

3rd Annual Prescription Drug Abuse Symposium

*Safe and Effective Management of Chronic, Non-cancer Pain
in Primary Care*

Education Breakout Session

December 19, 2012

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Objectives for this breakout session:

- “Terminology Clarification”
- Causes of the “opioid explosion”
- Prevalence of misuse and abuse
- Common illegitimate ways people obtain prescription drugs
- Review effectiveness of opioids in CNCP

What prescription drugs are we talking about?

1. Opioids – OxyContin, Percocet, Vicodin, MS Contin, Dilaudid
2. Central Nervous System depressants – Xanax, Ativan, the class of barbituates
3. Stimulants – Dexedrine, Adderall, Ritalin, Concerta

Abuse

ADDICTION

Misuse

Non-medical use

Dependence

PHYSICAL DEPENDENCE

Tolerance

Pseudoaddiction

Withdrawal

Substance abuse

DSM Criteria

Lack of consensus and an understanding and proper use on terminology regarding pain therapy and its use, misuse, and abuse among clinicians, patients, pharmacists, insurers, diagnostic coding agencies, medical societies, regulators, government agencies, and pharmaceutical manufacturers.

Main Area of Confusion:

“Substance” Dependence

VS

“Physical” Dependence



The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV):

	Substance Dependence	Which means: Substance Abuse → Substance Dependence
DSM-IV Criteria	3 or more in past 12 months: <ol style="list-style-type: none"> 1. <u>Increased</u> amounts of substance to achieve intoxication 2. <u>Withdrawal</u> symptoms 3. Use of substance in larger amounts/longer than intended 4. Unsuccessful attempts to cut back 5. Chronic behavior to obtain substance 6. Reduced activities due to substance use 7. Continue use even with physical problem 	You may start out a typical substance abuser: recurrent, but intermittent trouble as a consequence of recreational binges. Can progress into substance dependence: continuous and compulsive pattern of use Substance Abuse as first step that eventually leads to Substance Dependence.

DSM-IV		Substance Abuse → Substance Dependence
Clinician's Definition*	<p>“Physical Dependence” – Physiologic process; a predictable event in prescribing opioids, BZDs, barbiturates, and stimulants. Characterized by <u>withdrawal</u> if the drug is abruptly stopped and <u>tolerance</u></p>	Physiologic dependence  Addiction

When talking about Prescription Drug Abuse, the word **Dependence** is being used in two distinct ways:

Physical Dependence – Biologic Phenomena

Misuse/Abuse – Behavioral Phenomena
(Substance Dependence)

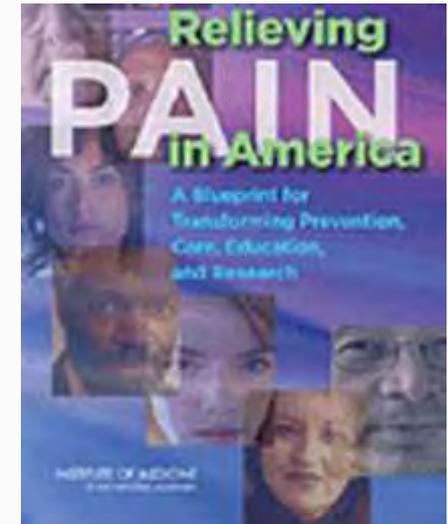
A major revision: DSM-V is due for publication May 2013, and the release will occur during APA's 2013 Annual Meeting.

Eliminating the separate categories of **Substance Abuse and Substance Dependence** and replacing them with one unified category: Substance Use Disorder, labeling the overall section "The Addiction and Related Disorders"

In summary of terminology:

Term	Definition	Example
Appropriate Use -physical dependence predictably occurs in chronic use	Use of controlled substance as prescribed for defined condition	10-day course of post-op narcotics taken as prescribed
Misuse/inappropriate use	Use of controlled substance for reason other than for which it was prescribed or in dosage different than prescribed	Single episode of narcotic used twice as often as prescribed; use of old Rx for new clinical problem w/o MD consultation
Abuse	Use of controlled substance outside normally accepted standards of use, resulting in disability and/or dysfunction	Continued misuse despite interventions Recreational purposes unrelated to medical condition
Catastrophic Use (Addiction)	Use of controlled substance that involves illegal activity or places patient in immediate harm	Altering prescription or selling controlled substances Overdose

Focus of the remainder of the talk:
Opioid use in Chronic Non-Cancer Pain



The IOM believes that when opioids are used as prescribed, they can be safe and effective for acute post-op pain, procedural pain, and patients near the end of life who desire more pain relief.

Fact 1

There is good evidence that opioid prescriptions are increasing rapidly

Pain Physician: July Special Issue 2012; 15:S1-566

Trends in opioid use

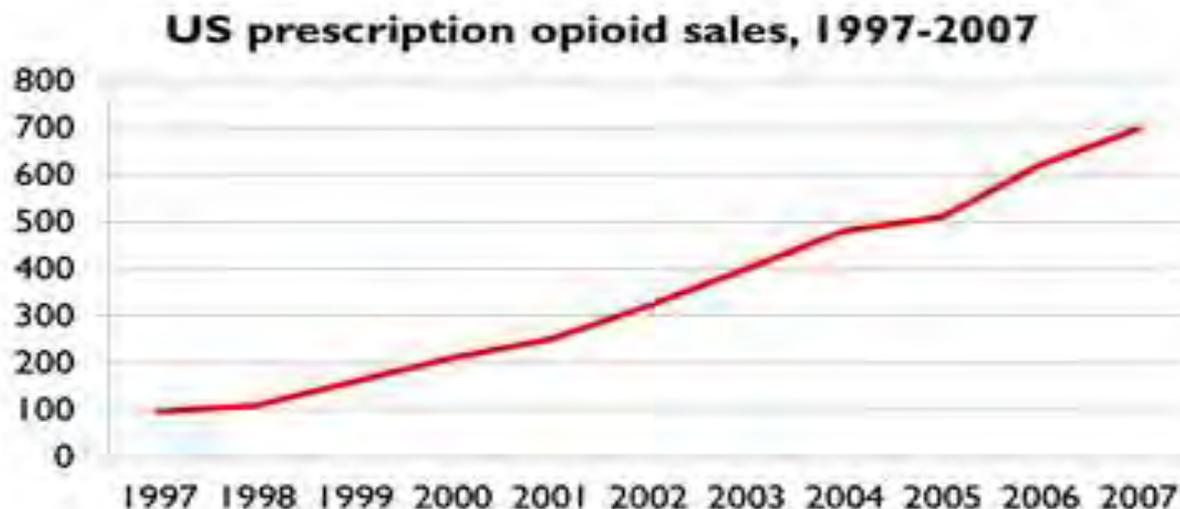
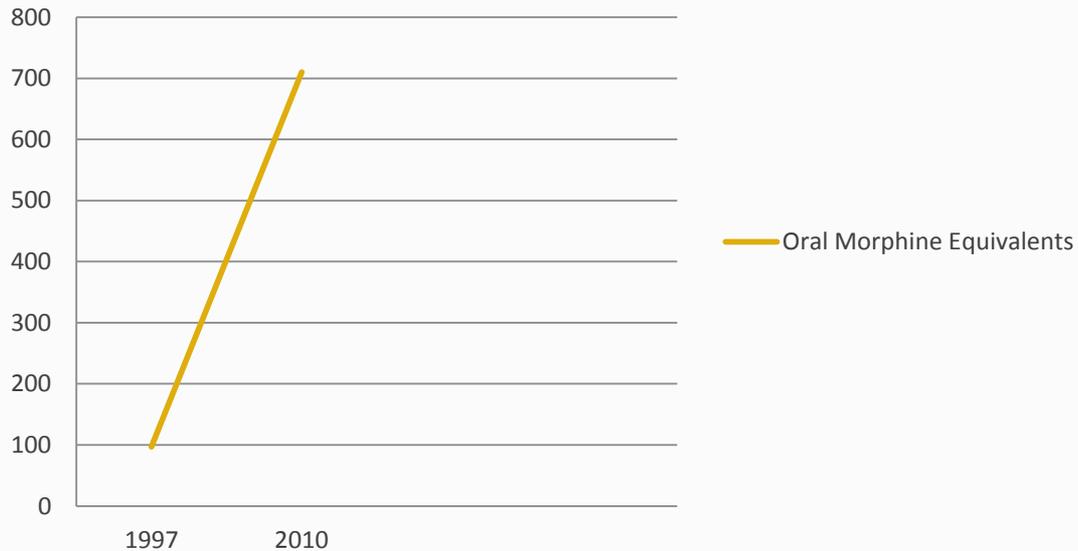


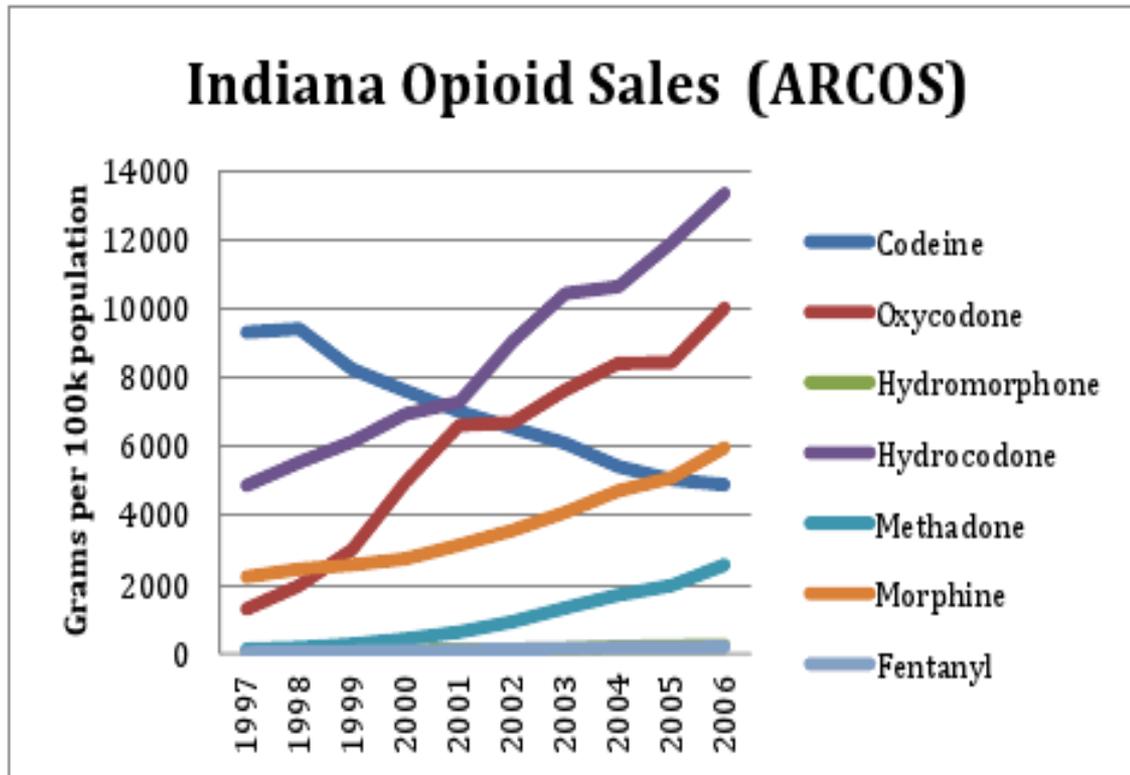
Figure adapted from CDC Grand Rounds, 2/17/11; data source DEA ARCOS

Sales and Distribution of Opioids



1997 = 97 mg OME per person in US

2007 = 710 mg OME per person in US



Why the explosion?

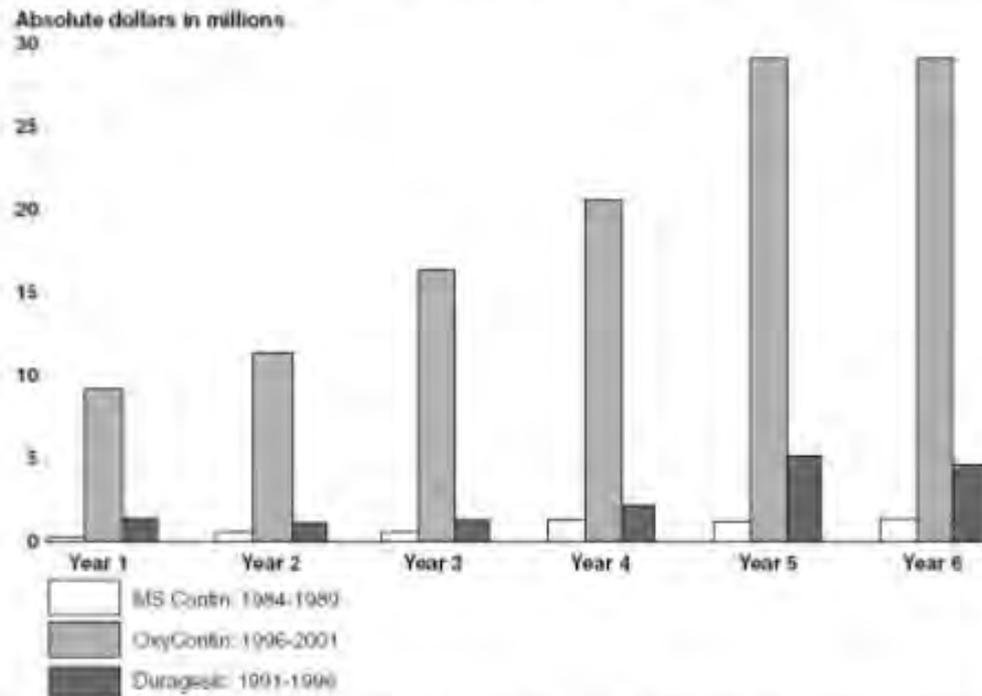
- Coincided with liberalization of laws governing opioid prescribing for the treatment of CNCP by the state medical boards in 1997.

The Board recognizes that controlled substances including opioid analgesics may be essential in the treatment of acute pain due to trauma or surgery and chronic pain, whether due to cancer or non-cancer origins.

- New pain standards from Joint Commission in 2000
- Aggressive marketing of long-acting opioids by the pharmaceutical industry
- Growing public awareness of the right to pain relief

Dollars Spent Marketing OxyContin (1996-2001)

Figure 1: Promotional Spending for Three Opioid Analgesics in First 6 Years of Sales



Source: United States General Accounting Office: Dec. 2003, "OxyContin Abuse and Diversion and Efforts to Address the Problem."

Problem:

The explosive use of therapeutic opioids is complicated by a lack of evidence regarding their effectiveness, long-term efficacy, and safety data in CNCP

Evidence of Effectiveness of Opioids in CNCP

The Manchester University College of Pharmacy Drug Information Center Conducted a Medline Search using the terms “analgesic, opioid”, and “pain, Chronic” with or without the term “NOT cancer” with results limited to studies Conducted in humans and published in English. Observational and interventional Studies inherently related to use of opioids for CNCP were included.

Results:

- Four controlled clinical trials
- Six non-controlled clinical trials
- Six observational studies

Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for CNCP: A meta-analysis of effectiveness and side effects. *Can Med Assoc J* 2006;174(1589-1594)

- 41 trials = 6,019 patients, average age 58.1, 63% female, 85% white
- 90% trials were either funded by or had one or more co-authors affiliated with the pharmaceutical industry
- Only 17 were actually randomized
- Only 30 trials were judged to have adequate blinding
- Study duration was on average 5 weeks

Results:

- **33% drop out rate in the opioid group**
- **Results in favor of morphine and oxycodone for pain relief, but other drugs produced better functional outcomes (naprosyn)**
- **The authors interpreted the results as WEAK**

Steiner D, Munera S, Hale M, et al. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic to severe low back pain: A randomized, double-blind study. *J Pain* 2011;12(11):1163-1173.

- 662 patients completed the 3 month run in period – this selected for patients who responded well to BTDS, which decreases the generalizability of the results
- Patient were randomize 1:1:1 to BTDS 5 mg, BTDS 20mg, and oxycodone 5 mg q6
- Endpoint was average pain over last 24 hours on 7 point scale

Results:

- **Only 66% of the patients completed the 12 week trial**
- **The authors concluded BTDS 20 mg patch was more effective than 5 mg and it was well tolerated**
- **59% of low dose and 77% of high dose experienced adverse effects**
- **Trial did not look at improvement in overall function**

Friedmann N, Klutzaritz V, Webster L. Long-term safety of Remoxy® (extended-release oxycodone) in patients with moderate to severe chronic osteoarthritis or low back pain. *Pain Med* 2011;12:755-760.

- 882 patients that were opioid naïve (failed NSAIDs, tramadol, or other opioids)
- Started on Remoxy 5 mg twice daily and titrated for 12 months
- Efficacy primarily determined on 11-point pain scale
- Lack of any control group

Results:

- **46% of patients completed the study; most common reason for discontinuation was adverse events (39%), other (26%), and protocol violations (19%)**
- **Authors concluded it was safe, tolerable, and efficacious for chronic hip, knee, and low back pain (baseline pain intensity score 6.4/10, mean at 12 months 4.3/10)**
- **Lack of control = less rigorous assessment**
- **Only efficacy assessment was mean pain score; no functional efficacy**

Wallace M, Thippawong J. Open-label study on the long-term efficacy, safety, and impact on quality of life of OROS hydromorphone ER in patients with chronic low back pain. *Pain Med* 2010;11:1477-1488.

- Initially a 6 week open-label study; then patients were allowed to continue (titrating the dose) for 6 months
- Of the 131 eligible patients, 113 patients enrolled; patients were excluded for opioid intolerances such as constipation and vomiting
- Primary efficacy was mean pain relief on a 1-5 scale

Results:

- **The authors state hydromorphone ER is efficacious and tolerable for up to 6 mths**
- **Limited by the lack of control, making it difficult to determine the role of opioids in this disease state**
- **As in many other studies, evaluating the efficacy of pain medications using only monthly visits increases the risk of error and bias.**
- **At final assessment, mean pain rating was 2.5/5 compared to 2.0/5 at baseline**

Naliboff BD, Wu SM, Schieffer B et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain* 2011;12(2):288-296.

- 135 patients enrolled in a specialty pain clinic at a VA (94% male, 74% musculoskeletal)
- Pts. with history of substance abuse were excluded
- They compared two dosing strategies: stable dose (minimal dose increases) vs. escalating doses
- Patients were on various opioids (hydrocodone, oxycodone, codeine, morphine, methadone or oxycodone ER)
- Primary outcome was change from 0 to 10 on pain scale.

Results:

- 33% of stable dose pts and 26% of escalating group were removed from the study due to opioid misuse/noncompliance
- No statistically significant differences in primary outcome (baseline 6 vs 7, at 12 months 5.6 vs 6.2)
- Authors concluded opioid misuse was high, so careful monitoring is needed; did see small improvements in self-reported relief in escalating group

Summary of evidence:

1. Data regarding the efficacy of opioids in CNCP is lacking
2. Overall, duration of exposure was low (average 329 days), the most popular opioids (combinations with acetaminophen) were not assessed, discontinuations were high, and high proportions of patients experienced adverse effects.
3. Serious adverse events and those relating to overdose were rare
4. Primary efficacy endpoint was **commonly a visual pain analog scale**, rather than looking at functional improvement (ie Brief Pain Inventory – Short Form)

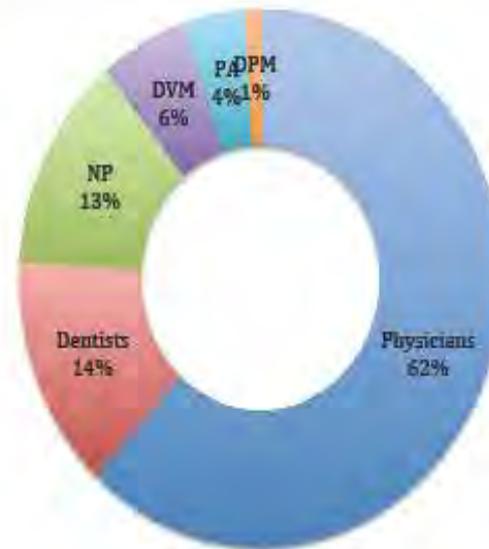
Fact 2

The US has a closed loop system of control over controlled substances.

With the exception of approximately 9% being obtained from out of the country via illegal channels and the small amounts obtained via theft....

The vast amount of controlled substances used in the US are prescribed by physicians.

23,331 Potential Controlled Substance Prescribers in Indiana (IPS Research)



The weak link in control of drugs in the system is after patients procure the medications from physicians - - the patients subsequently divert the medications without the physician's knowledge.

Inappropriate Use

Misuse

Abuse

Addiction

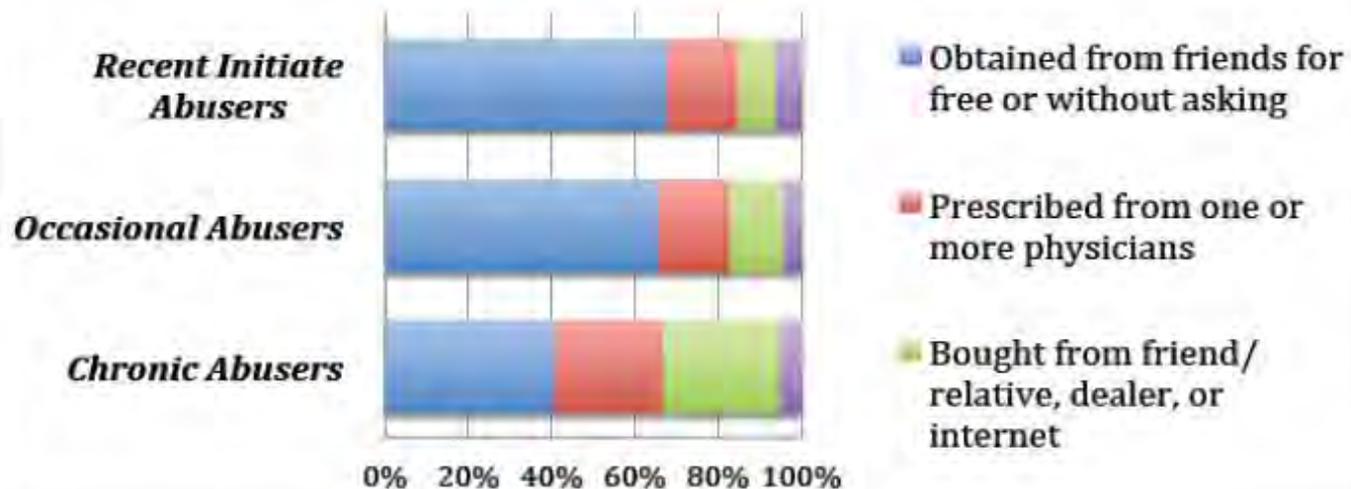
The single major issue surrounding opioid substance abuse is sharing of drugs among patients with their friends and families.

Among persons aged 12 or older who used pain relievers non-medically in the past 12 months:

- 55% reported that they received the drug for free from a friend or relative
- 11.4% bought or took the drug from a friend or relative
- 4.4% procured the pain relievers from a drug dealer or other stranger
- 0.4% reported buying the drug on the Internet

Sources of Abused Prescription Medications

Office of National Drug Control Policy
April 25, 2012

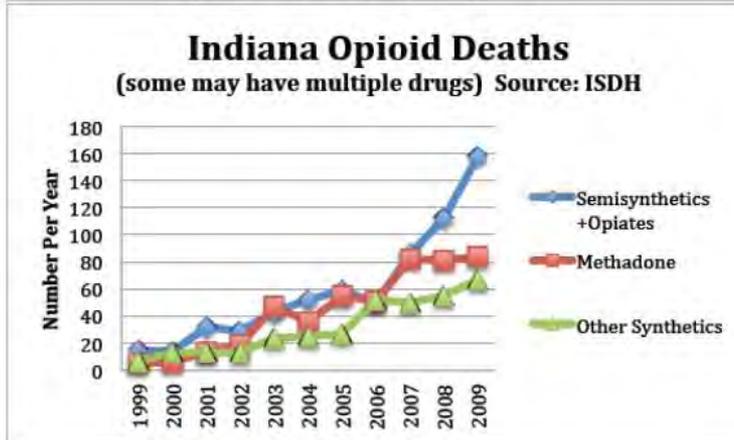
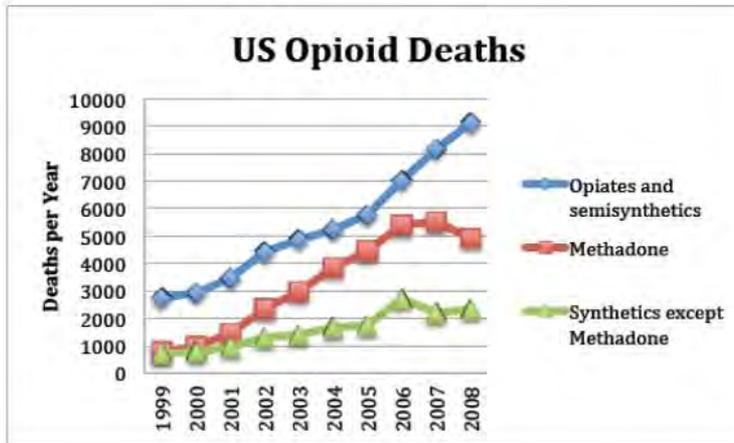


There is good evidence that non-medical use of opioids is extensive.

There is good evidence that approximately 1/3 of chronic pain patients may not use prescribed opioids as directed or may abuse them

Fact 3 ??

Indiana ranks 16th nationally in opioid drug deaths per 100,000 population with a rate increase that is accelerating above pace of the national average



Opioid Dose and Mortality

Several studies have examined this issue and uniformly have found that there is a correlation between increasing opioid doses prescribed and death.

However, the validity of these studies is compromised

- Patients that died may have actually been taking more drug than prescribed
- Have other sources for opioids or sedative hypnotics
- Taking other drugs that contributed to death

A large case-cohort study found VA patients receiving > 100 mg/day OME had a 4.5 hazard risk compared to those receiving 1-20 mg OME

Jama. 2011;305(13):1315-1321.

***Interestingly, this study excluded fentanyl and methadone - - due to difficulty of translating those dosages to Oral Morphine Equivalents

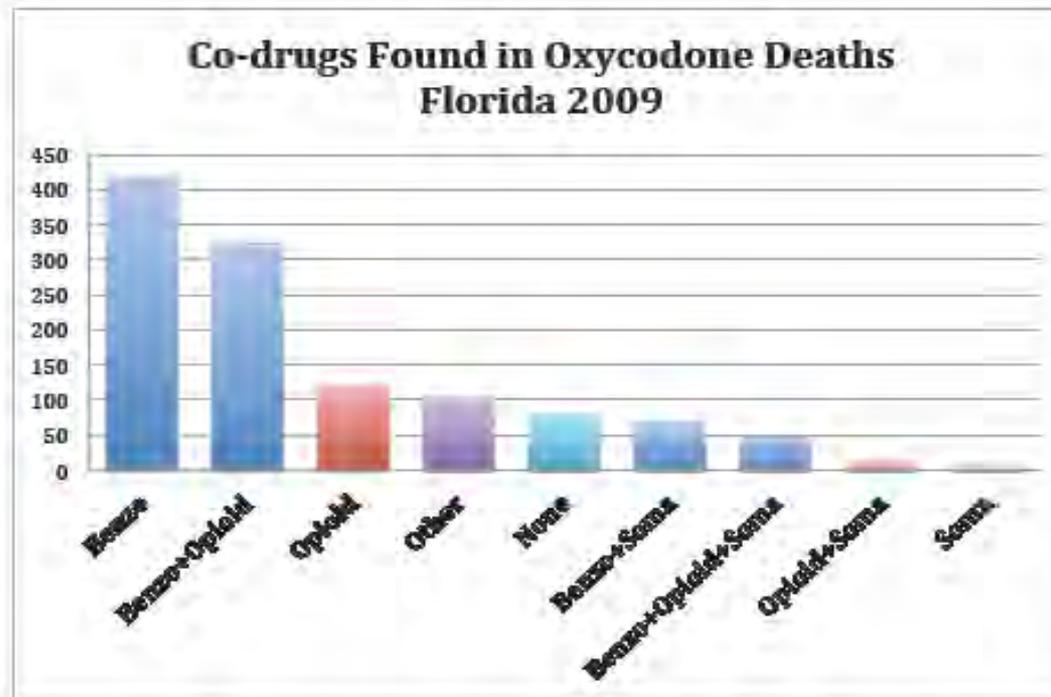
Fact 4

Clearly, drug overdose is causally linked to amount of opioid prescribed.

But because all of the evidence looking at this connection is retrospective, case-cohort design, they are limited to just finding a potential relationship, not cause and effect.

Fact 5

A major factor in drug overdose deaths associated with opioid use is the use of other prescription and non-prescription drugs, especially those with sedative properties.



Polypharmacy deaths (those involving more than one drug) are the rule rather than the exception. In Florida in 2009, 92% of oxycodone deaths were associated with other drugs, 90% of methadone deaths, 87% of hydrocodone deaths, and 82% of morphine deaths had significant other prescription drugs found, most often benzodiazepines.

Recent matched case-control study looked at 300 persons who died of unintentional drug overdoses in New Mexico during 2006-2008.

Increased risk was associated with: one or more sedative/hypnotic prescriptions (AOR 3.0)

Paulozzi LJ, Kilbourne EM, Shah NG, et al. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med.* 2012 Jan;13(1):87-95.

Fact 6

The number of decedents that actually had prescriptions for all of the drugs they were taking at time of death is surprisingly low – suggesting that it is more common to overdose with drugs or co-drugs being obtained from others than from taking prescriptions as written by physicians.

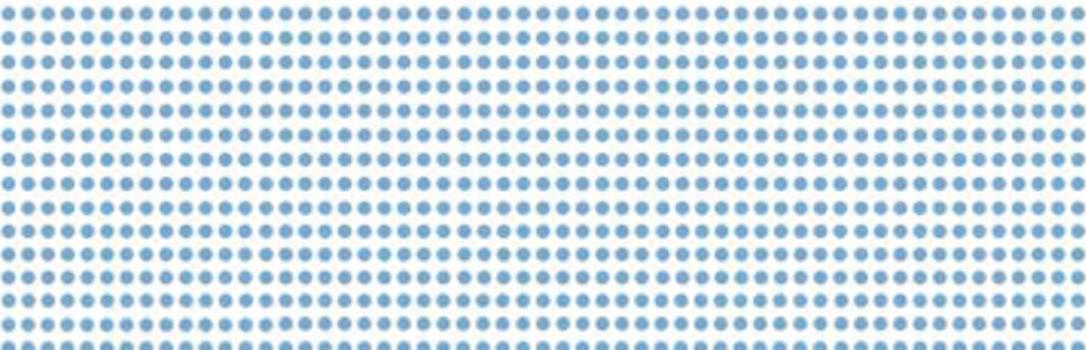
For every **1** death there are...



 **10** treatment admissions for abuse⁹

 **32** emergency dept visits for misuse or abuse⁶

 **130** people who abuse or are dependent⁷

 **825** nonmedical users⁷

References:

1. Indiana Center for Health Policy. Fatal Drug Overdoses: A growing concern in Indiana. Research for a Healthier Indiana; Mar 2008
2. Centers for Disease Control and Prevention. Vital Signs: Overdoses of prescription opioid pain relievers: United States, 1999-2008. MMWR 60(43):1487-92.
3. Naliboff BD, Wu SM, Schieffer B et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain 2011; 12(2):288-296.
4. Steiner D, Munera C, Hale M et al. Efficacy and safety of buprenorphine transdermal system (BTDS) for Chronic moderate to severe low back pain: A randomized, double-blind study. J Pain 2011;12(11):1163-1173.
5. Wild JE, Grond S, Kuperwasser B et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract 2010; 10(5): 416-427.
6. Iglesia FA, Pace GW, Robinson GL et al. Tolerability and efficacy of two synergistic ratios of oral morphine and oxycodone combinations versus morphine in patients with chronic noncancer pain. J Opioid Manag. 2012 Mar-Apr; 8(2):89-98.
7. Friedmann N, Kluraritz V, Webster L. Long-term safety of Remoxy (extended-release oxycodone) in patients with moderate to severe chronic osteoarthritis or low back pain. Pain Med 2011; 12:755-760.
8. Nalamachu SR, Narayana A, Janka L. Long-term dosing, safety, and tolerability of fentanyl buccal tablet in the management of noncancer related breakthrough pain in opioid tolerant patients. Curr Med Res Opin 2011; 27(4):751-60.
9. Fine PG, Messina J, Zie F et al. Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: An 18-month study. J Pain Sym Manag 2010; 40(5): 747-759.

References continued:

10. Sandner-Kiesling A, Leyendecker P, Hopp M et al. Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non-cancer chronic pain. *Int J Clin Pract* 2010;64(6): 763-774.
11. Wallace M, Thipphawong J. Open-label study on the long-term safety and efficacy of morphine and sequestered naltrexone, in patients with chronic, moderate to severe pain. *J Pain Sym Manag* 2010; 40(5):734-746.
12. Webster LR, Brewer R, Wang C et al. Long-term safety and efficacy of morphine sulfate and naltrexone hydrochloride extended release capsules, a novel formulation containing morphine and sequestered naltrexone, in patients with chronic, Moderate to severe pain. *J Pain Sym Manag* 2010; 40(5): 734-746.
13. Bohnert ASB, Valenstein M, Bair MJ et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 2011; 305(13): 1315-1321.
14. Indiana Pain Society Legislative Report on Pain Clinics and Opioid Prescribing in Indiana 2012.
15. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part I – Evidence Assessment. *Pain Physician* 2012; 15:S1-S66.
16. Isaacson JH, Hopper JA, Alford DP, and Parran T. Prescription Drug use and Abuse. *Postgrad Med* 2005; 118(1): 19-25.
17. American College of Preventative Medicine ACPM: Use, abuse, misuse, and disposal of prescription pain medication time tool. A Clinical Reference. 2011.