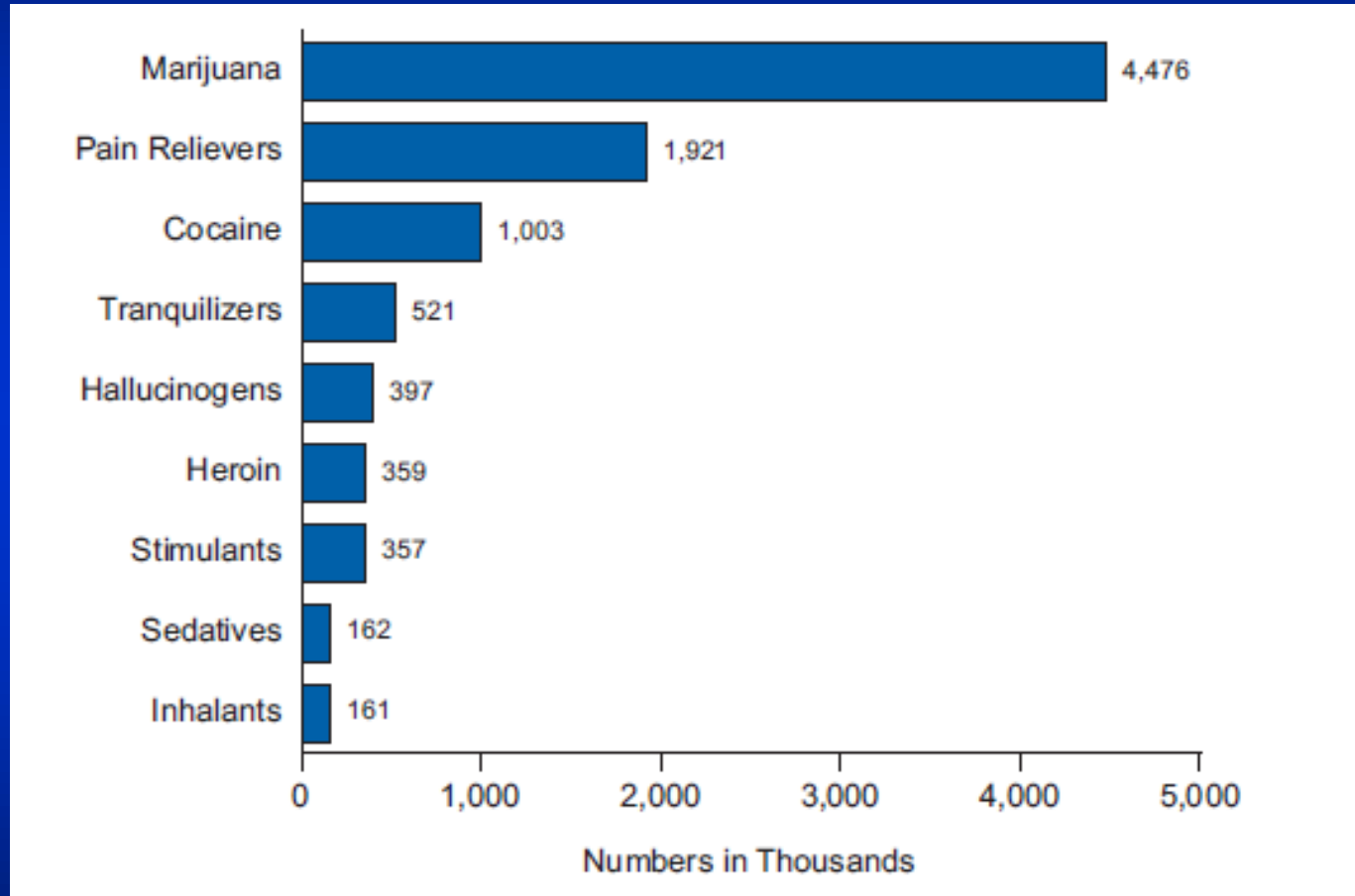
- In 1999 8 % of the opiate treatment admissions were for opiates other than heroin
- In 2009 33 % of the opiate treatment admissions were for opiates other than heroin

NSDUH 2009

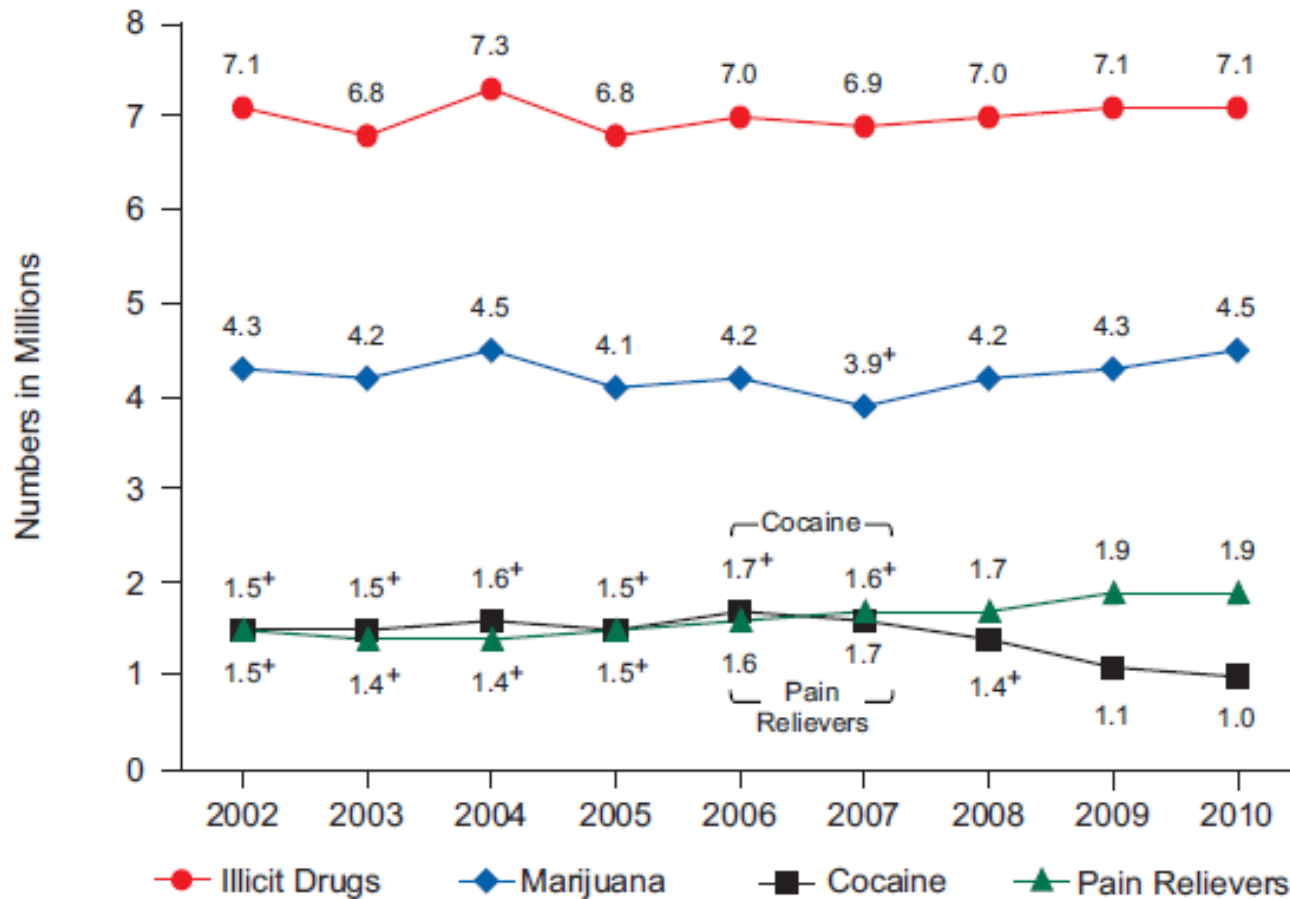
Figure 7.2 Dependence on or Abuse of Specific Illicit Drugs in the Past Year among Persons Aged 12 or Older: 2008



Abuse or Dependence in the 12 and Older Population: NSDUH 2010

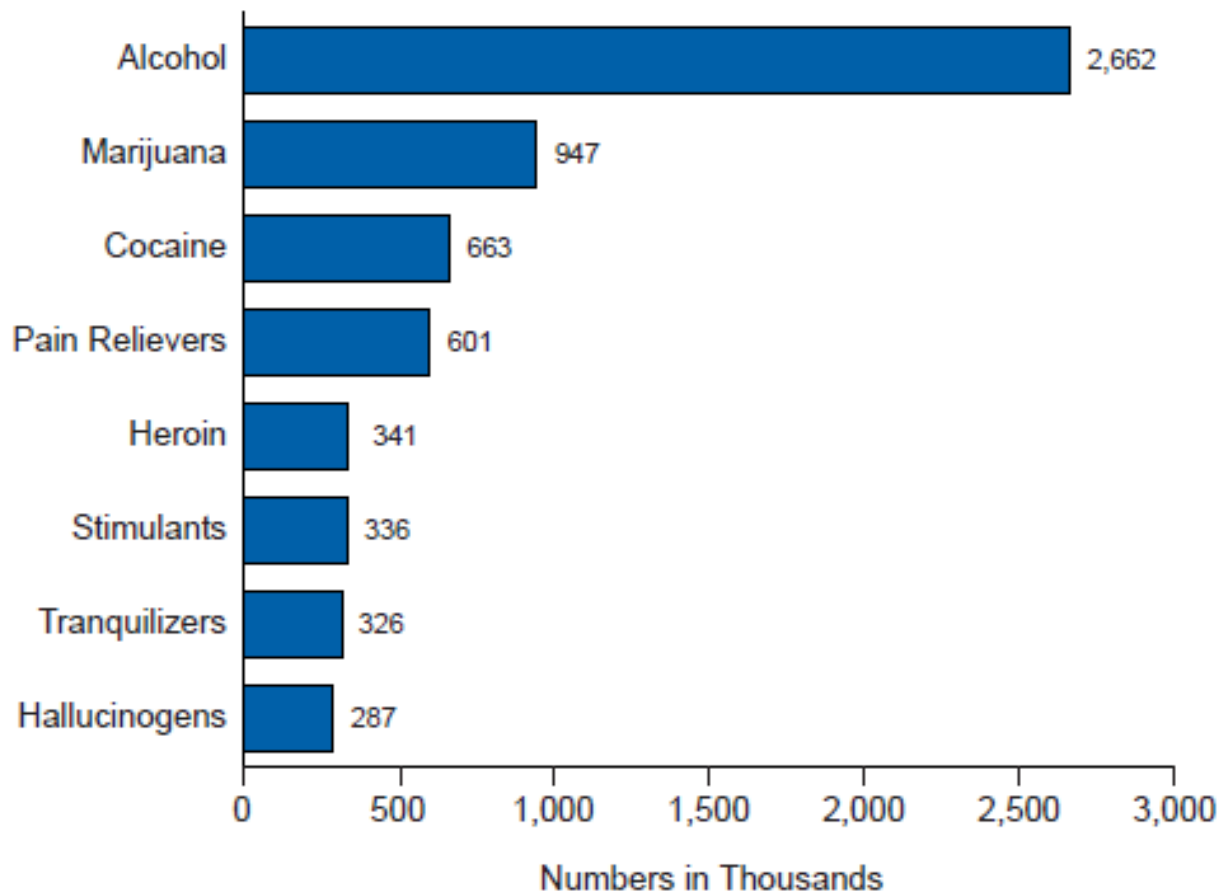


Abuse or Dependence in the NSDUH: 2002-2010

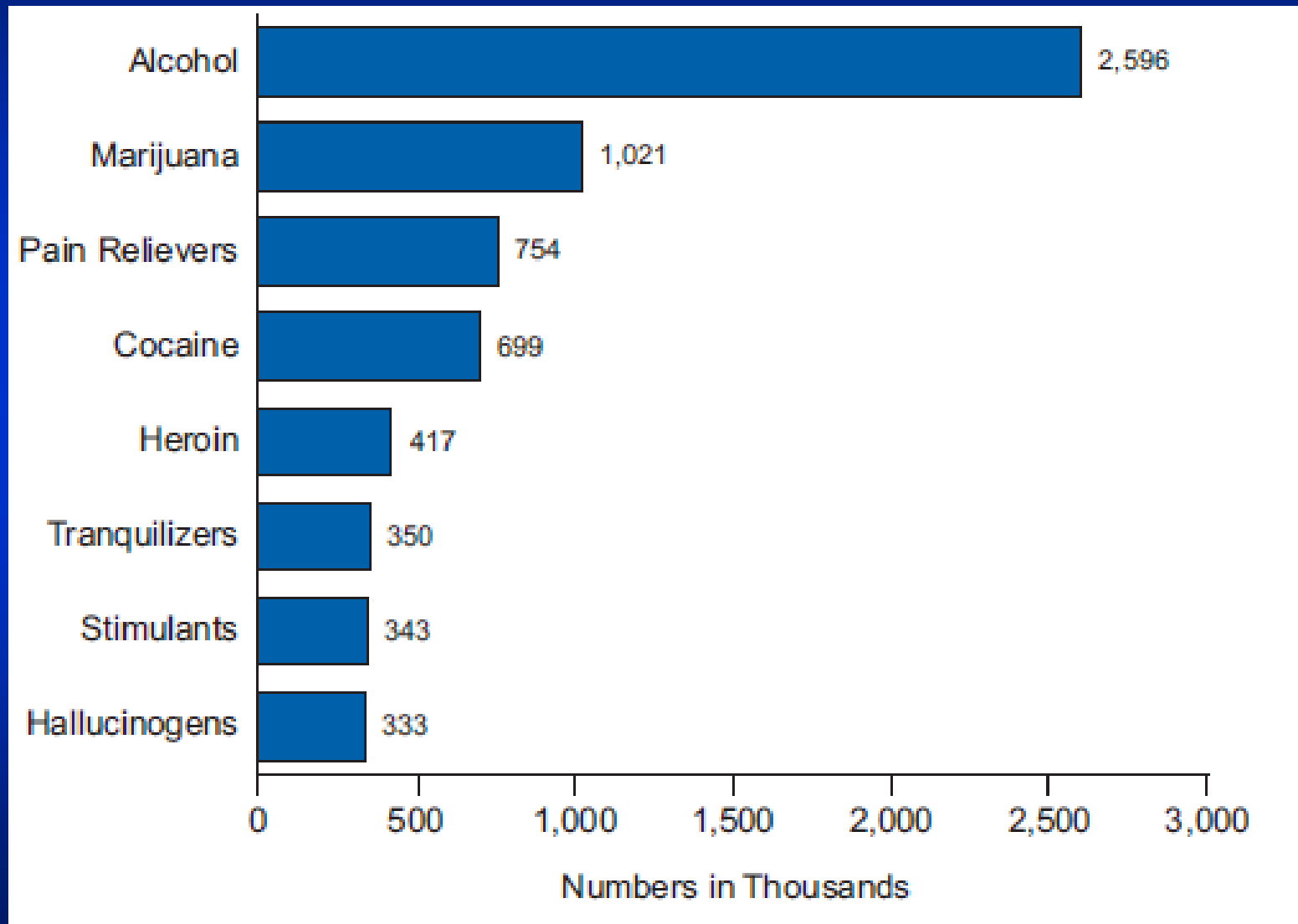


NSDUH 2009

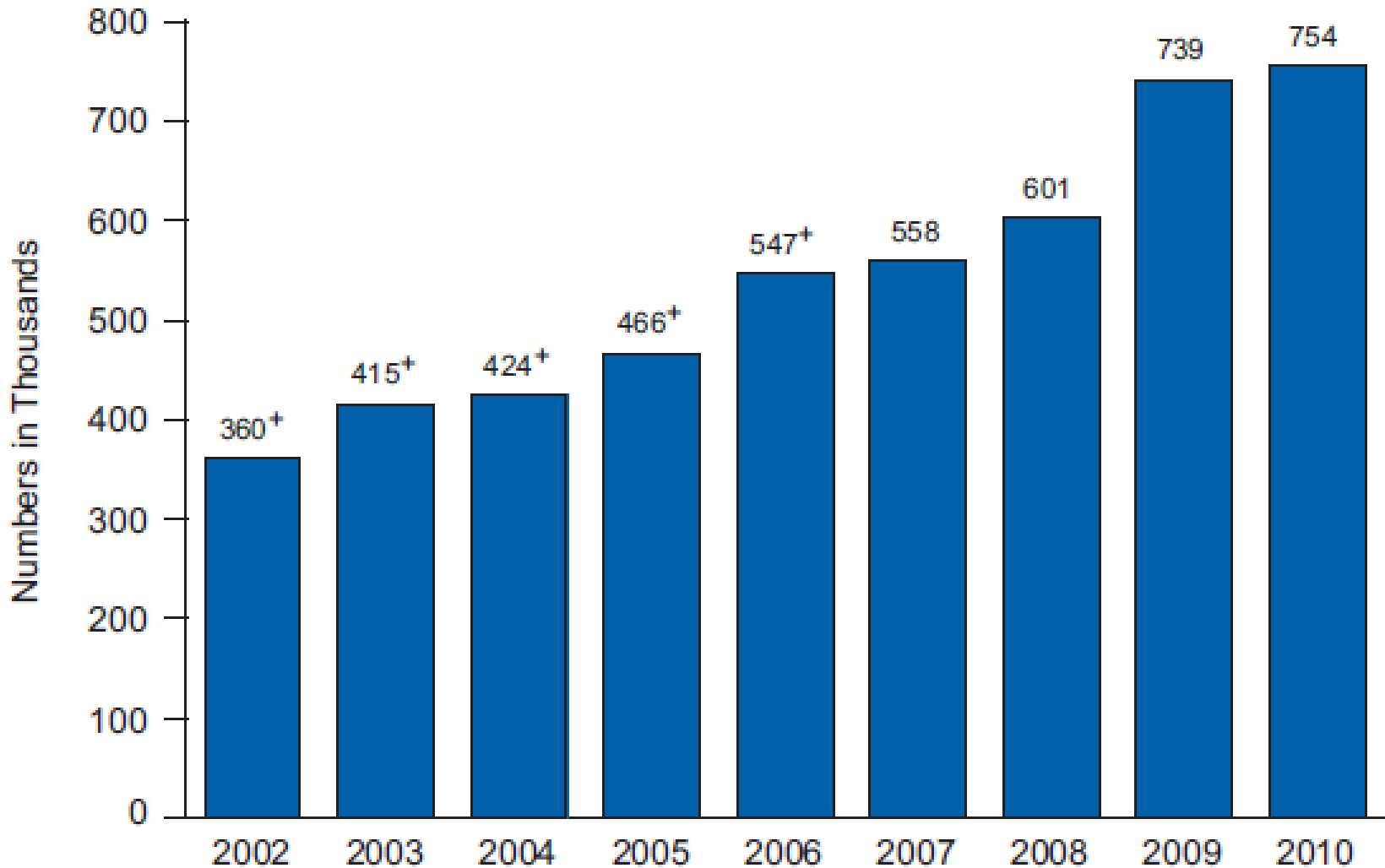
Figure 7.8 Substances for Which Most Recent Treatment Was Received in the Past Year among Persons Aged 12 or Older: 2008



Treatment Statistics: NSDUH 2010



Treatment for Pain Reliever Dependence: NSDUH 2002-2010



Increasing deaths from opioid analgesics in the United States[†]

Leonard J. Paulozzi MD, MPH^{1*}, Daniel S. Budnitz MD, MPH² and Yongli Xi MS³

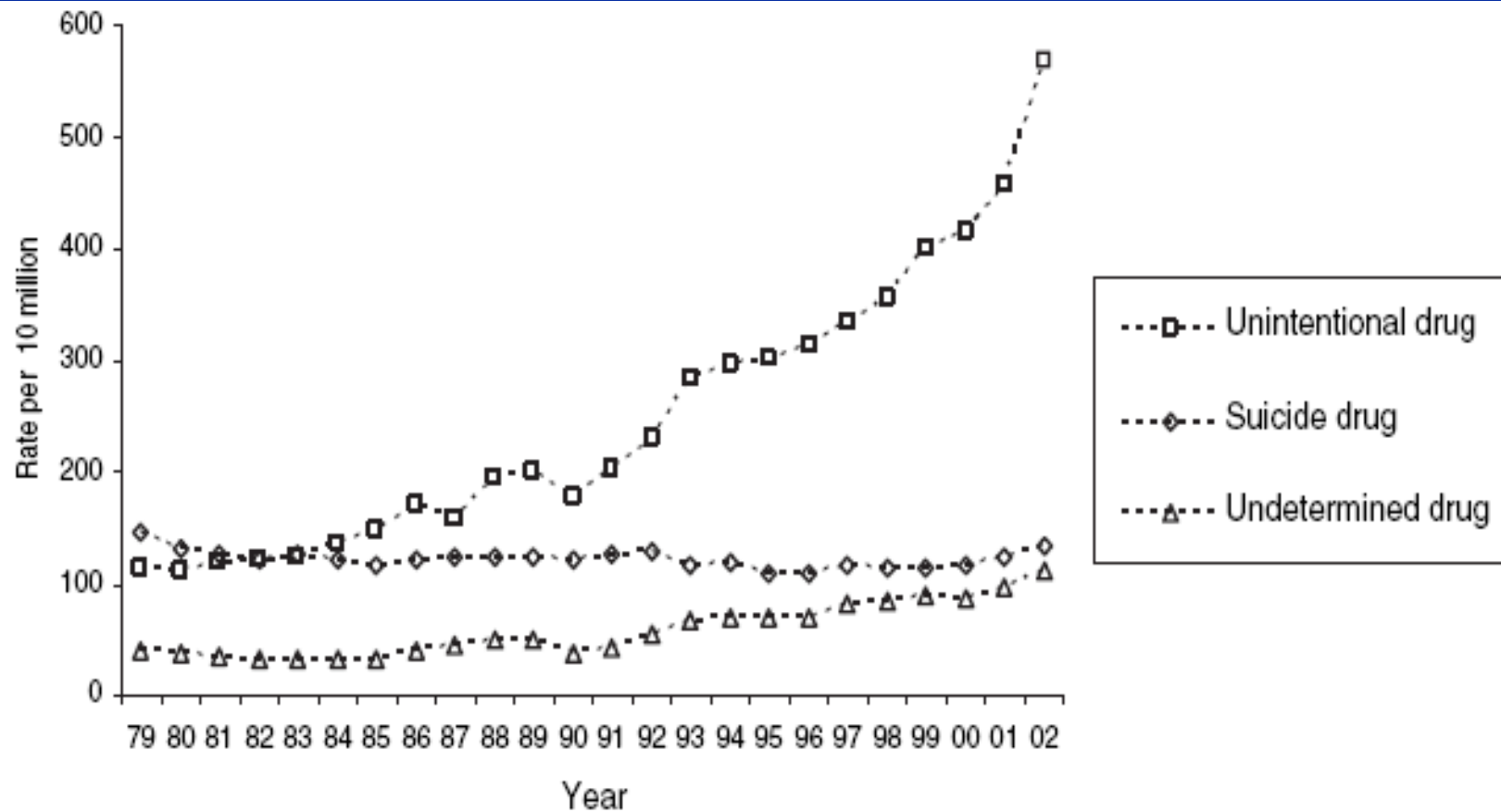
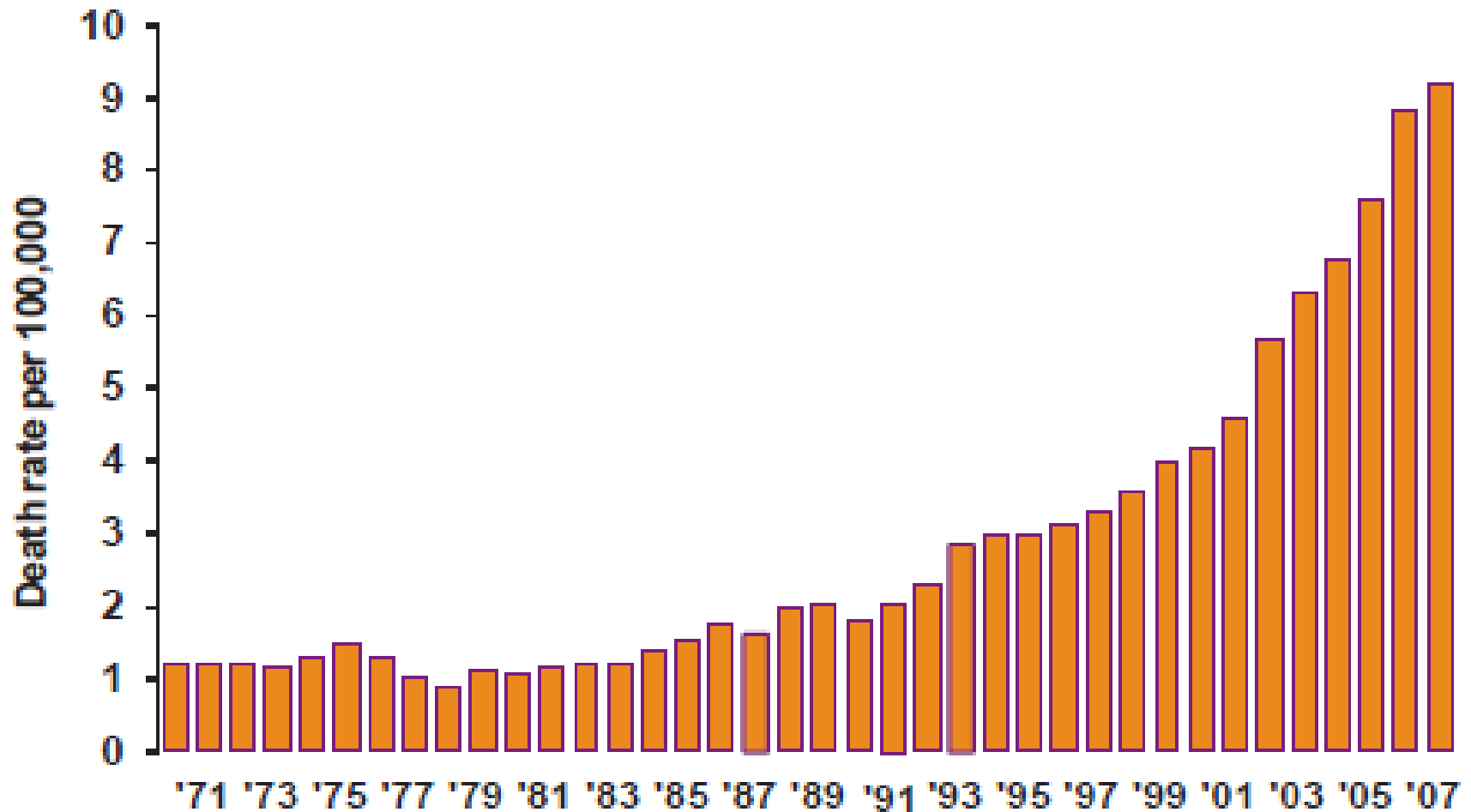
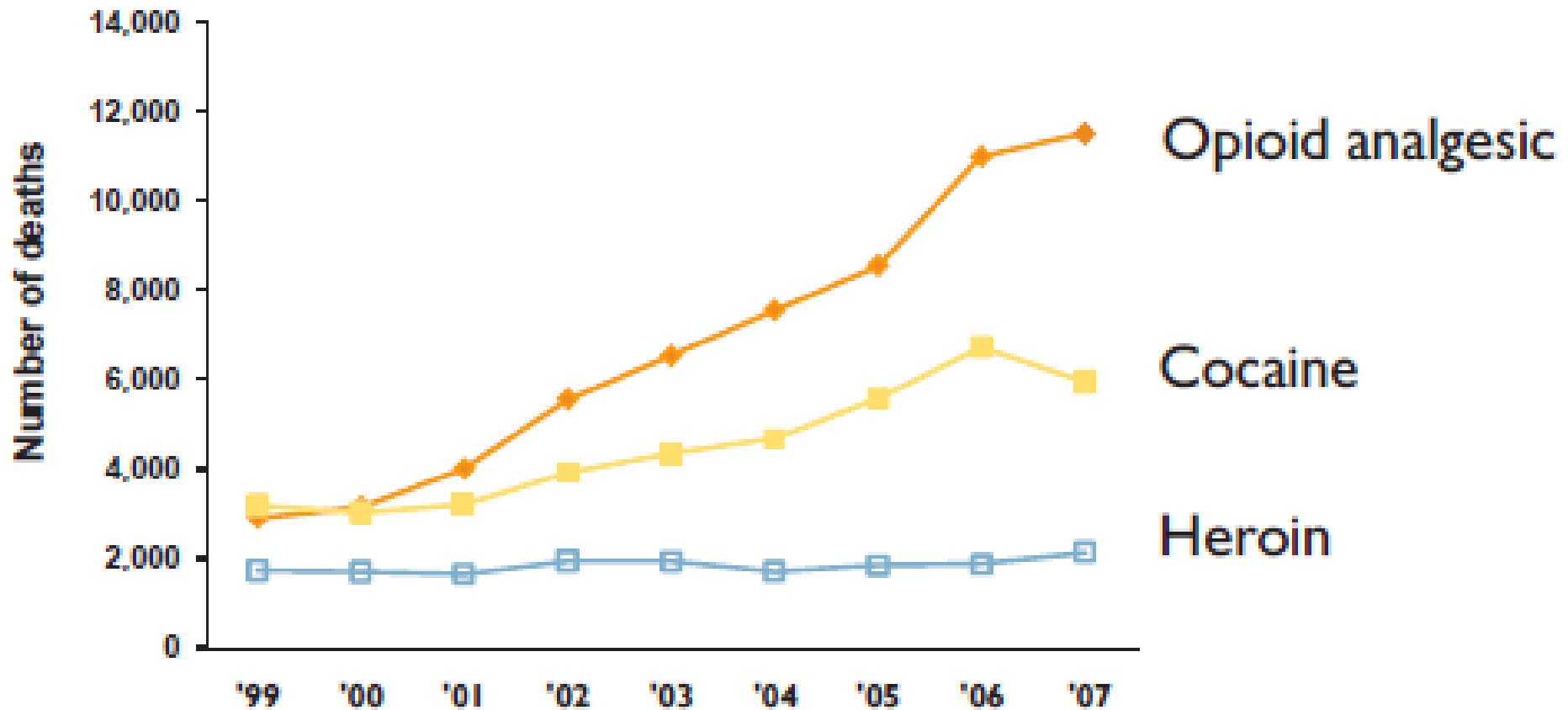


Figure 1. Drug poisoning mortality rates by manner of death, US, 1979–2002. Drug poisoning deaths are coded by ICD-9 E codes from 1979 to 1998 and by ICD-10 X and Y codes from 1999 to 2002. Codes used were: E850-858 and X40-44 for unintentional, E950.0-950.5 and X60-64 for suicide, and E980.0-980.5 and Y10-14 for undetermined poisoning

Drug-Induced Deaths in the US



Opioid Analgesic Deaths Contrasted to Cocaine and Heroin



Efficacy of Opioids for Chronic non-Cancer Pain

Noble et al 2008

- 17 studies of oral, intrathecal, or transdermal opioid delivery involving over 2,700 patients who received opioids chronically for up to 18 months
- With oral meds, patients reported a 63.4 % reduction in pain scores
- 32.5 % dropped out due to adverse events
- 11.9 % dropped out due to inadequate pain relief
- Low rates of abuse /addiction reported
- Only assessed in 7 studies
 - 1 case in 2042 patients in 7 studies
- In other 10 studies 3 cases out of 532 patients

Efficacy of Opioids for Chronic non-Cancer Pain

Manchikanti et al, 2011

Table 2. Results of studies evaluating the long-term effectiveness of morphine.

Study/ Methods	Participants	Opioids Studied	Outcome(s)	Conclusion(s)	Complications	Result(S)
Allan et al (106) Open, randomized, parallel group multicenter study 13 months	Chronic low back pain N=680	Sustained release oral morphine versus transdermal fentanyl	Pain relief; bowel function, quality of life, disease progression, and side effects	Sustained release strong opioids can safely be used in opioid naive patients	Most common adverse events leading to discontinuation were nausea (37%), vomiting and constipation.	Significant proportion of patients on sustained release morphine experienced pain relief.
Caldwell et al (107) Double-blind trial, followed by open-label extension trial	184 with chronic osteoarthritis 181 participants entered the open-label trial	Placebo, Avinza, or MS Contin in double-blind trial	Pain relief; physical functioning; stiffness	Efficacy was comparable between 2 modes of administration.	Most common adverse effects were constipation and nausea	Significant improvement in pain relief and sleep measures
Zenz et al (108) Narrative descriptive report	100 patients who were chronically given opioids for treatment of nonmalignant pain, with 23 patients receiving morphine SR	Sustained release morphine, sustained release dihydrocodeine, buprenorphine	VAS, Karnofsky Performance Status Scale used to assess function	Results indicate that opioids can be effective in chronic nonmalignant pain, with side effects that are comparable to those that complicate the treatment of cancer pain	Common side effects were constipation and nausea	Good pain relief was obtained in 51 patients and partial pain relief was reported by 28 patients. Only 21 patients had no beneficial effect from opioid therapy
Maler et al (137) Narrative descriptive report	121 patients with chronic non-cancer pain	Sustained release morphine	Pain relief and quality of life.	Pain relief correlated with improvement in functional status	There was no development of tolerance	Significantly lower pain intensity and improved physical state and quality of life
Tassain et al (138) Long-term prospective study	28 chronic non-cancer pain patients, 18 received oral sustained morphine, 10 patients stopped morphine due to side effects and were followed as control group	Oral sustained morphine	Pain relief and cognitive functioning Follow-up period of 12 months	There was no impairment of any neuropsychological variables over time	Side effects included constipation, loss of appetite, nausea, dry mouth, drowsiness, somnolence, fatigue, subjective memory impairment, sweating, and pruritus	Morphine produced persistent pain relief and improved quality of life and mood

Rates of Aberrant Behaviors during Opioid Therapy

Fleming et al 2007

- 801 patients on chronic opioid therapy by 235 physicians were interviewed regarding aberrant behaviors:
- 26 % reported purposeful oversedation
- 39 % increased dose without prescription
- 8.5% obtained more opioids from other doctors
- 18 % used for purposes other than pain relief
- 20 % drank alcohol concurrently to relieve pain
- 12 % hoarded pain medications

Opioid Problems in a Chronic Pain Population

Banta-Green et al 2009

Prescription Drug Use Questionnaire (PDUQ) and CIDI DSM-IV opioid item endorsements and results of exploratory factor analyses.

FACTORS items paraphrased	Item endorsement % (n=704)	Factor Analysis 1 PDUQ			Factor Analysis 2 PDUQ & CIDI DSM-IV			
Addictive behaviors								
Requested early refill	21 (148)	0.42	0.1	0.21	0.17	0.44	0.22	-0.04
Used for other symptoms e.g. sleep, anxiety	13 (88)	0.35	0.06	0.04	0.09	0.38	0.01	0.02
Used alcohol for pain	6 (44)	0.54	-0.23	0.16	0.12	0.48	0.16	-0.25
Ever bought opioids on the street	2 (13)	0.88	0.22	0.16	0.08	0.81	0.27	0.14
Doctor ever refused Rx due to abuse concern	7 (47)	0.36	0.32	0.41	-0.02	0.39	0.48	0.31
Ever borrowed opiate medicines	11 (74)	0.41	0.09	0.28	-0.08	0.44	0.33	0.11
You had any AOD problem	19 (135)	0.69	0.06	-0.26	0.08	0.67	-0.19	0.04
You have been treated for any AOD problem	13 (95)	0.75	0.05	-0.14	0.03	0.72	-0.07	0.04
Addictive concerns								
You think you might be addicted	14 (102)	0.15	0.76	-0.09	0.31	0.11	-0.03	0.56
Doctor told you were addicted	6 (45)	0.22	0.85	-0.13	0.28	0.22	0	0.63
Lost meds and needed replaced	15 (105)	-0.13	0.35	0.06	0.2	-0.16	0.07	0.33
Family concerned about your being addicted	7 (48)	0.12	0.66	0.06	0.3	0.11	0.11	0.51
Pain treatment problems								
Pain been inadequately treated past 90 days	31 (215)	0	-0.02	0.48	-0.05	0	0.47	0
Angry or mistrustful of doctor	17 (117)	-0.06	0.27	0.58	-0.14	0.01	0.62	0.34
Increase amount used past 90 days	21 (151)	-0.03	-0.14	0.58	0.22	-0.15	0.63	-0.35
Doctor ever refused Rx due to abuse concern	7 (47)	0.36	0.32	0.41	-0.02	0.39	0.48	0.31
Opioid abuse and dependence								
Use despite psych/med consequences	9 (64)				0.55	0.2	0.02	0.1
Lifetime interference opioids work, job, home	10 (70)				0.68	-0.07	0	-0.04
Lifetime problems with family/friends, work, cops	5 (37)				0.73	0.19	0.13	-0.01
Need more opiates to get same effect	38 (271)				0.46	0.03	0.33	0.02
Wanted to stop or cut down	55 (384)				0.74	-0.29	0.10	0.10
Spent a lot of time using/getting opiates	6 (45)				0.50	0.26	-0.04	0.24
Ever used opiates larger amounts, longer time	7 (46)				0.57	0.29	-0.01	0.12
Reduced important activities to get or use	3 (18)				0.78	0.14	-0.27	-0.04
Withdrawal symptoms	41 (286)				0.59	0.26	-0.04	0.11

Bold values are factor loadings greater than 0.30.

Opioid Problems in a Chronic Pain Population

Banta-Green et al 2009

- Study respondents were white (89%), 62 % female with an average age of 55 (SD =10)
- Non-respondents (n= 587) were more likely to be male, younger, and have a higher prescribed average daily dose of opioids

Risk Factors for Dependence in Pain Patients

Boscarino et al 2010

- Identified 705 patients in a health care system who received 4 or more opioid prescription in a 12 month period
- Current opioid dependence prevalence in this study was 26 %
- Corresponds to dependence reports of 24 % in VA patients and 31 % in chronic non-cancer pain patients in a primary care center (Reid et al, 2002)

Risk Factors for Dependence in Pain Patients

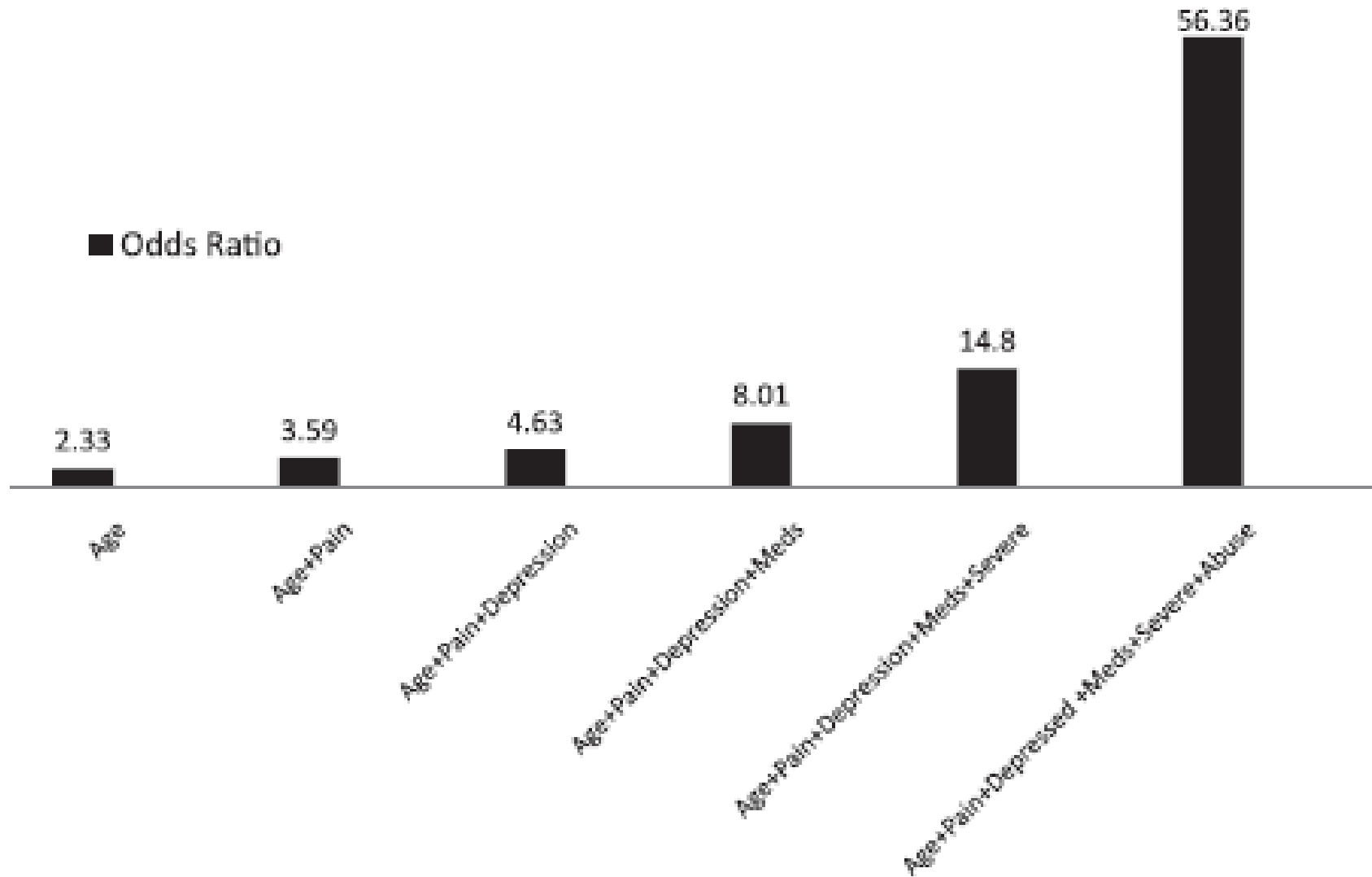
Boscarino et al 2010

Table 2 Multivariate logistic regressions predicting life-time and current prescription opioid dependence based on DSM-IV criteria ($n = 705$).^a

<i>Predictor variables</i>	<i>Model 1: life-time dependence*</i>			<i>Model 2: current dependence**</i>		
	<i>OR</i>	<i>95% CI</i>	<i>P-value</i>	<i>OR</i>	<i>95% CI</i>	<i>P-value</i>
Less than 65 years old	2.80	1.83–4.28	<0.001	2.33	1.55–3.53	0.001
Reported pain interferes with life/work	1.94	1.21–3.10	0.010	1.54	0.94–2.50	0.079
History of opioid abuse	3.95	2.39–6.53	<0.001	3.81	2.56–5.67	<0.001
History of high dependence severity	3.00	1.58–5.69	0.003	1.85	1.38–2.46	0.001
Opioid orders past 3 years (highest quintile)	1.75	1.18–2.58	0.009	–	–	–
Positive screen for antisocial personality	1.44	1.09–1.91	0.015	–	–	–
History of major depression	–	–	–	1.29	1.05–1.60	0.022
Currently use psychotropic medications	–	–	–	1.73	1.21–2.47	0.006

Risk Factors for Dependence in Pain Patients

Boscarino et al 2010



Opioids for Chronic Non-Cancer Pain Management

- May not produce adequate pain relief in as much as 1/3 patients
- May have intolerable side-effects in 1/8 patients
- May be associated with abuse and dependence in 1/4 patients, representing ~ 1 % of the adult U.S. population
- The number of patients seeking treatment for opioid dependence has more than doubled in the last 10 years and has surpassed the number of individuals seeking treatment for heroin dependence
- Fatalities associated with opioid use have increased ~ nine fold since 1979

Summary

- Opiate abuse and dependence is an increasing public health problem associated with significant morbidity and mortality
- Although the FDA is considering REMS for opiate prescribing, the efficacy of the approach is unknown
- Chronic non-cancer pain needs to be managed better
 - Inadequate pain relief co-exists with the overuse and abuse of opiates
 - Opiate side-effects can be intolerable
- There is a pressing need for better analgesics lacking abuse potential that would improve the management of chronic non-cancer pain