3rd Annual Prescription Drug Abuse Symposium

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

Education Breakout Session

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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 barbiturates

3. Stimulants – Dexedrine, Adderall, Ritalin, Concerta

National Institute on Drug Abuse (NIDA) 2010
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):

<table>
<thead>
<tr>
<th>DSM-IV Criteria</th>
<th>Substance Dependence</th>
<th>Which means: Substance Abuse → Substance Dependence</th>
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</thead>
<tbody>
<tr>
<td>3 or more in past 12 months:</td>
<td>Increased amounts of substance to achieve intoxication</td>
<td>You may start out a typical substance abuser: recurrent, but intermittent trouble as a consequence of recreational binges.</td>
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<tr>
<td>1.</td>
<td>Withdrawal symptoms</td>
<td>Can progress into substance dependence: continuous and compulsive pattern of use</td>
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<td>2.</td>
<td>Use of substance in larger amounts/longer than intended</td>
<td>Substance Abuse as first step that eventually leads to Substance Dependence.</td>
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<td>3.</td>
<td>Unsuccessful attempts to cut back</td>
<td></td>
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<td>4.</td>
<td>Chronic behavior to obtain substance</td>
<td></td>
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<td>5.</td>
<td>Reduced activities due to substance use</td>
<td></td>
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<td>6.</td>
<td>Continue use even with physical problem</td>
<td></td>
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<tr>
<td>DSM-IV</td>
<td>Substance Abuse → Substance Dependence</td>
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<tr>
<td><strong>Physician’s Definition</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td><strong>Physiologic dependence</strong></td>
<td></td>
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<tr>
<td>“Physical Dependence” – Physiologic process; a predictable event in prescribing opioids, BZDs, barbiturates, and stimulants. Characterized by withdrawal if the drug is abruptly stopped and tolerance</td>
<td>Addiction</td>
<td></td>
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*The Free Dictionary by Farfex*
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:

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

IOM Institute of Medicine, Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. The National Academies Press, Washington DC 2011
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

US prescription opioid sales, 1997-2007

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

- 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

- 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

- 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

- 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

- 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 \textit{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.
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.
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

Substance Abuse and Mental Health Services Adm. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. HHS Pub 11-4658, 2011
Sources of Abused Prescription Medications
Office of National Drug Control Policy
April 25, 2012

- Recent Initiate Abusers: Obtained from friends for free or without asking
- Occasional Abusers: Prescribed from one or more physicians
- Chronic Abusers: Bought from friend/relative, dealer, or internet
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.
US Opioid Deaths

Indiana Opioid Deaths
(some may have multiple drugs) Source: ISDH
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.


***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)

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 abuse
- 32 emergency dept visits for misuse or abuse
- 130 people who abuse or are dependent
- 825 nonmedical users
References:

1. Indiana Center for Health Policy. Fatal Drug Overdoses: A growing concern in Indiana. Research for a Healthier Indiana; Mar 2008
References continued: