

Neonatal Abstinence Syndrome



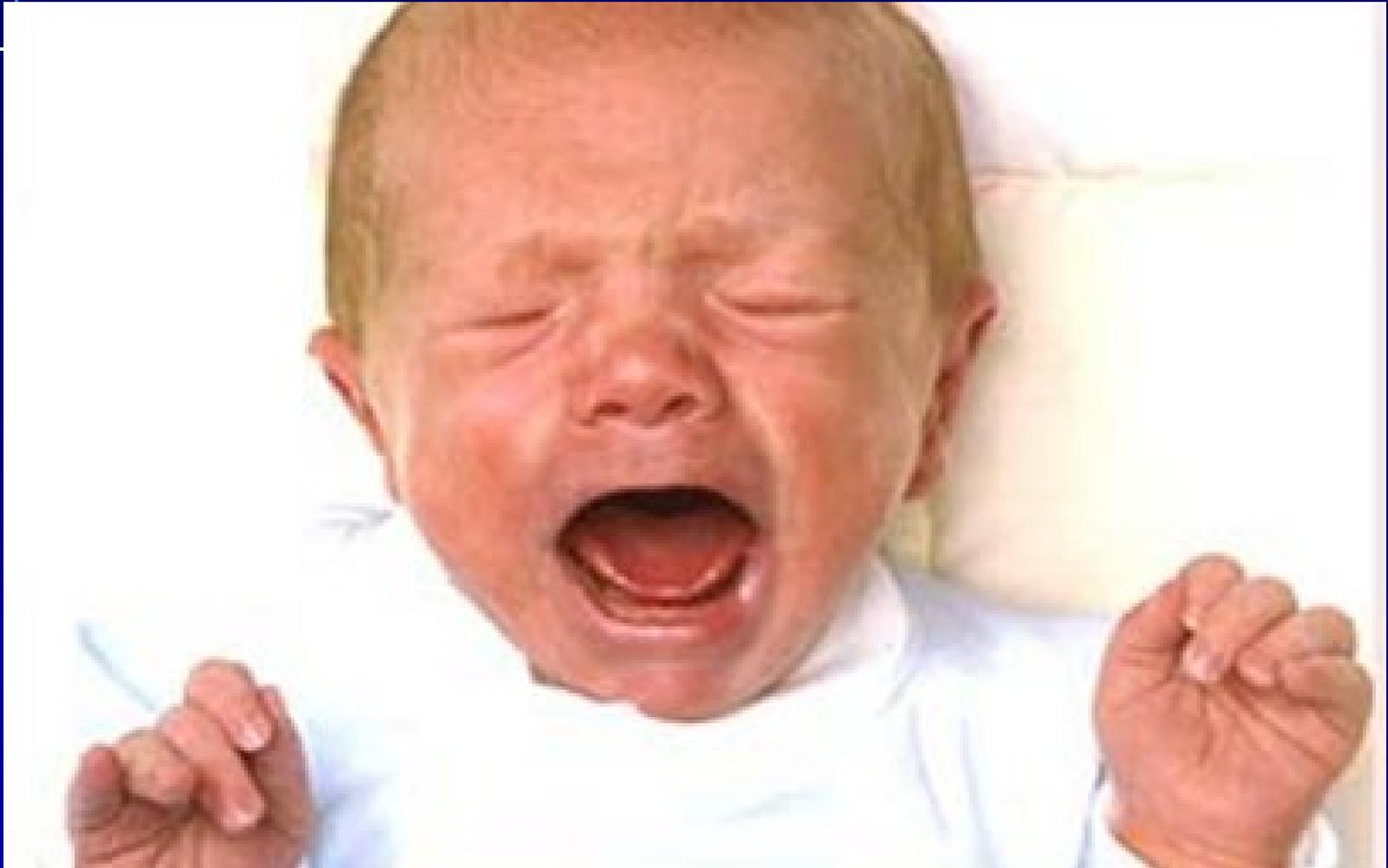
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Director of Neonatology, St. Francis Health Center

Neonatal Opiate Withdrawal A New Epidemic

- What we saw- More Cases of NAS (one baby/year in 2001, now one/week 2012)
- How we studied it. Reviewed Indiana Cases and US Cases
- What we found.

Opiate Withdrawal in Babies



Objective of 2012 Study

- Review NAS trends over last decade
- Indiana vs. National NAS trends
- maternal characteristics vs. NAS
- Prescription Trends

Design/Methods

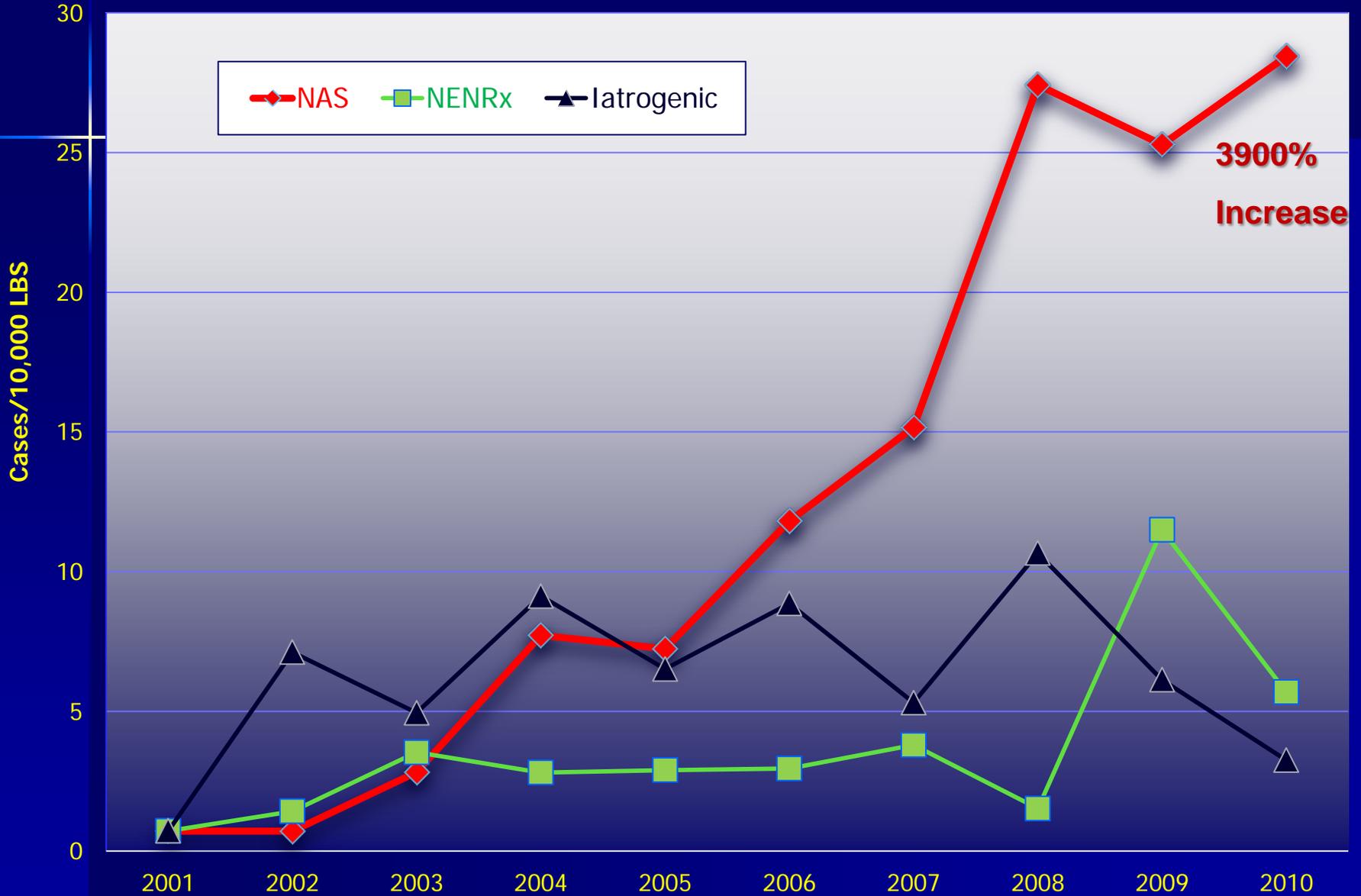
- St Francis and IU Neonatology Service (IUNS) NAS cases were reviewed from Neodata.
- Indiana NAS cases from Indiana State Department of Health, Hospital Discharge Database, 2002-2010.
- National NAS cases from the Nationwide Inpatient Sample (NIS), Healthcare Cost & Utilization Project (HCUP) for 1997-2009.
- National dispensed drug (grams/100,000 pop) report from ARCOS (1997-2006).
- Opiate prescriptions/year from SDI'S Vector One (VONA).
- Drugs analyzed were limited to out-patient oral opiate containing agents (oxycontin, hydrocodone, morphine, methadone).
- Trends for NAS rates, opiate prescription rates, lengths of stay and total charges for the study years were analyzed using regression models.

Results

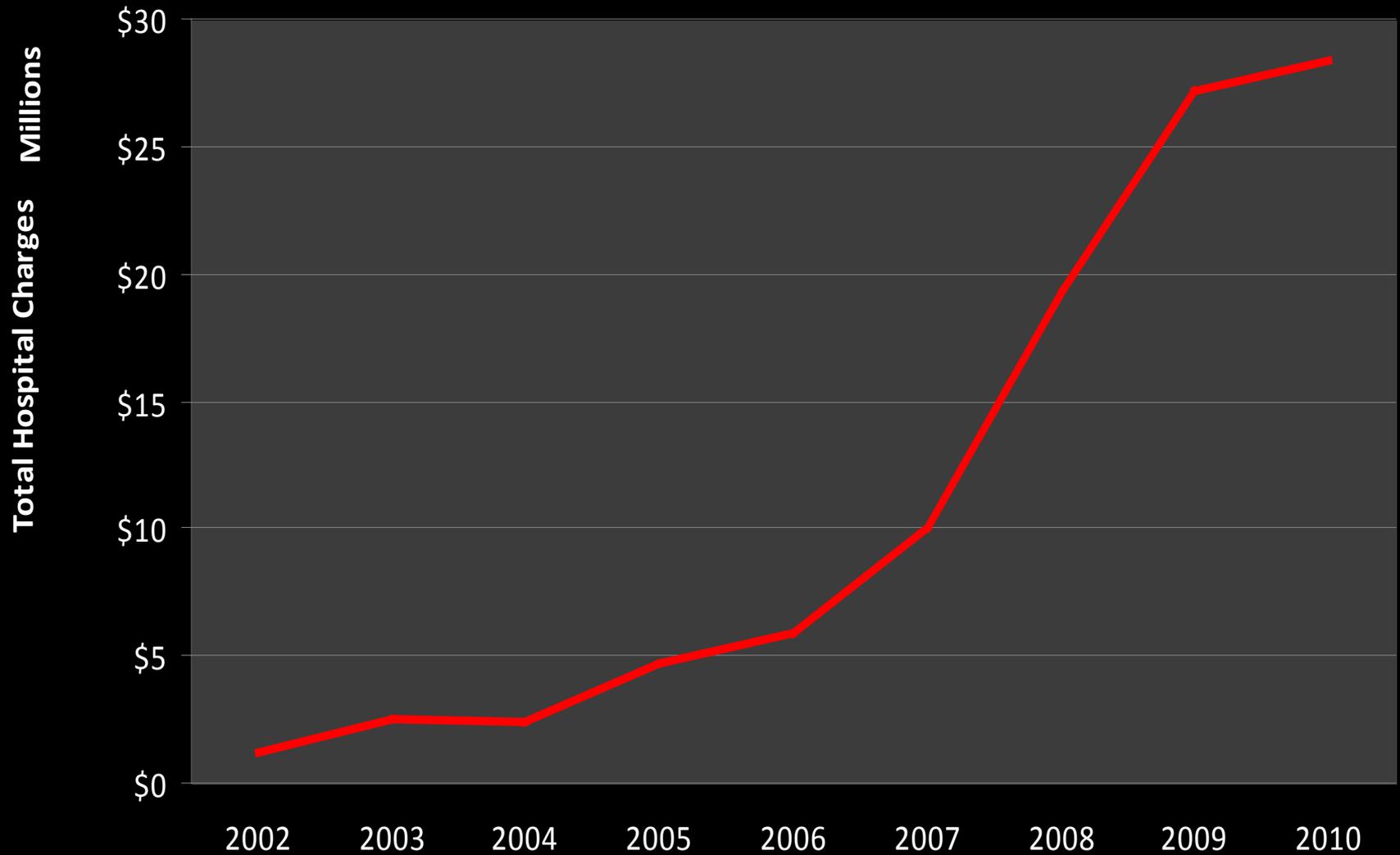
- NAS cases increased at a yearly rate of 0.32 per 1,000 births nationwide and 0.42 per 1,000 births in Indiana (p 's < 0.01).
- Similar increases were seen in IUNAS cases.
- Prescriptions of oxycodone, hydrocodone, morphine and methadone increased at rates of 1198, 919, 621, and 347 per 100,000 cases per year from 2002 to 2006 nationwide.
- Similar increases were also noticed in the state of Indiana.
- Annual charges for NAS cases increased from \$3,842,747 in 1997 to \$90,455,522 in 2009 which was significant both for the Nation ($p < 0.05$) and Indiana ($p < 0.01$) cost data respectively, after adjusting for inflation using consumer price index.

Neonatal Opiate Withdrawal

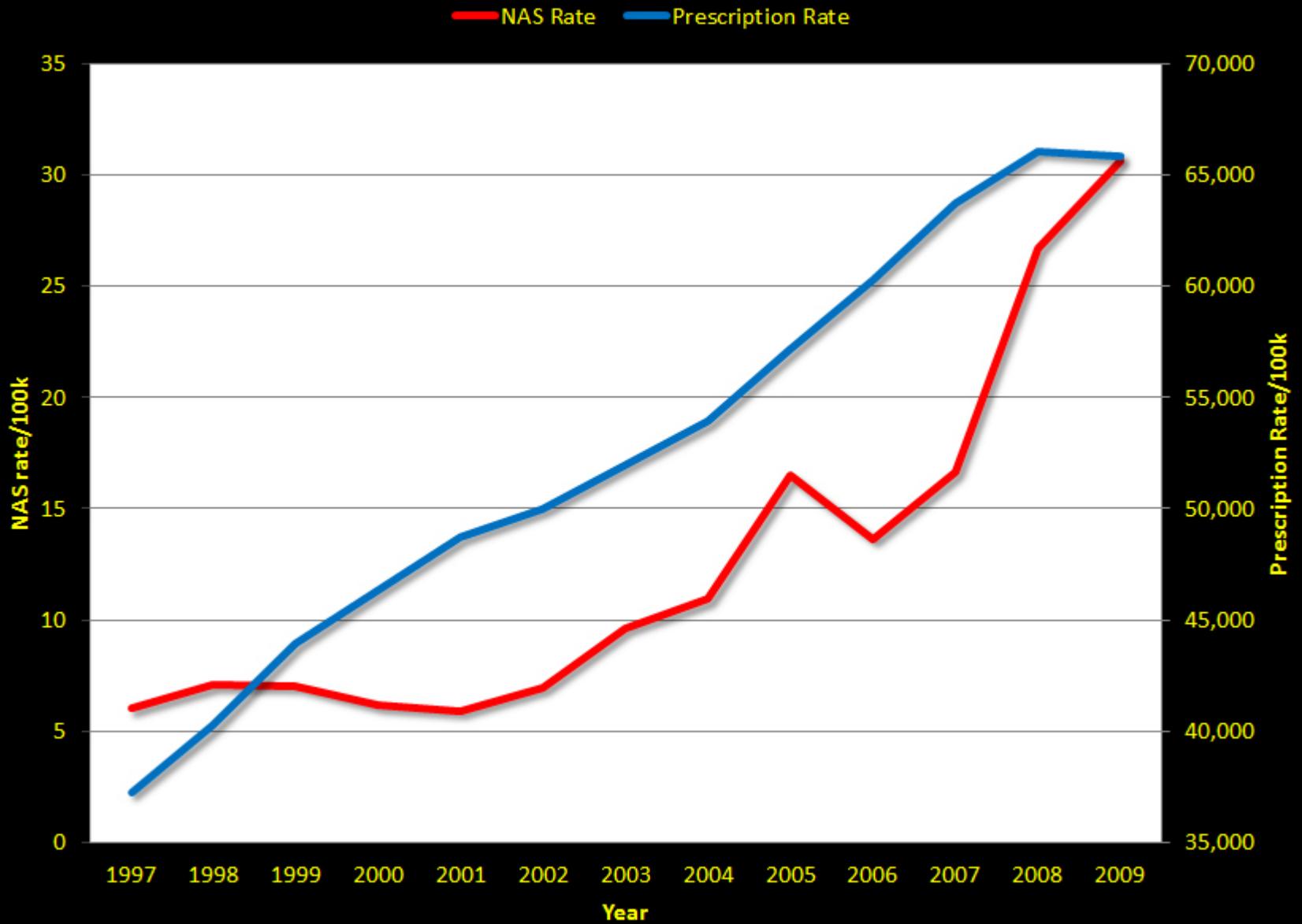
Riley Network (2001-2010)



NAS Hospital Charges - Indiana

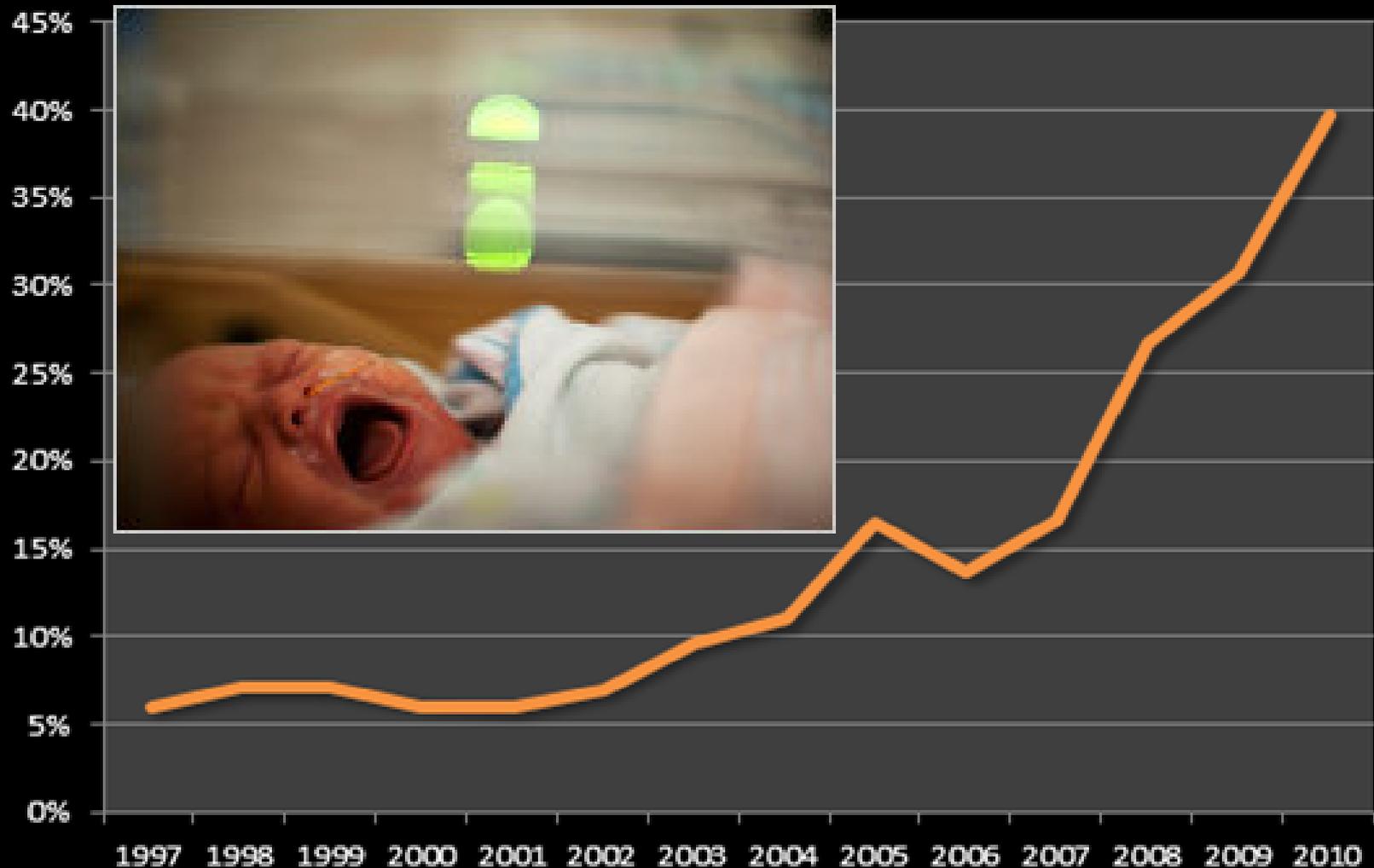


NAS vs. Opioid Prescriptions, U.S. 1997-2009



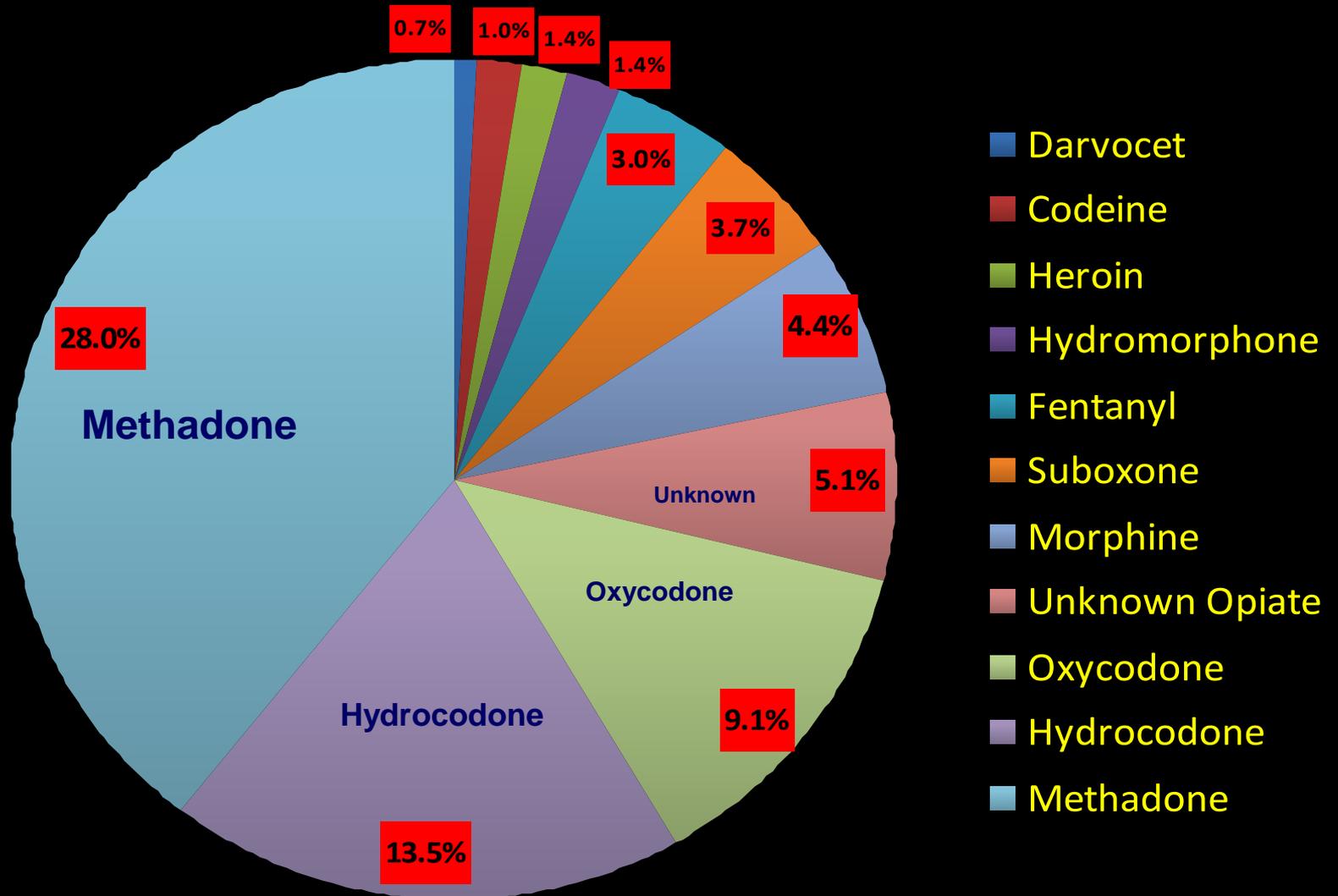
The NAS Epidemic; Cases Still Climbing

National NAS Rates per 1000 Live Births
National Hospital Inpatient Sample

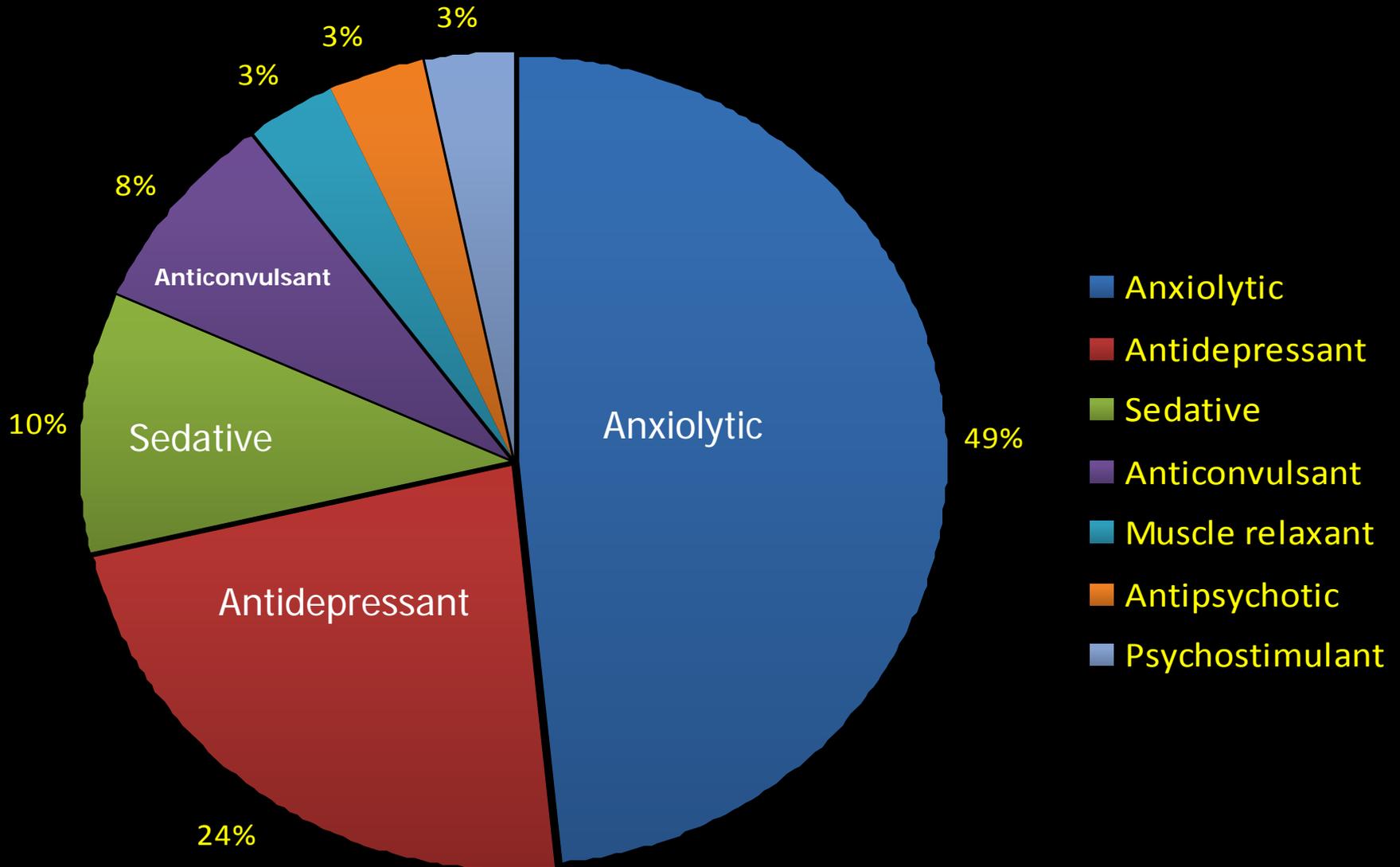


Opiates in NAS cases

(Riley Network)



Other Prescription Drugs in NAS



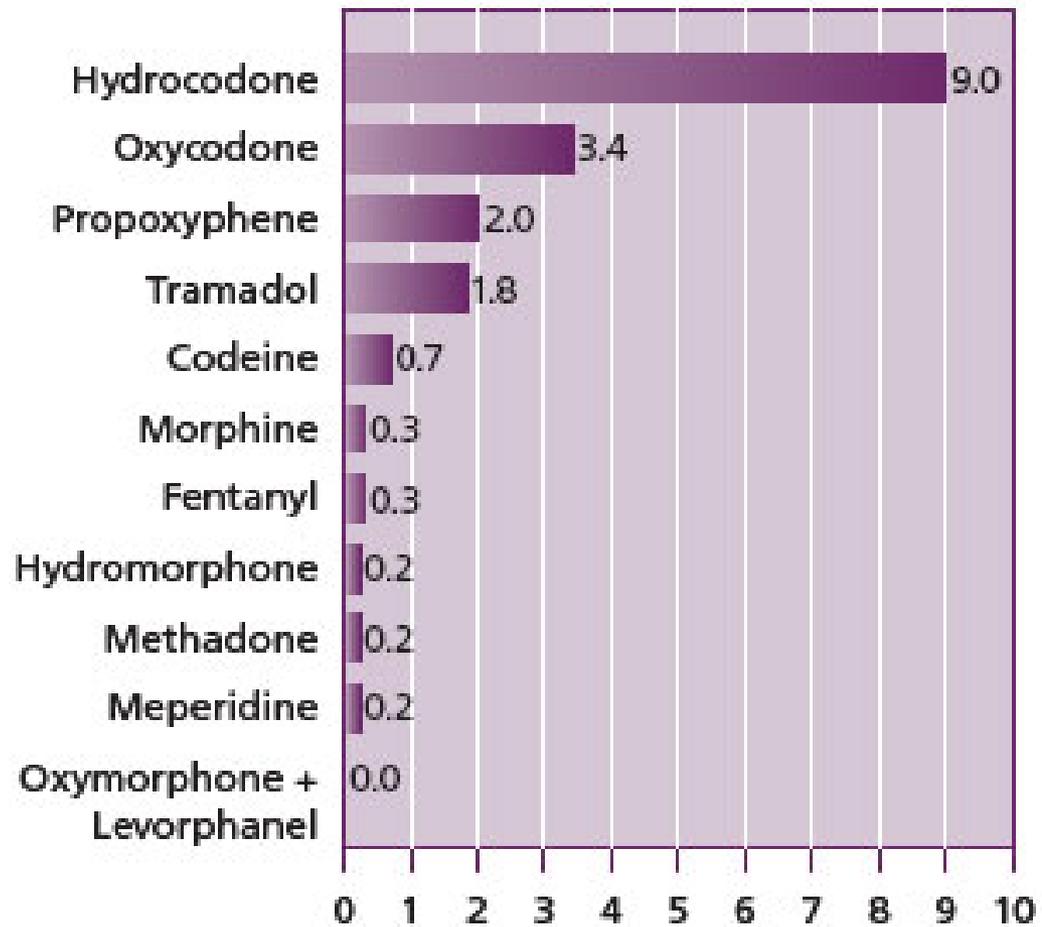
Who, What, When, Where?

- Who? Women (ages 13-35)
- What? Opiates are prescribed (along with NSAIDS)
- When? Pain (car accident, ankle sprain, surgery, tooth extraction).
- By whom? Doctor, Dentist
- Become Opiate dependent
- Become Pregnant
- Fetal Brain Development begins with opiates in blood stream.

Conclusions

- Neonatal opiate withdrawal and opiate prescriptions both significantly increased.
- NAS costs increased to \$100 million per annum.
- War on Pain  opiate prescriptions 
unintended consequence
- Attempts to reduce the ever-mounting numbers of opiate-exposed fetuses should be a major national priority.
- 70% of Mothers received 1st opiate from Doctor or Dentist.

Figure 2. Prescription characteristics of the opioids used in pain management⁹



Patients > 18 years old with Opioid prescriptions

Rise in Neonatal Opiate Withdrawal: Causes

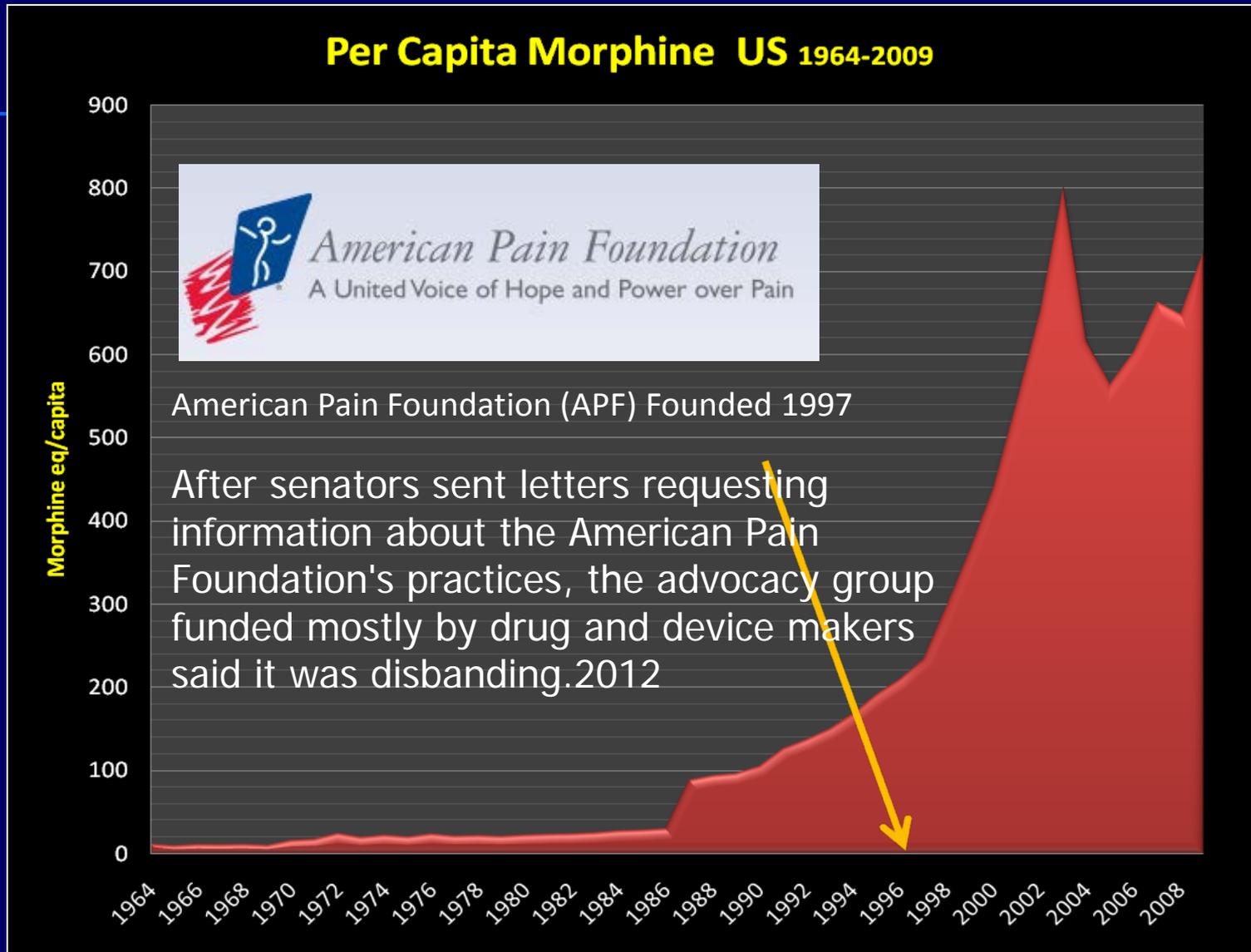
- More mothers opiate dependent at onset of pregnancy?
- More methadone or suboxone treatment of opiate dependent pregnant women?
- Improved detection of neonates at risk for opiate withdrawal?

Trends in Opiate Exposure in Reproductive Age Women

Hospitals . . . may screen all pregnant women . . . some may test selectively . . . others may rely on the intuitions of the attending physician.

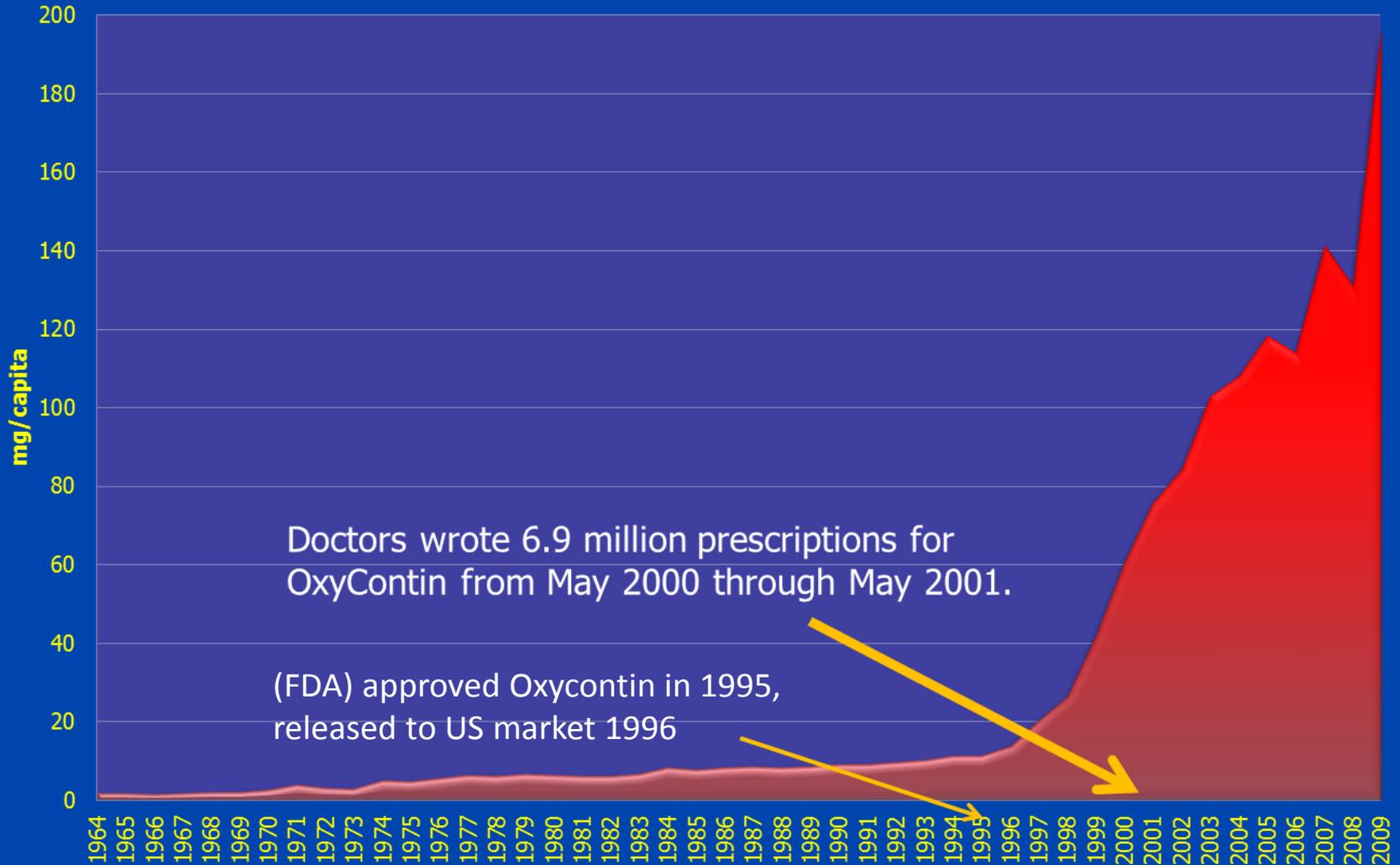
Estimating the Number of Substance-Exposed Infants; Deanna S. Gomby, Patricia H. Shiono. Spring 1991, Journal Issue: Drug-Exposed Infants Vol 1 Num1

Morphine: 700mg per US Citizen

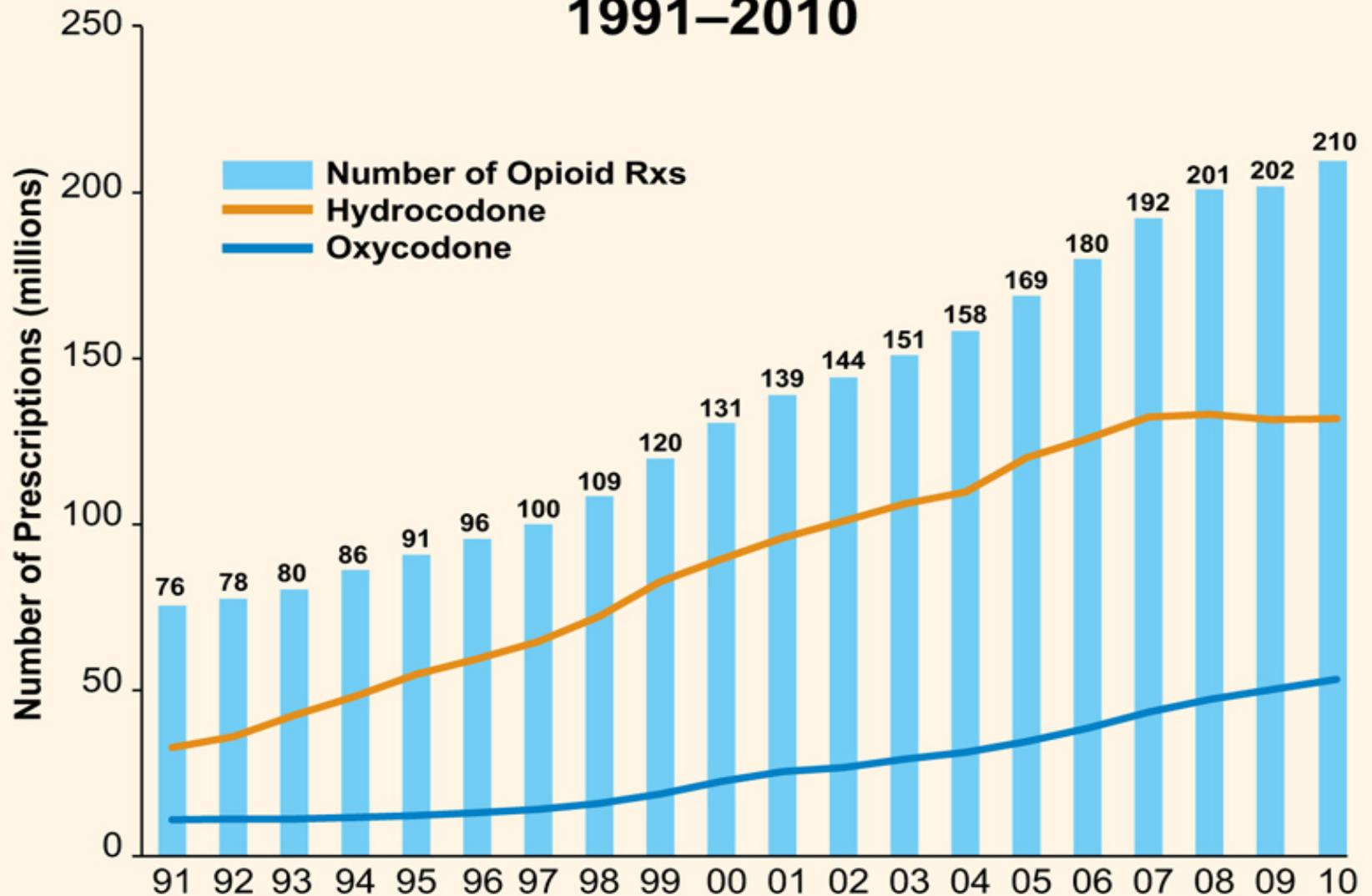


Oxycontin Debut 1996

Oxycodone per Capita US 1964-2009



Total Number of Opioid Prescriptions Dispensed by U.S. Retail Pharmacies, 1991–2010



Source: SDI's Vector One®: National (VONA)

Consequences of Fetal Opiate Exposure

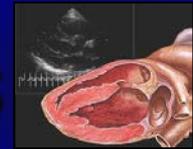
- Birth Defects
- Central Nervous System Changes
- Susceptibility to Addiction
- Sexual Behavioral Changes?

Maternal Opioids vs. Birth Defects

Cheryl S. Broussard, PhD; Sonja A. Rasmussen, MD, MS; Jennita Reefhuis, PhD; Jan M. Friedman, MD, PhD; Michael W. Jann, PharmD; Tiffany Riehle-Colarusso, MD, MSE; Margaret A. Honein, PhD, MPH; for the National Birth Defect Prevention Study. Amer Jour Obstet &Gynecol April 2011

- Conoventricular septal defects

(OR, 2.7; 95% CI, 1.1– 6.3)

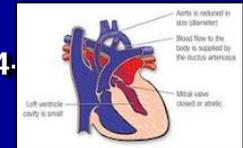


- Atrioventricular septal defects

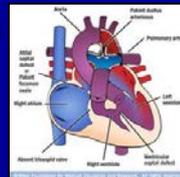
(OR, 2.0;95% CI, 1.2–3.6)



- Hypoplastic left heart (OR, 2.4; 95% CI, 1.4–



- Pulmonary valve stenosis (OR, 1.7 (1.2–2.6)



- Spina bifida (OR, 2.0; 95% CI, 1.3–3.2)



- Gastroschisis (OR, 1.8; 95% CI, 1.1–2.9)



CNS Effects of Prenatal Opiate Exposure; Human Studies

- short attention span
- hyperactivity
- sleep disturbances

Rosen T.S., Johnson H.L., Long-term effects of prenatal methadone maintenance. NIDA Res Monogr (1985) 59 : pp 73-83

- mild memory and perceptual difficulties in older children, but overall test scores are still within the normal range

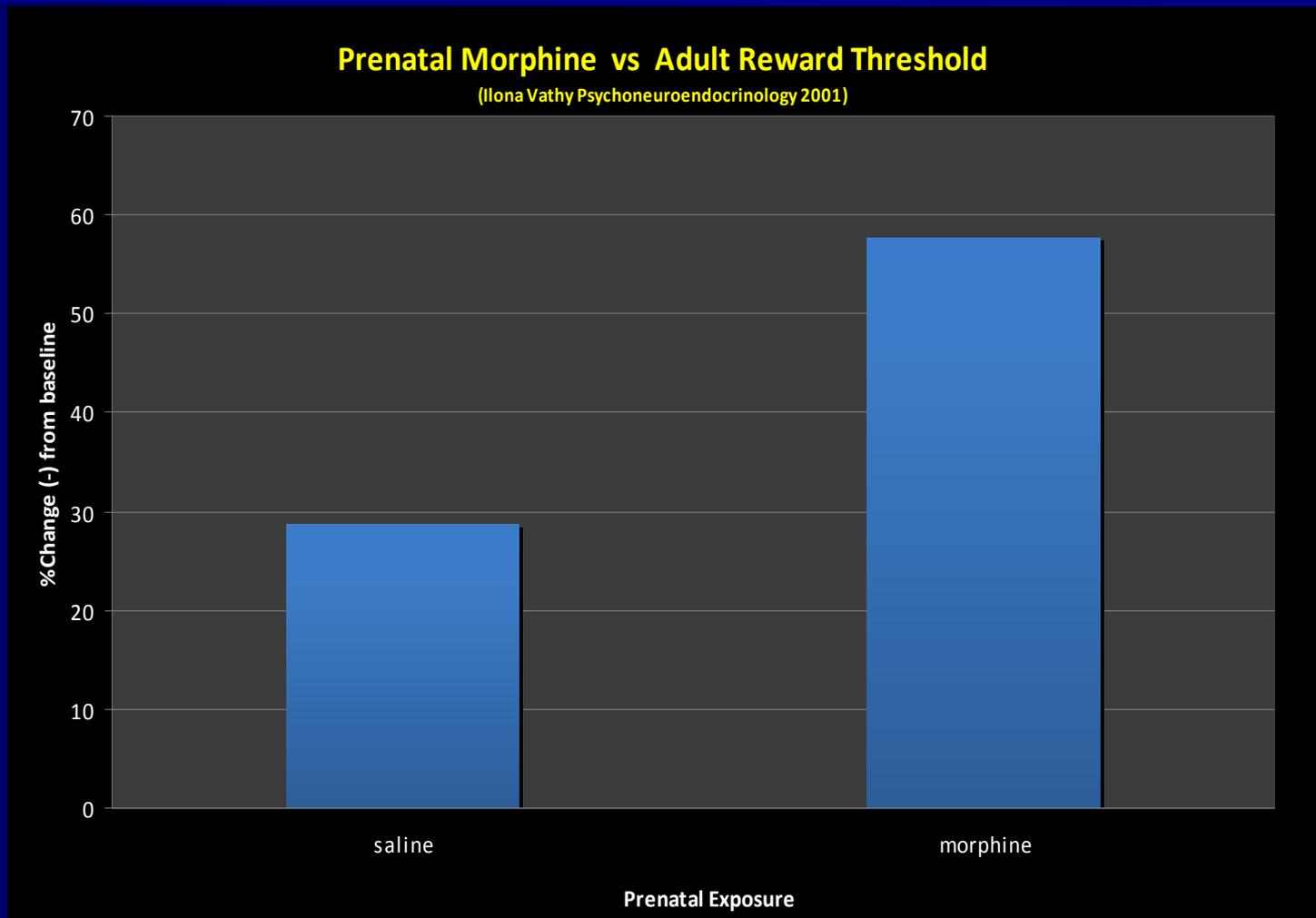
Lifschitz M.H., Wilson G.S., Patterns of growth and development in narcotic-exposed children. NIDA Res Monogr (1991) 114 : pp 323-339.

Fetal Opiate Exposure Alters Adult Reward Threshold



Ilona Vathy

Developmental
Psychobiology
Volume 49, Issue 5,
pages 463–473, July
2007



Prenatal Methadone Slowed Adult Learning

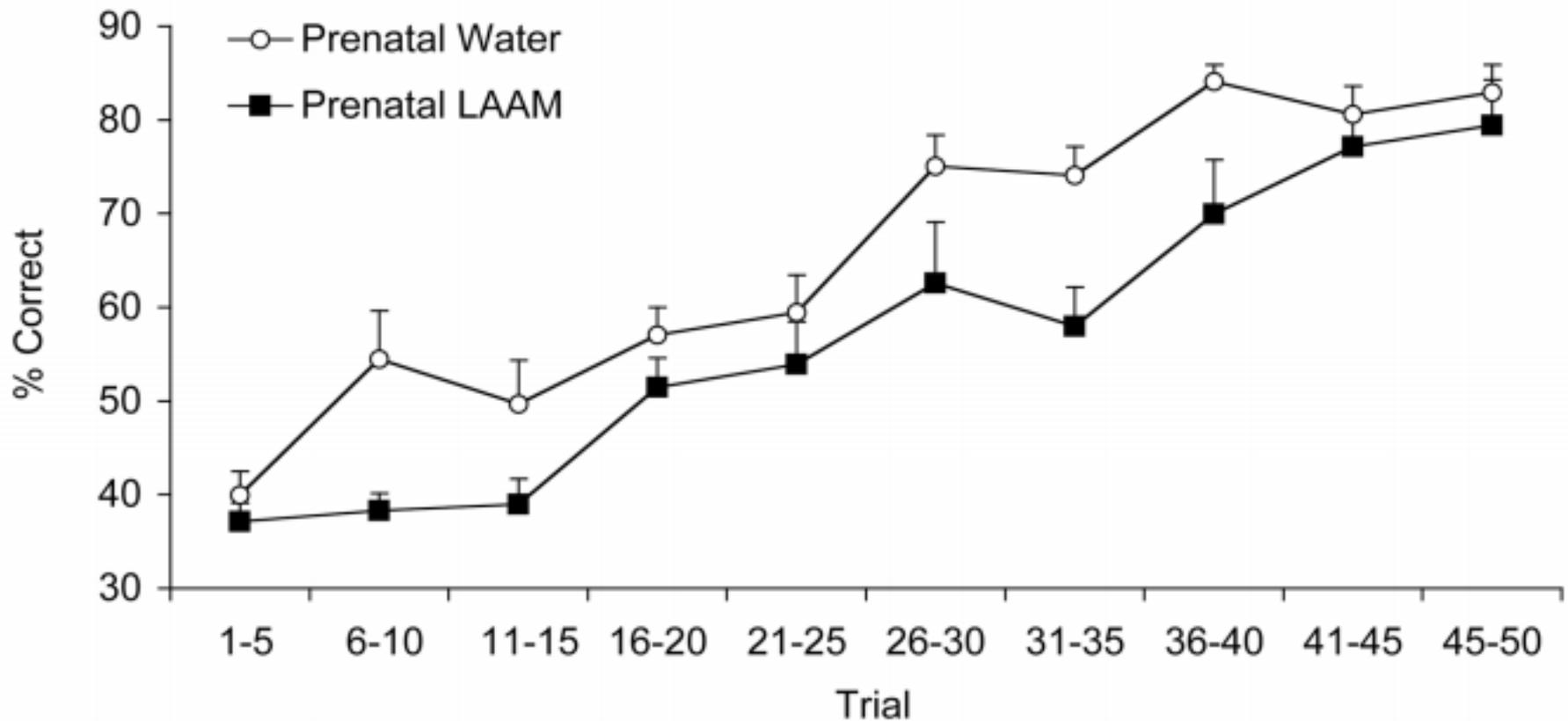
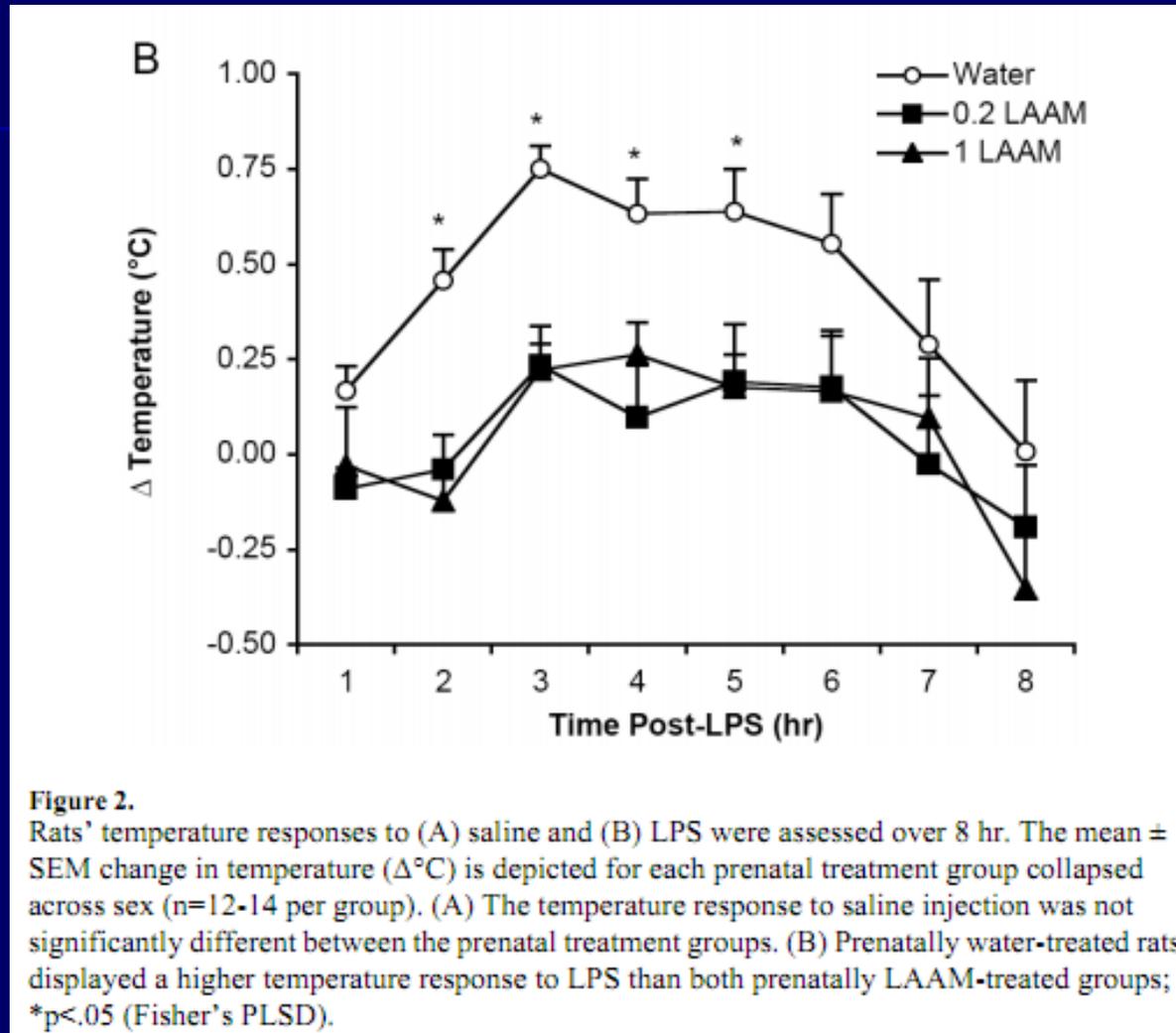


Figure 1.

Prenatal LAAM-treated male rats (dark squares) had reduced performance in the radial arm maze compared with prenatal water-treated rats (open circles) as assessed by the percent of correct responses. However by the final trial blocks, there was no difference between the groups. Data depict mean \pm SEM for trial blocks of 5 trials. (N = 6 per group).

Prenatal Opiates Blunted Fever Response



Brain White Matter Altered by Prenatal Opioids.



Clusters of voxels (≥ 100) with significant ($P < .05$) group differences in FA are shown in red-yellow as they appear in the WM skeleton shown in green. For all clusters, FA was lower in the prenatally substance-exposed children.

K.B. Walhovd, L.T. Westlye, V. Moe, K. Slinning, P. Due-Tønnessen, A. Bjørnerud, A. van der Kouwe, A.M. Dale, A.M. Fjell

Walhovd AJNR 31 May 2010 www.ajnr.org

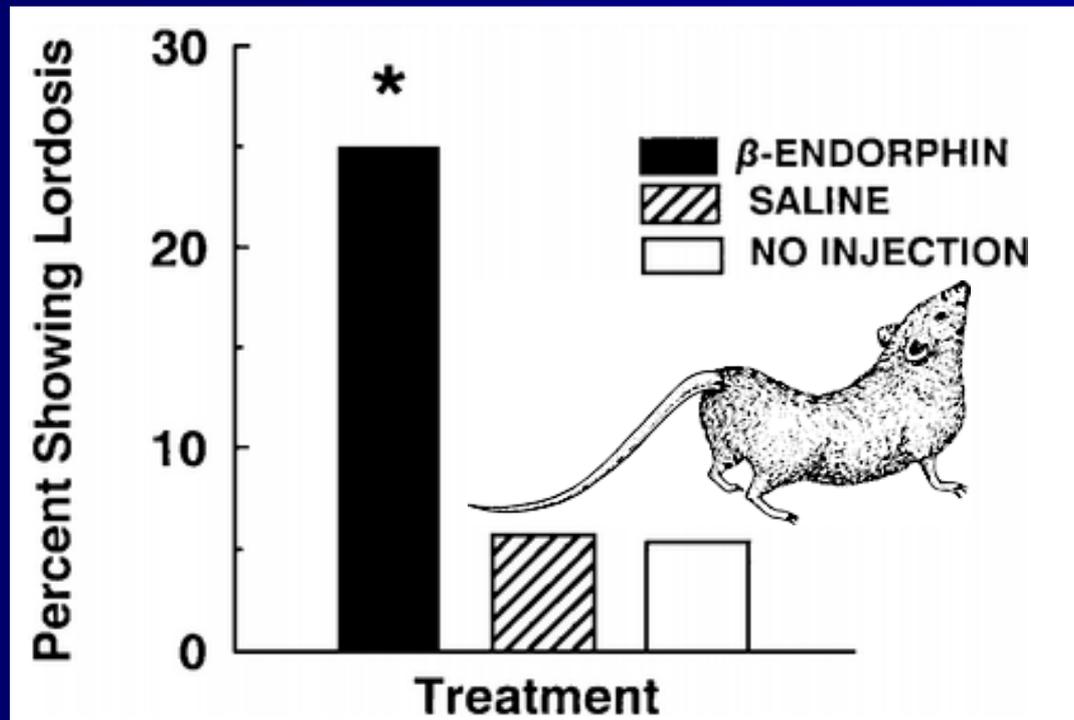
Prenatal Opiates Increase Risk of Both Opiate and Cocaine Addiction

- Prenatal exposure to morphine enhanced rates of heroin and of cocaine, but not of saline self-administration.

N F Ramsey, R J Niesink, J M Van Ree *Drug and Alcohol Dependence* (1993) Volume: 33, Issue: 1, Pages: 41-51

Prenatal Opiate Feminizes Adult Male Sexual Behavior

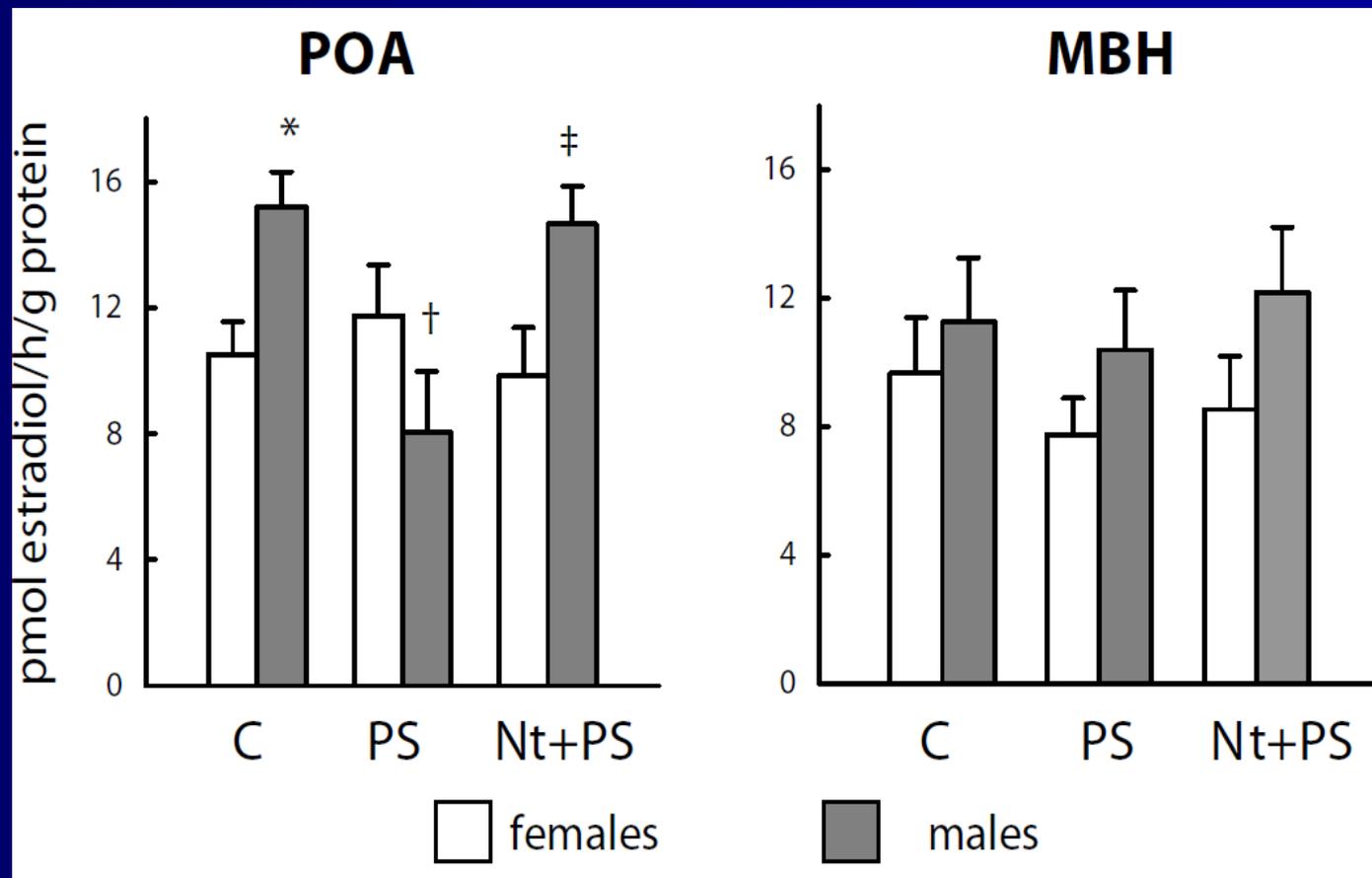
- Gagin, Cohen, Shavit Pharmacol Biochem Behav. 1997 Oct; 58(2):345-8



Opioids induce neurochemical feminization of the brain in prenatally stressed male rats

Neuroendocrinology Letters No.1 February Vol.26, 2005 Alexander G. Reznikov, Nadezhda D. Nosenko & Larisa V. Tarasenko

Prenatal naltrexone (Nt) effect on aromatase activity in the preoptic area (POA) and medial basal hypothalamus (MBH) of 10 day-old prenatally stressed (PS) rats. Data represent mean — S.E.M. (pmol estradiol/h/g protein) for 4-8 determinations. * $p < 0.05$ versus control females, † $p < 0.05$ versus control males, ‡ $p < 0.05$ versus females Nt+PS.



Summary; Neonatology Goals

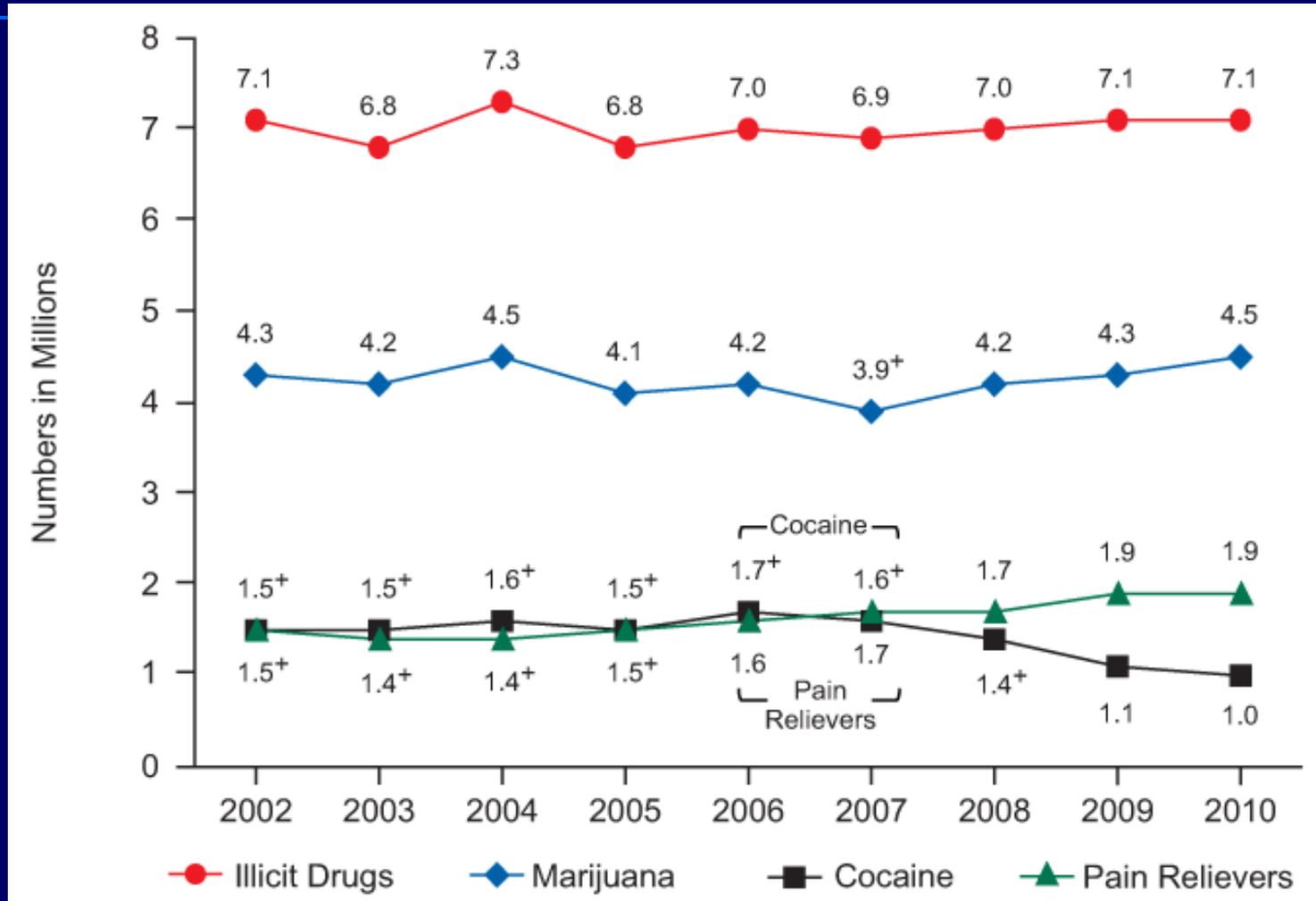
- Pregnancy Rx with **Suboxone** will shorten withdrawal and hospital stay.
- **Preadmission consultation** (e.g. Ilana Torine) will reduce parental anxiety and frustration.
- **Standardized NICU care** improve assessment of NAS and treatment protocols.
- **National Awareness** of the fetus as a "Civilian Casualty" of the War on Pain.

Thanks

- Kyle Miller (Center Grove HS Honor's Program)
- Cathy Proctor (Research Coordinator)
- Abhay Singhal, MD
- Jun Ying, PhD
- Gina Ellis, Pharm. D, St Francis Hospital
- NICU Directors (JoAnn Matory, Marya Strand, Ilana Torine, William Engle)
- Sponsor David Ingram, MD

Illicit Drug Dependence or Abuse in the Past Year among Persons Aged 12 or Older: 2002-2010

How the NSDUH missed the opiate epidemic.



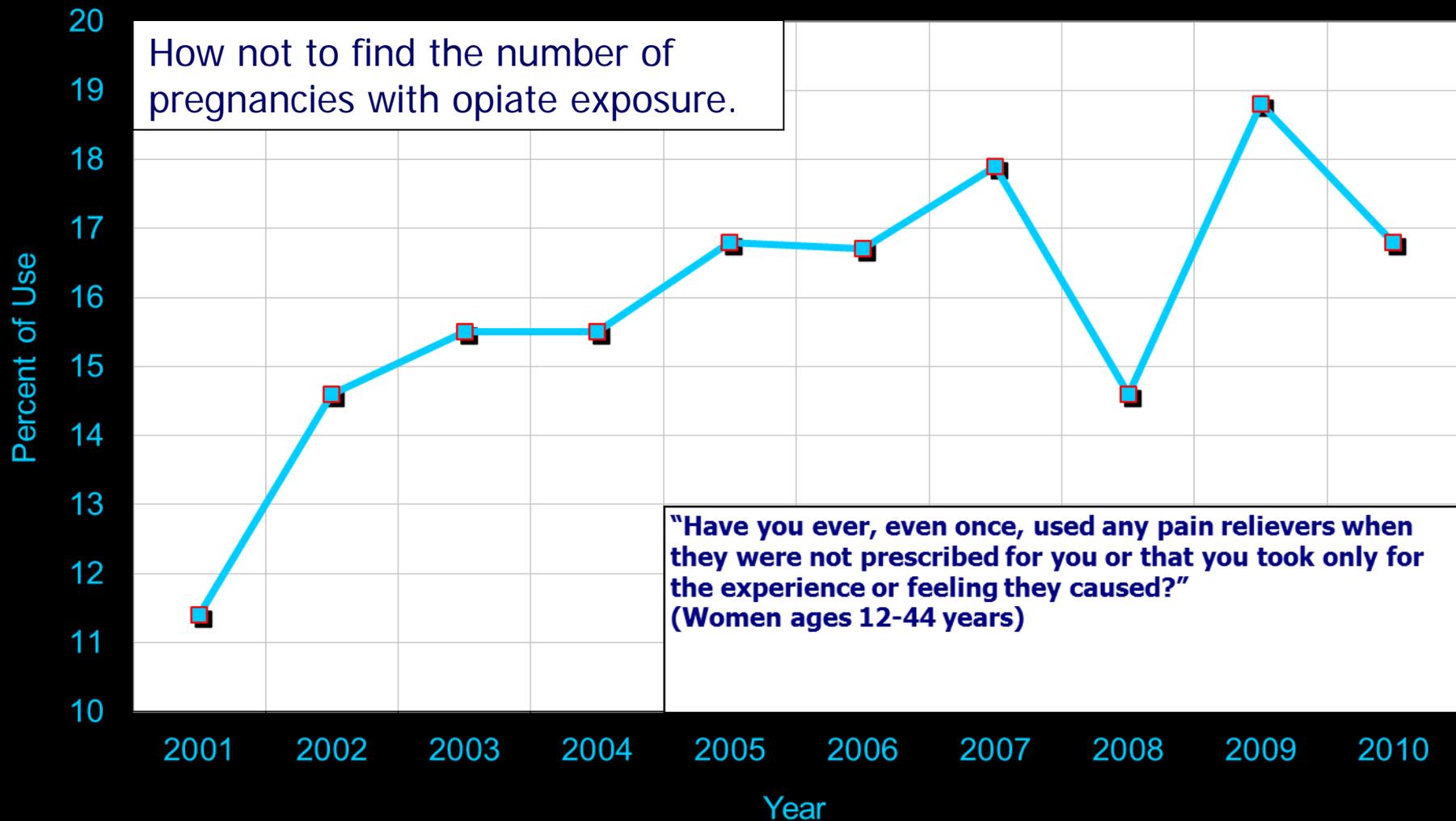
NSDUH

Trying not to Find.

- Illicit drug use represents <10% of all drugs used.
- Daily opiate dependence (under prescription) is not considered illicit use.
- Drug dependency (of the doctor kind) was not even on the radar screen.
- Why not?

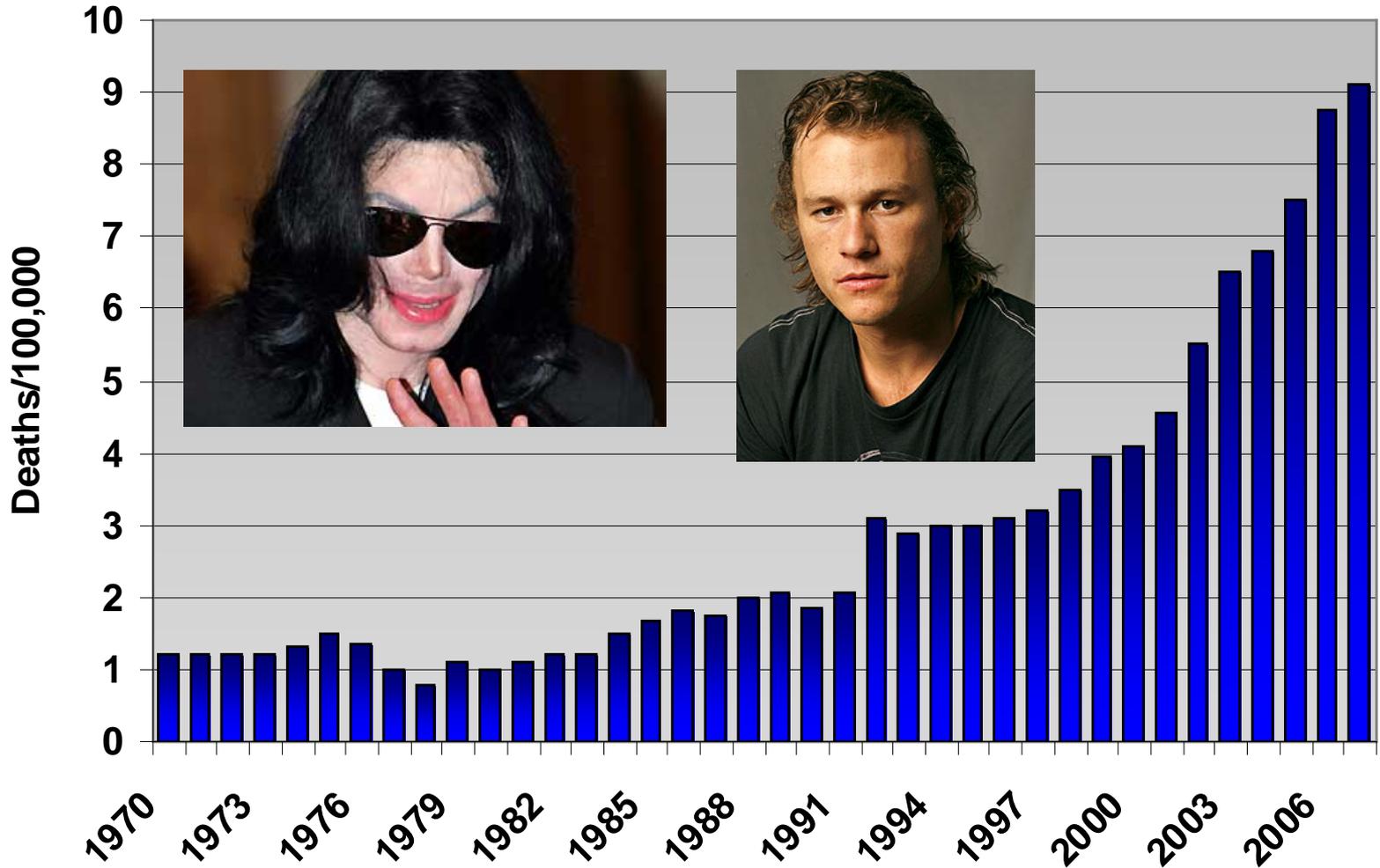
Illicit Pain Medication Use During Pregnancy

SAMHSA - National Survey on Drug Use and Health



Drug Overdose Deaths up 5X since 1990

Overdose Deaths US 1970-2007
(Unintentional)

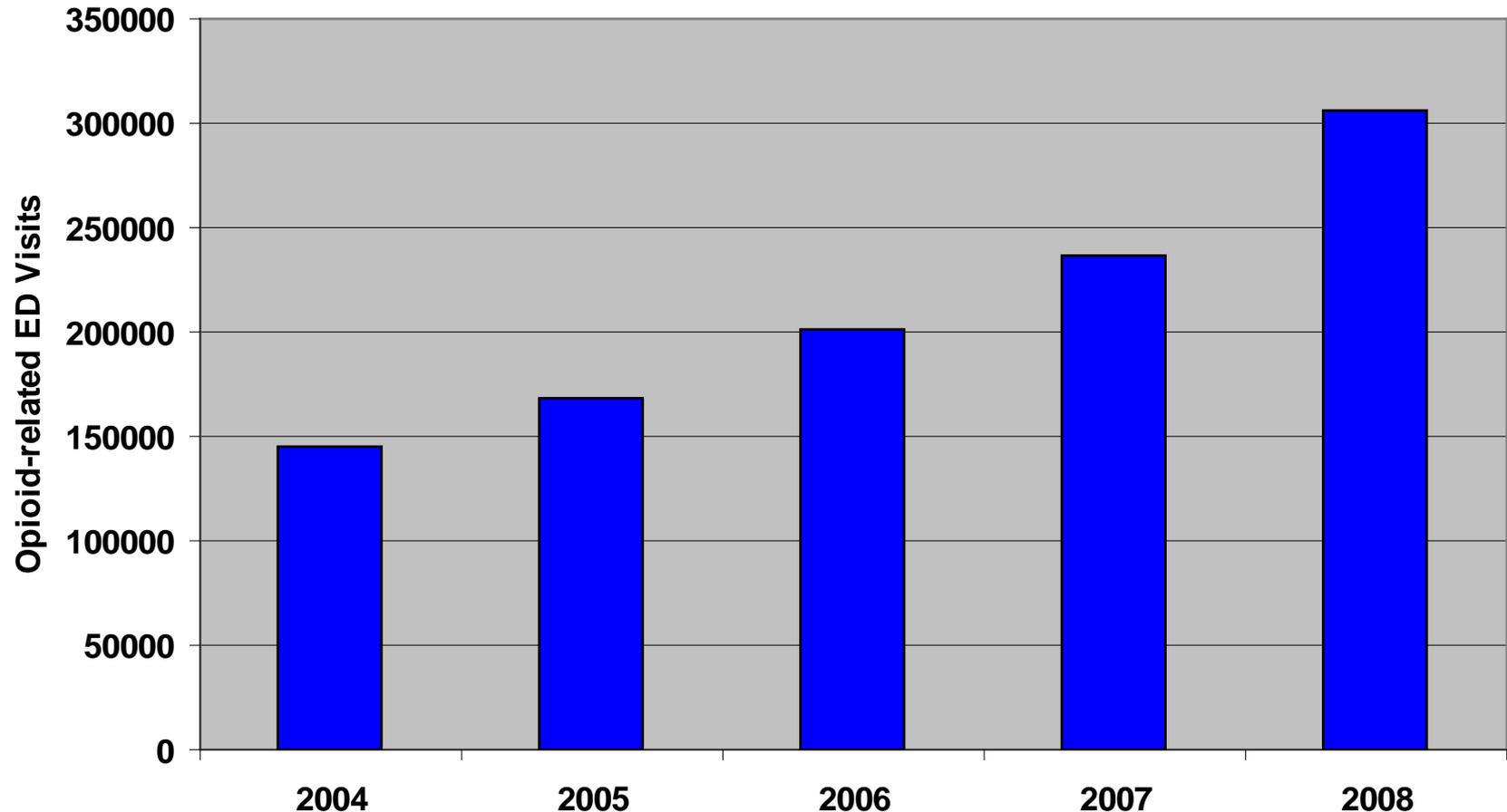


Manufactured Death in Indiana

- From 1999 to 2009, **unintentional poisoning**, (prescription drug overdose), skyrocketed **502 %** in Indiana, Dr. Joan Duwve Indiana State Health Department.
- Over the decade, **unintentional poisoning became the leading cause of injury death**, outpacing unintentional motor vehicle accidents, suicide with a firearm, and homicide with a firearm.

Emergency Room Visits Up

Opioid-Related ED Visits up by 111%

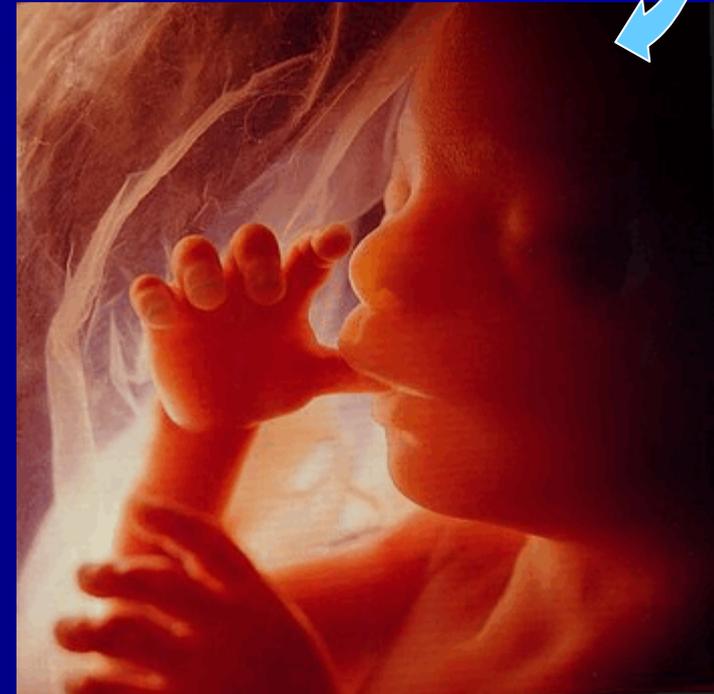


Pill Mills Migrating to Indiana

- Clark County Wellness, the clinic relocated from Georgetown, Ky., shortly after the Kentucky General Assembly enacted new legislation targeting pill mills.
- Dr. Lea Ann Marlow, the physician at Clark County Wellness Center in Jeffersonville, has written more than 8,000 prescriptions for 3,489 patients since January in Kentucky and Indiana

Drug Company; Doctor; Patient

- Dr. Jose Villavicencio (Columbus, In) license revoked (prescribed a 13 y/o vicodin & Xanax). He prescribed 300 milligrams of oxycodone per day to patients.



Indictment of Purdue Pharma. Criminal Misrepresentation of OxyContin

- Sales representatives told some healthcare providers that the drug had less euphoric effect and less abuse potential than short-acting opioids and exaggerated the differences between blood plasma levels achieved by OxyContin compared to the levels of other painkillers;
- Supervisors and employees drafted an article about a study of the use of the drug in osteoarthritis patients that was published in a medical journal, and the article was given to representatives for distribution to falsely represent that patients taking OxyContin at doses below 60 milligrams per day could be discontinued abruptly without withdrawal symptoms;
- Sales representatives told healthcare providers that a statement on the drug's package -- "delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug" -- meant that it did not produce a buzz or euphoria and had less addiction potential.

Purdue Pharma

- Purdue pleads out, will pay **\$634 million in fines** (3 top execs+Co will pay \$634,515,475 in fines).
- A few days after paying \$20 million to 27 **state attorneys general** to settle similar civil allegations, Purdue Frederick Co. pleaded guilty in a Virginia federal court Thursday to criminal charges of misbranding the addictive and abusable nature of its prescription painkiller OxyContin
- Chief Operating Officer Michael Friedman, Executive Vice President and Chief Legal Officer Howard Udell and former Executive Vice President of Worldwide Medical Affairs Paul Goldenheim each pleaded guilty to a misdemeanor charge of misbranding OxyContin.

Conclusion

(positive spin)

- Pain Epidemic Finally Appreciated
- Effective Pain Relief Finally Made Available.
- Unintended Consequences (death, opiate dependency, lost work, fetal addiction) **unavoidable collateral damage.**

Conclusion

(negative spin)

- Opiate Abuse Epidemic Has Occurred on Our Watch.
- Pharmaceutical Company Made
- Physician Pushed
- Patient Victimized
- Fetus Condemned

