Abuse-Deterrent Opioid Formulations in Pain Management Decisions

Is now the time?

Supported by an educational grant from **Teva Pharmaceuticals**

CENTER FOR Independent Healthcare Education

Vemco MedEd VMC

Jointly provided by Center for Independent Healthcare Education and Vemco MedEd

Case Study

Bill – a patient with chronic low back pain

- Demographics:
  - 45 years old
  - Divorced, father of two children ages 11 and 16.
    - Shares joint custody with his ex-wife and has the children every other weekend and every other Thursday and Friday
  - Occupation – Real Estate sales
  - Hobbies – snow skiing, deep sea diving, ballroom dancing
  - Social life – dating, likes to have a glass or two of wine with dinner

Case Study

Bill – a patient with chronic low back pain

- History
  - Diagnosis
    - Chronic low back pain, injured in a snow ski competition
    - Patient rates pain as 6–7 on a “0 to 10” scale
- Patient goals:
  - Become more functional again, allowing him to continue his hobby of competitive downhill ski racing
  - Not to be considered a “druggie” by his kids

Case Study

Bill – a patient with chronic low back pain

- Treatment plan:
  - Initially started on NSAIDs and Tramadol prn
  - Due to unresolved pain, and diminished functioning, two months ago the patient's primary care physician prescribed the following:
    - » Gabapentin, of which the patient is currently receiving 600 mg TID.
    - » Hydrocodone + acetaminophen 10/325 mg, 1 tablet up to four times a day. Patient states that he takes on a regular basis three times a day.
    - » Pharmacist notes that the patient appears to be compliant with his gabapentin and is using about 120 tablets of the hydrocodone-acetaminophen per month.

Determining the Right Patient

Pain Relief Seeking

- Disease progression
- Poorly opioid responsive pain
- Withdrawal mediated pain
- Opioid analgesic tolerance
- Opioid-induced hyperalgesia

Pain Relief and Drug Seeking

- e.g. pain with co-morbid addiction, patient taking some for pain and diverting some for income

Drug Seeking

- Addiction
- Other psychiatric diagnosis
- Criminal intent (diversion)

Ethical Principles of Pain Management

- Balancing act
  - “Prevent harm”, “Remove harm”, “Do good”
  - “Provide compassionate care”
  - “Do no harm”
  - “Patient rights”

Chronic Pain is a Serious Public Health Issue

- Chronic pain affects millions of U.S. adults on a daily basis[1]
  - Includes conditions such as low back pain, osteoarthritis, cancer pain
  - May impact routine activities
- Patient-centered, multimodal, multidisciplinary treatment approach is the cornerstone of best-practice model
  - Medical, interventional and non-interventional approaches
- Opioids may offer substantial long-term benefit and improved quality of life

1. **Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. 2011. Available at: https://www.ncbi.nlm.nih.gov/books/NBK91497/.**

Opioids as a "Friend" of Pain Management

- As sole entities, no risk of GI bleeds, renal toxicity, hepatotoxicity
- Strongest of analgesics
- Quick onset
- Ability to dose-titrate upwards rapidly with many opioids
- Ability to provide analgesia in a variety of pain syndromes

Opioids as a "Foe" of Pain Management

- Sedation, constipation
- Risk of dependency, addiction
- Lack of anti-inflammatory effect
- Tolerance, neuroadaptation, hyperalgesia
- Potential of misuse, abuse and diversion

Prescription Pain Medications… good, bad, ugly?

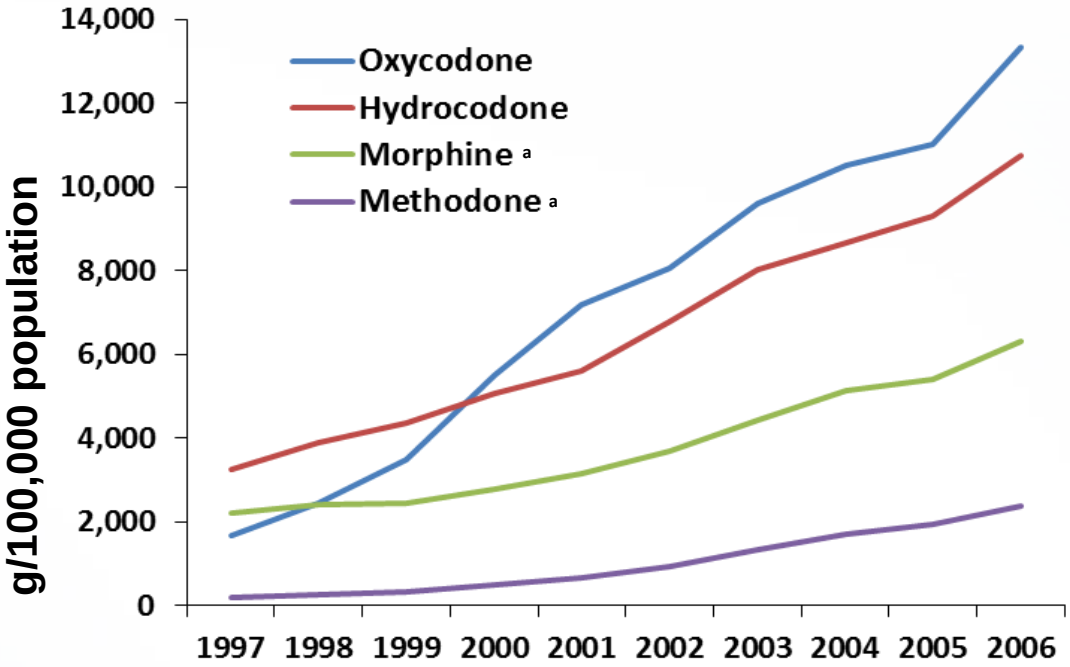
- Prescription drugs are abused more often than any other drug, except marijuana and alcohol.
- A recent study indicated that >54 million people aged ≥12 years had abused prescription drugs at some point in their lives and nearly 15 million people had done so in 2014.
  - More than 6.5 million people had abused prescription drugs in the month preceding the study and would qualify as current abusers.
  - Represents >2.5% of population age 12+ years old

Substance Abuse & Mental Health Services Administration (SAMHSA). *Prescription Drug Misuse and Abuse.* Available at: http://www.samhsa.gov/prescription-drug-misuse-abuse. (last updated Sept. 29, 2014).
Center for Behavioral Health Statistics & Quality, SAMHSA & RTI International. Available at: http://www.samhsa.gov.

Opioid Use for Chronic Noncancer Pain

- Opioids are increasingly prescribed to treat moderate-to-severe pain in patients with nonmalignant diseases[1,2]
- Common conditions treated with opioids include back pain, osteoarthritis, fibromyalgia, and headache[2]

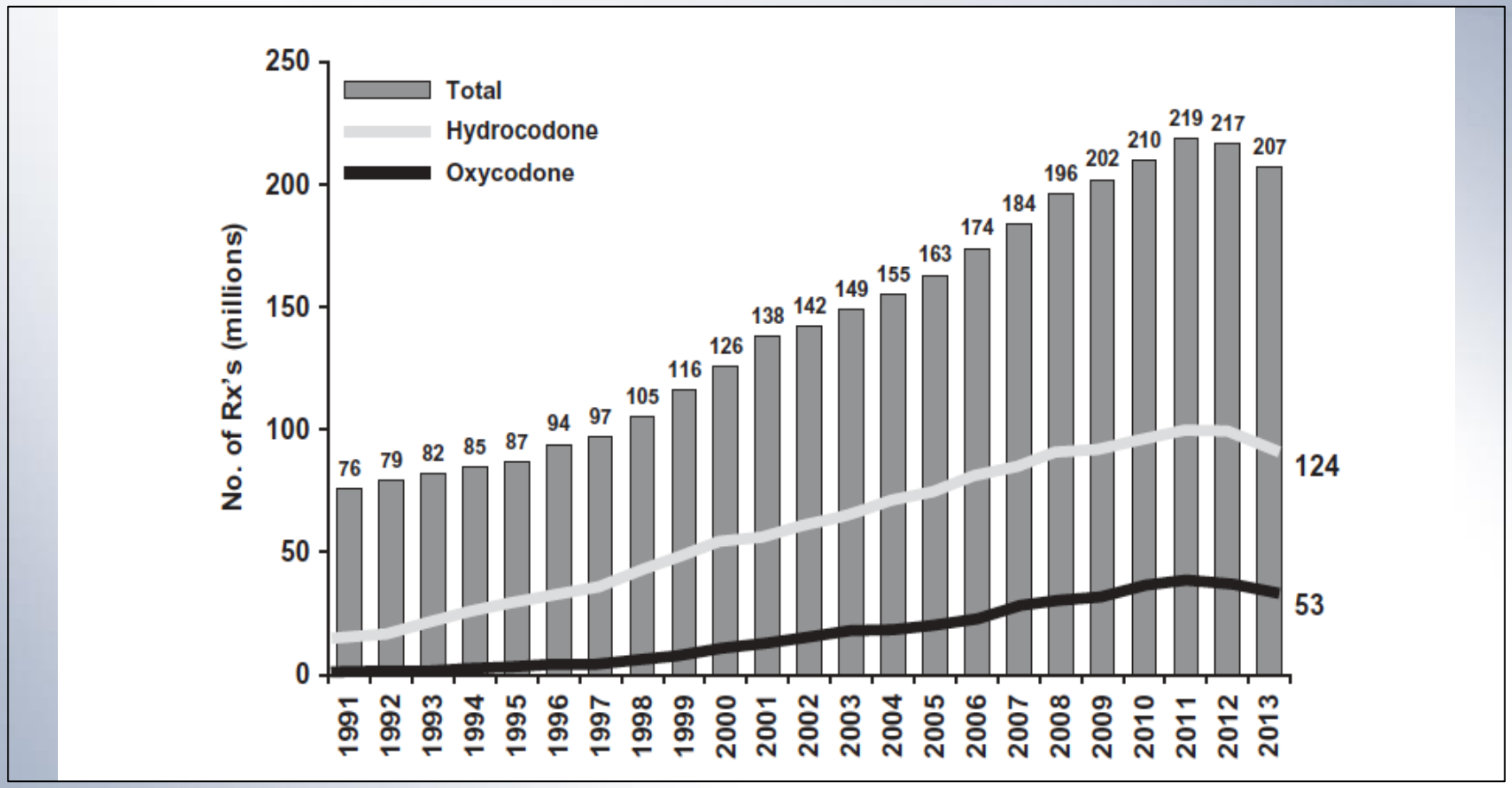
Therapeutic Opioid Use in US (g/100,000 population)[1]



[a]For year 2000, data is not available, the average of 1999 and 2001 was taken.
Used with permission.

1. Manchikanti L, Singh A. *Pain Physician*. 2008;11(suppl):S63-S88.
2. Chou R, et al. *J Pain*. 2009;10:113-130.

Opioid Prescriptions in the US 1991 - 2013

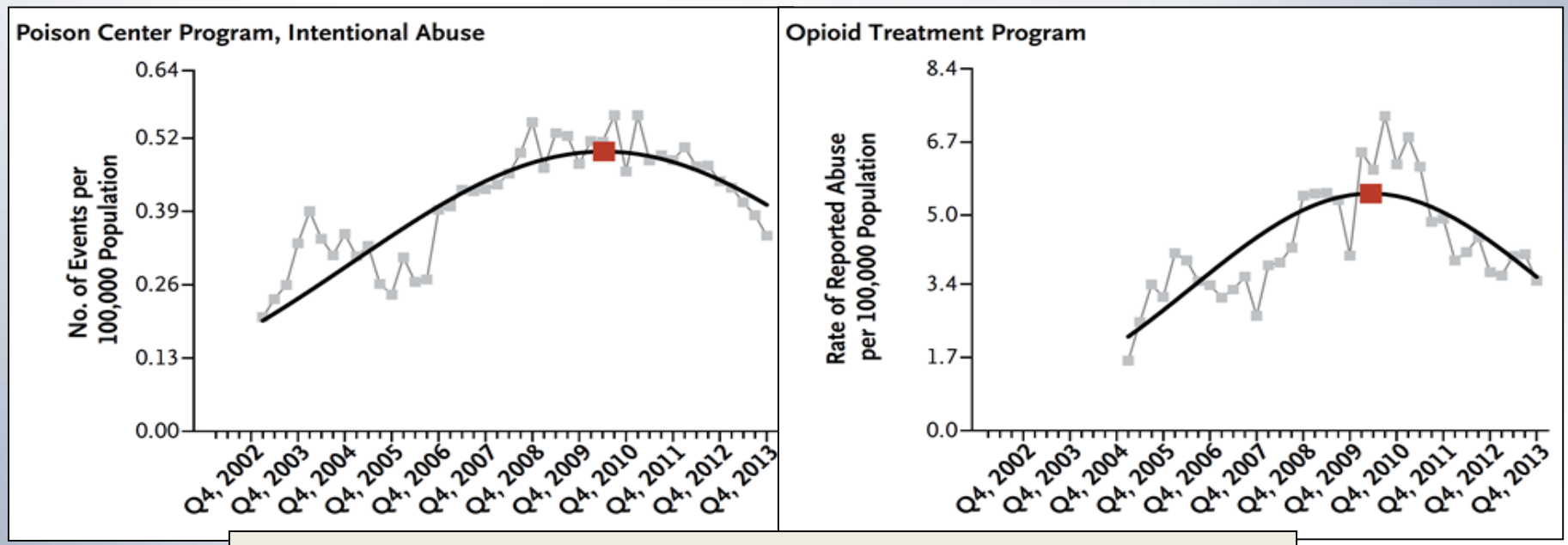


Opioid prescriptions dispensed by US retail pharmacies. IMS Health, National Prescription Audit, Years 1997–2013, Data Extracted 2014

Diagram from: Gudin JA, Nalamachu SR. *Postgraduate Medicine*. 2016;128:97-105.

A Step in the Right Direction?

Several indices have shown rates of abuse and diversion have decreased from 2010 to 2013



How might we continue to improve upon this?

Reproduced from Dart RC, et al. *N Engl J Med*. 2015;372(3):241-248.

Abuse and Diversion of Opioids a Public Health Issue

- Four-fold increase in deaths associated with opioids since 1999[1,2]
- 420,000 ED visits in 2011 related to misuse or abuse of Rx opioids[3]
- Abuse costs payers >$72 billion per year in direct healthcare costs[4]

1. CDC/HCHS, National Vital Statistics System, Mortality File. Available at: https://www.cdc.gov/nchs/nvss/deaths.htm.
2. CDC National Center for Health Statistics 2016. Available at: https://www.cdc.gov/nchs/data/databriefs/db166.htm.
3. SAMSHA: Highlights of the 2011 Drug Abuse Warning Network (DAWN) findings on drug-related emergency department visits. 2013. Available at: https://www.samhsa.gov/data/sites/default/files/DAWN127/DAWN127/sr127-DAWN-highlights.pdf.
4. Katz NP, et al. *Am J Managed Care.* 2013;19:295-302.

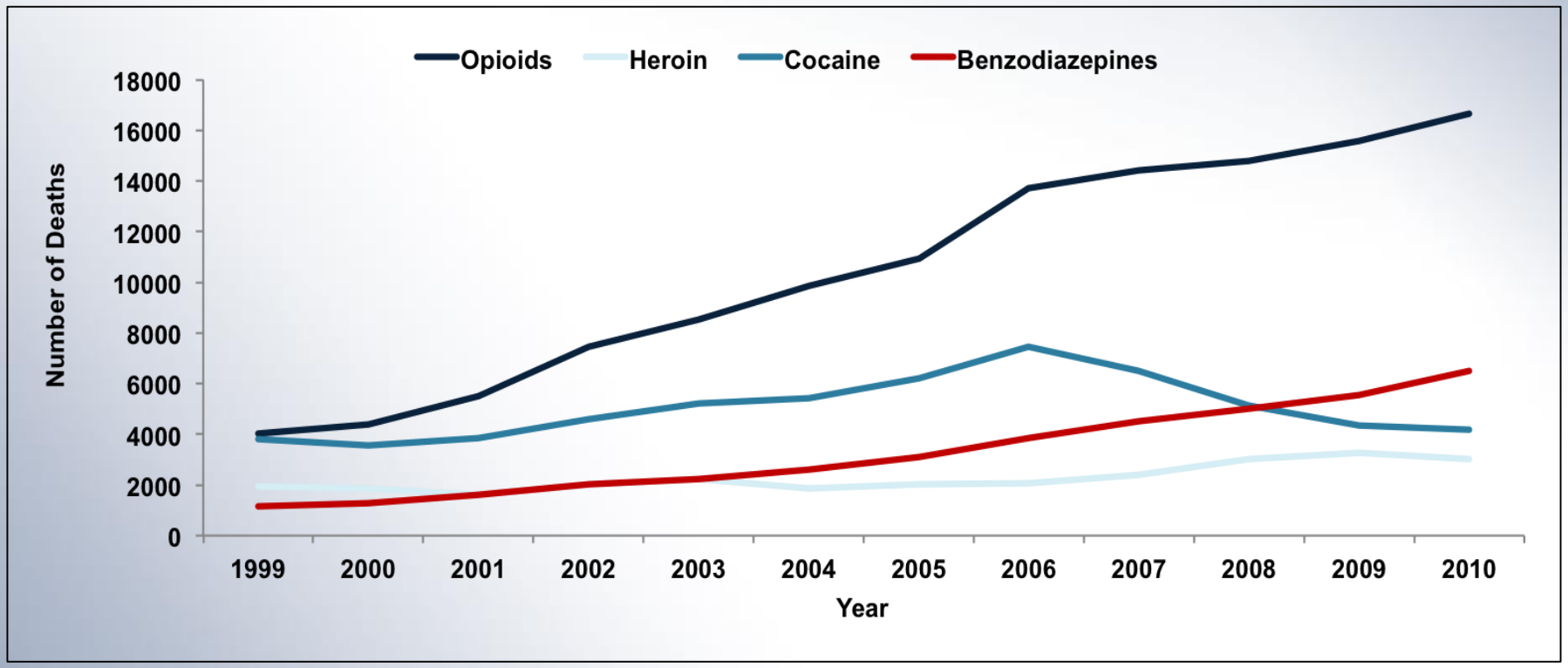
The Human Toll

- Prescription drug abuse has led to health problems, addiction and death.
  - Statistics show that 44 people die in the United States every day from an overdose of prescription painkillers, more than cocaine and heroin combined.
  - In 2014, prescription drug abuse accounted for nearly 22,000 drug overdose deaths (half of all drug overdoses).
    - Two types of prescription drugs are largely responsible: painkillers (opioid analgesics) and tranquilizers (benzodiazepines).
    - More than 16,000 of the prescription drug overdose deaths were related to the painkillers.

CDC. *Understanding the Epidemic.* Available at: http://www.cdc.gov/drugoverdose/epidemic/public.html.
CDC, *CDC Grand Rounds: Prescription Drug Overdoses — A U.S. Epidemic. Morbid Mortal Wkly Rep*. 2012;61(01):10-13. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm.
Levi J, et al. Trust for America's Health & Robert Wood Johnson Foundation. Available at: http://healthyamericans.org/assets/files/TFAH-2015-InjuryRpt-final6.18.pdf.

Unintended Consequences of Opioid Use

Drug Overdose Deaths by Major Drug Type
United States, 1999–2010



Centers for Disease Control. Primary Care and Public Health Initiative. Prescription Drug Abuse and Overdose: Public Health Perspective. October 24, 2012. Available at: http://www.supportprop.org/resources/prescription-drug-abuse-and-overdose-public-health-perspective/.

Balancing Access to Chronic Pain Therapy While Lessening Abuse

- Opioids have proven benefit for patients with pain disorders
- Patients need access to opioids to optimally treat chronic pain conditions
  - Pharmacies not stocking opioids
  - Pharmacists rejecting prescriptions / refusing to fill
- Physicians ostracized if they treat “too many” pain patients.
- Prescribers need to work jointly to manage risk while maintaining availability

Regulatory Attempts at Making Extended-Release Opioids Safer

FDA 2014 REMS Blueprint

- **STEP 1:** Voluntary Extended-Release Opioid Analgesic Education Programs
  - Goals of programs:
    - Understand how to assess patients for treatment with ER/LA opioid analgesics.
    - Be familiar with how to initiate therapy, modify dose and discontinue use of ER/LA opioid analgesics.
    - Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
    - Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
    - Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

FDA 2014 REMS Blueprint

- **Step 2:** FDA ER Opioid Labeling Changes
  - New indication for ER/LA opioid analgesics.
    - “Indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.”
    - "Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [Tradename] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.”

FDA 2014 REMS Blueprint

- **Step 2:** FDA ER Opioid Labeling Changes *(continued)*
  - Updated language for the following Warnings and Precautions:
    - Addiction, Abuse, and Misuse
      - ER/LA Opioid Analgesics exposes users to risks of addictions, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions.
    - Life-Threatening Respiratory Depression
      - Serious life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow ER/LA Opioid Analgesics tablets whole to avoid exposure/ingestion to a potentially fatal dose.

The Impact of State Policy and Systems-Level Interventions on Prescription Drug Overdose

Intervention	Findings
State legislation • Pill Mills, Doctor Shopping, and Good Samaritan laws	**Low evidence quality** from 3 states where multiple efforts in place at the same time with inadequate controls
Prescription drug monitoring programs	**No clear effects** on total opioid prescribing or health outcomes. Data only up through 2008, Impact of proactive reporting or provider mandates not known
Insurance and pharmacy benefits manager	**Low evidence quality** because lack of comparison groups, short-term follow-up and inadequate statistical testing
Safe storage and disposal	**Extremely low evidence** quality from lack of baseline data and comparison groups, small sample size, short-term follow-up, health outcomes not assessed and inadequate controls
Clinical guidelines	**Low evidence quality** from lack of baseline data and comparison groups, small sample size, short-term follow-up and inadequate controls
Education: Patient and Providers	**Moderate to low evidence quality**. Few studies of patient education. Studies of providers find some adoption of safer prescribing, but less impact on patient outcomes
Naloxone distribution	**Some evidence of effectiveness** in reducing opioid overdose death rates, but overall low evidence quality. Data based on people who inject heroin

Haegerich TM, et al. *Drug Alcohol Depend.* 2014:145;34-47.

CDC Guidelines for Prescribing Opioids for Chronic Pain (2016)

- Twelve specific recommendations surrounding patient selection, dosing limits, monitoring patients, referrals for addiction and goals of care.
- Categorization of recommendations based on their assessment:
  - No evidence shows a long-term benefit of opioids in pain and function for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials <6 weeks in duration).
  - Extensive evidence shows the possible harms of opioids (including abuse and dependence, overdose, myocardial infarction, motor vehicle crashes).
  - Extensive evidence suggests benefits of alternative treatments compared with long-term opioid therapy, including nonpharmacologic therapy and nonopioid pharmacologic therapy, with less harm.

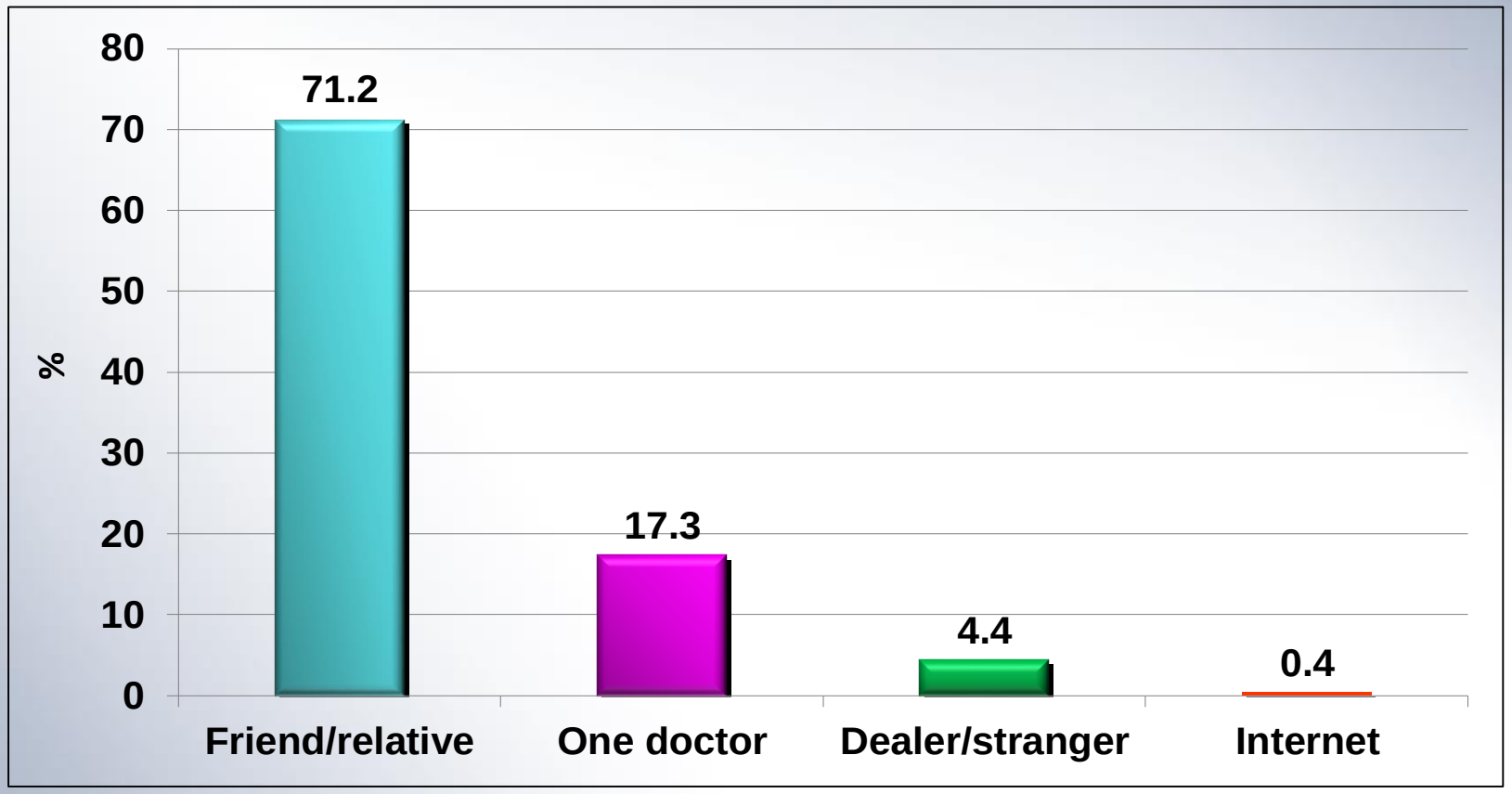
Misuse, Abuse, Diversion

Is there any way to stop this?

Definitions

- **Misuse**
  - Using an opioid for purposes other than intended
    - Depression, sleep, anxiety, constipation pain, euphoria, “party time”
- **Abuse**
  - Manipulating an opioid delivery system, or using an opioid at a higher than prescribed dose to attempt to obtain a faster onset, or greater euphoria
  - FDA definition: “Intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect”
- **Diversion**
  - Selling/giving/buying a portion of a prescription to/from another person
  - Stealing medication from a friend/relative/stranger

Pain Relievers Obtained for Nonmedical Use



***Source of drugs for the most recent nonmedical use of pain relievers reported by persons aged 12 or older in the United States 2010.**

SAMHSA. *Results From the 2010 National Survey on Drug Use and Health.* HHS Publication No. (SMA) 11-4658, 2011. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUHNationalFindingsResults2010-web/2k10ResultsRev/NSDUHresultsRev2010.pdf.

What are Some Common Methods of Abuse?

Primary routes of opioid abuse[1]	• Oral (chewing, swallowing additional pills) • Inhaling (e.g., snorting, vaporization) • Parenteral (IV, IM, SC) • Smoking
Primary forms of opioid manipulation[2]	• Crushing or grinding into small particles or powder • Dissolving in a solvent (e.g., alcohol, acetone) • Extraction by exposure to hot or cold temperatures (microwaving, freezing)

IV, intravenous; IM, intramuscular; SC, subcutaneous

1. Schaeffer T. *J Med Toxicol*. 2012;8(4):400-407.
2. U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling. April 2015 https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

Routes of Abuse: Prescription Opioid Analgesics

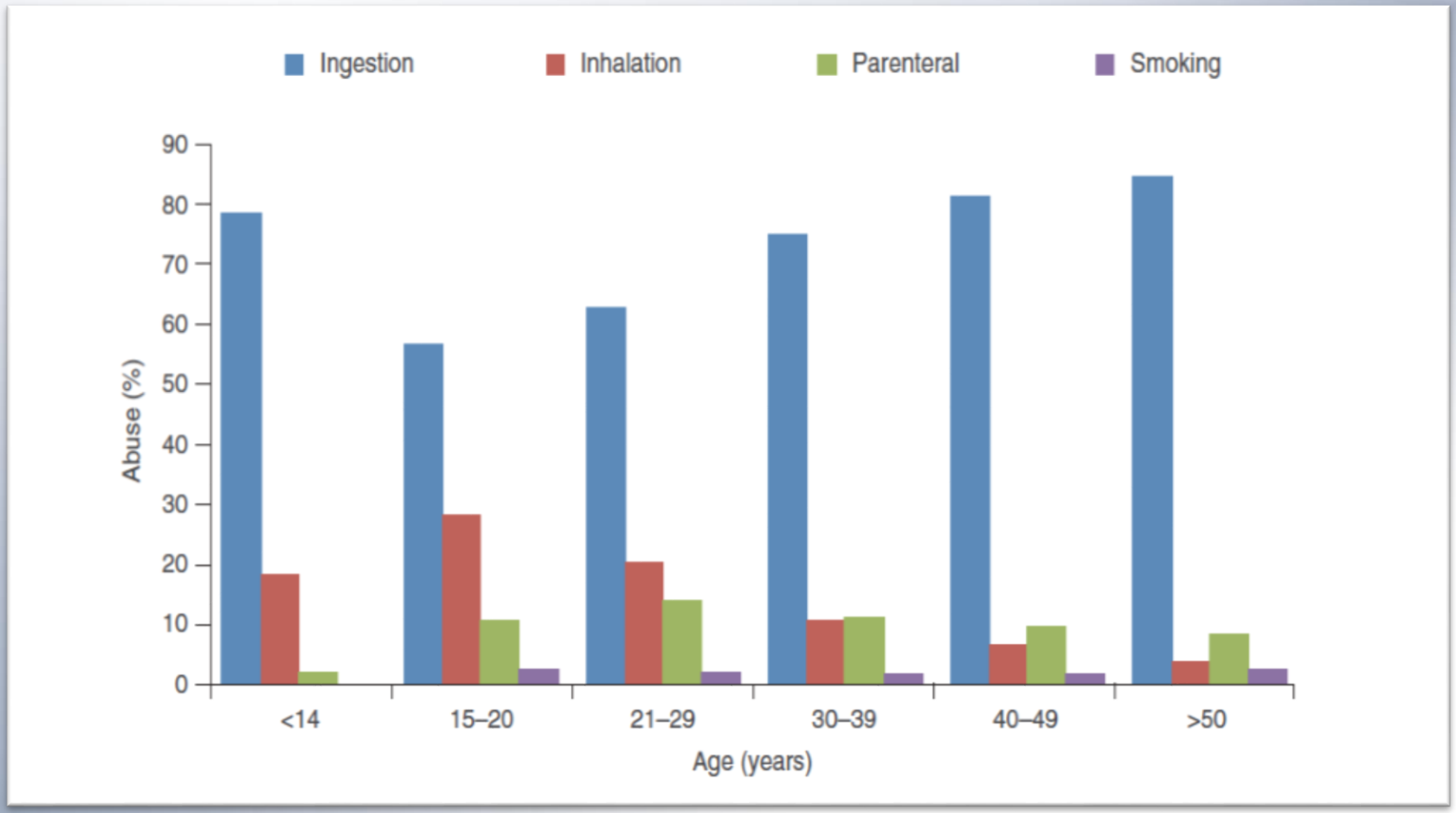
Table 1. Key US data on routes of abuse of prescription opioid analgesics.

Population	Year	No. of subjects	Route of abuse (%)		
			Oral	Inhalation*	Injection
Individuals categorized as "users" of OxyContin presenting at substance-abuse treatment programs	2001–2004	981	72	11	17
Drug users in New York City	2004–2006	586	68	15	4
Undergraduate university students	2005	4580	97	18	0.5
Prescription opioid abusers	Not specified	791	91	68	24
Substance abuse admissions/Treatment Episode Data Set (TEDS)	2012	169,868	59	24	17

*Including snorting, smoking and inhaling.

Table from: Gasior M, et al. *Postgraduate Medicine.* 2016;128:85-96.

Route of Abuse of Prescription Opioid Analgesics According to Age



Graphic from: Gasior M, et al. *Postgraduate Medicine.* 2016;128:85-96.
Katz N, et al. *Am J Drug Alcohol Abuse*. 2011;37:205–217.

Opioid Abusers Usually Seek to Convert ER Opioid to IR Opioid

- Physical manipulation of ER opioid is typical
  - Abusers crush and grind
  - Some seek chemical extraction with solvents

- Abuse quotient (AQ = C_{max}/T_{max})
  - A measure of the average rate of increase in plasma opioid concentration over the interval between treatment administration and the time of maximum opioid concentration
  - High C_{max} and short T_{max} = HIGH abuse quotient

Majority of Abusers Spend <10 Minutes Manipulating ER Opioids

- Goal of ADF is to curb abuse for majority of abusers
- Many ADFs can be defeated with time and effort
- Knowing most common abuse methods allows appropriate evaluation of AD potential

Sellers EM, et al. *J Psychopharmacol*. 2013;27:808-16.
Perrino PJ, et al. Relative attractiveness of oxycodone/naloxone (OXN): comparative assessment of tampering potential and recreational drug user preferences for different opioid formulations. Presented at PainWeek. 2013. Abstract #86.

Defeating ADT…

(Fudin J. Pharmacy Times. January 25, 2015)

"None of the ADFs can address one lingering concern: all medications can be misused and abused if the user ingests medications that are not prescribed to them or ingests more tablets than prescribed, regardless of the technology."

"Furthermore, there are ways to circumvent some of these ADFs. Google "methods to crush OxyContin." There are several blogs and YouTube videos that offer techniques to crush the new formulation of OxyContin. A blog called Bluelight suggests that OxyContin users can place the drug into their mouths for roughly 1 to 2 minutes to dissolve the coating, and then allow it to dissolve in acidic beverages such as lemon juice or root beer. Once in the beverage, the tablets expand and start to break apart (in as little as 2 to 4 hours) and are easy to consume."

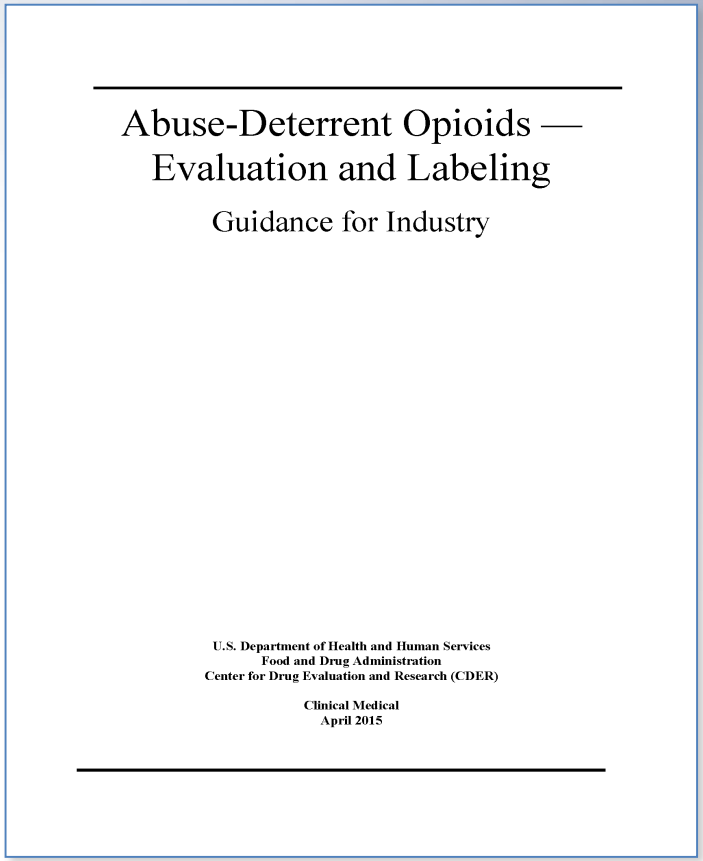
Case Study *(continued)*

Bill – a patient with chronic low back pain

- Follow-up
  - Primary care physician wants to put the patient on an extended-release opioid
    - The physician calls you to inquire regarding the safety of extended-release opioids with abuse-deterrent technologies (ADT).
    - The physician understands that there are three different extended-release hydrocodone products available with each claiming to have some sort of ADT, but are there differences between the products that would help the prescriber make the best decision for Bill?

Abuse-Deterrent Opioids – Evaluation and Labeling April 2015

- Replaces January 2013 Draft Guidance
- Explains FDA's current thinking about the studies that should be conducted
- Makes recommendations about how those studies should be performed and evaluated
- Outlines how to describe studies and their implications on product labeling



Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Clinical Medical
April 2015

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling. April 2015. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

Ideal Characteristics of Abuse-Deterrent Technology

- Minimize impact of abuse / misuse by retaining ER properties following manipulation
- Target known or expected routes of abuse by majority of abusers
- Deter intentional abuse, make less attractive to abusers
- Protect patients from rapid release of opioid from either innocent / unintentional or from intentional product manipulation
- Protect patients from dose-dumping with alcohol

Industry's Approaches to Abuse-Deterrent Opioids

The FDA Has Identified 7 Categories of Abuse-Deterrent Technologies

Agonist/Antagonist Combos

- May curb euphoria when formulation compromised
- Antagonist may be formulated to be clinically active only when tampered with

Aversion

- Substances may be added to create unpleasant effects when tampered with or taken at higher doses

Delivery System

- Drug-release designs or method of drug delivery can offer resistance to abuse

New Molecular Entities and Prodrugs

- May require enzymatic activation, different receptor binding profiles, slower CNS penetration, or other novel effects

Physical/Chemical Barriers

- May prevent chewing, crushing, cutting, grating, or grinding
- May resist extraction by solvents

Combination

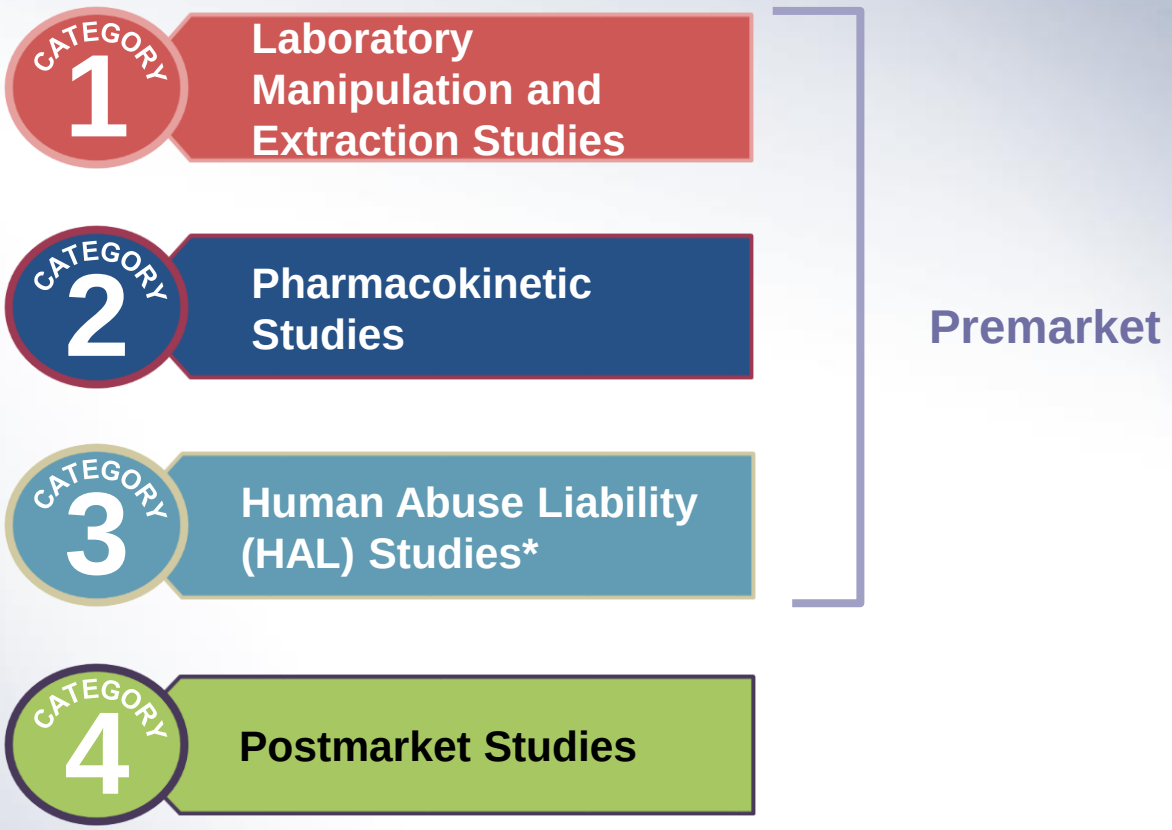
- Use of 2 or more technologies in 1 product to deter abuse

Novel Approaches

- Use of technologies not captured by any of the above

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling. April 2015. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

Study Categories to Evaluate Abuse-Deterrent Technologies



*** Also called human abuse liability (HAL) studies.**

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling. April 2015. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

CATEGORY 1

Laboratory Manipulation and Extraction Studies

Evaluate how easily the formulation can be manipulated and opioid extracted

Overview

Rationale for Category 1 Studies

- Evaluate how easily the formulation can be manipulated
- May also evaluate route-specific manipulation, such as:
  - Snorting (particle size distribution)
  - Smoking (vaporization temperature)
  - Injecting (concentration and viscosity)
  - May also provide information on crushing (particle size), exposure to temperature extremes, and/or solubility in common solvents

Mechanical Manipulation Studies

- Primary interest is particle size, which may influence opioid extractability
- Ordinary tools/utensils should be employed in testing





- Effect of heat and cold on mechanical manipulation

Solubility Studies

- Determine ease of solubility with various solvents (e.g., water, vinegar, ethanol, isopropanol, acetone, mineral spirits)

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling. April 2015. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

CATEGORY 2 Pharmacokinetic Studies[1]

Evaluate in vivo PK profiles of manipulated and intact formulations of drug vs. comparator

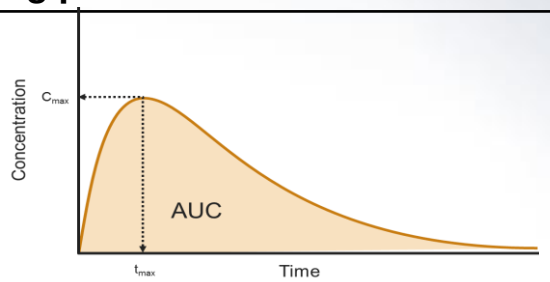
Overview

Rationale for Category 2 Studies

- Evaluate in vivo PK profiles of manipulated and intact drug vs. comparator[1]
- Can provide information on potential abuse quotient (C_{max}/T_{max})[1,2]
- Rate of rise and peak concentrations evaluated[1]
- May be used to study effect of alcohol and food on drug plasma concentration[1]

PK Endpoints[1]

- Maximum plasma concentration (C_{max})
- Time to reach C_{max} (T_{max})
- Area under the curve (AUC)
- Terminal elimination half-life



Other Areas of Interest (Intact vs. Manipulated Formulations)[1]

- Rate of rise of drug concentration (thought to contribute to abuse potential)
- Effect of food/alcohol on systemic exposure
- Adverse events

1. U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling. April 2015. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.
2. Webster LR. The question of opioid euphoria. http://www.dddmag.com/articles/2009/07/question-opioid-euphoria.

CATEGORY 3 — Human Abuse Liability (HAL) Studies*

Assess impact on appeal to abusers

In general, FDA recommends using a bipolar scale for the primary measure of drug liking

Overview

Rationale for Category 3 Studies:

- To assess the impact of formulation on appeal to abusers (i.e., drug liking) in a controlled environment
- Can be conducted for various routes of abuse

Evaluate impact of manipulation on:

- Onset
- Peak duration of activity
- Offset

Measurements of Interest

- Drug liking (E_{max})
- Good effects
- Bad effects
- Likelihood to use drug again

Bipolar Scale

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling. April 2015. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

Evaluation of ADT Testing

Category 1

- What tools were used to manipulate the formulation?
- What solvents were used for chemical extraction?
- How many routes of abuse were assessed?

Category 2

- What pharmacokinetic endpoints did the studies include?
- Is there a food or alcohol effect?
- What routes of abuse were tested?

Category 3

- How many Human Abuse Liability (HAL) studies were conducted?
- What routes of abuse were evaluated?
- How rigorous was the conduct of these studies?

Currently Available ER Opioids with ADT

Product Name	Opioid used	Description of technology *(in descending order of date of FDA product approval)*
Embeda®	Morphine	Addition of sequestered naltrexone – designed to release antagonist if crushed, and then snorted, or crushed, dissolved and then injected intravenously
OxyContin®	Oxycodone	INTAC polyethylene oxide matrix – designed to render tablet highly resistant to crushing; when exposed to water forms a gel leading to difficulty drawing into a syringe.
Opana®	Oxymorphone	INTAC polyethylene oxide matrix – designed to render tablet highly resistant to crushing; when exposed to water forms a gel leading to difficulty drawing into a syringe.
Nucynta®	Tapentadol	Polyethylene oxide matrix – designed to render tablet highly resistant to crushing or extraction of active drug (not FDA approved as having ADT)
Exalgo®	Hydromorphone	OROS technology - osmotically active bilayer core enclosed in a semipermeable tablet shell membrane – designed to minimize crushing and active drug extraction
Targiniq®	Oxycodone	Addition of naloxone – designed to block the euphoric effect if it's crushed and then snorted, or crushed, dissolved and then injected intravenously.

Currently Available ER Opioids with ADT *(cont.)*

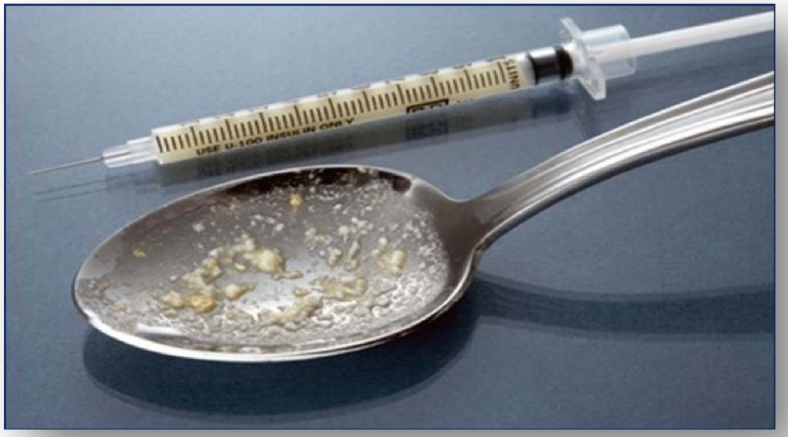
Product Name	Opioid used	Description of technology *(in descending order of date of FDA product approval)*
Hysingla®	Hydrocodone	Resistec polymer matrix – designed to be plastic-like, hard to break, becomes gel in water, thus difficult to use in a syringe
Zohydro®	Hydrocodone	BeadTek formulation – designed to make it hard to crush and snort. Not FDA-approved as ADT technology
Xtampza®	Oxycodone	DETERx microsphere technology – manipulation resistant, has no FDA warnings regarding crushing, chewing or breaking
Troxyca®	Oxycodone	Addition of sequestered naltrexone – designed to release antagonist if crushed, and then snorted, or crushed, dissolved and then injected intravenously
Ventrela®	Hydrocodone	CIMA technology combines three physical and chemical barriers (gelling, barrier and matrix) as a deterrent against the main forms of abuse: Crushing for snorting, IV extraction, and dose dumping in alcohol.
Arymo™ ER	Morphine sulfate	Guardian technology – polymer matrix tablet technology that resists physical and chemical manipulation; forms viscous hydrogel upon contact with liquid

Polymer matrix ADT

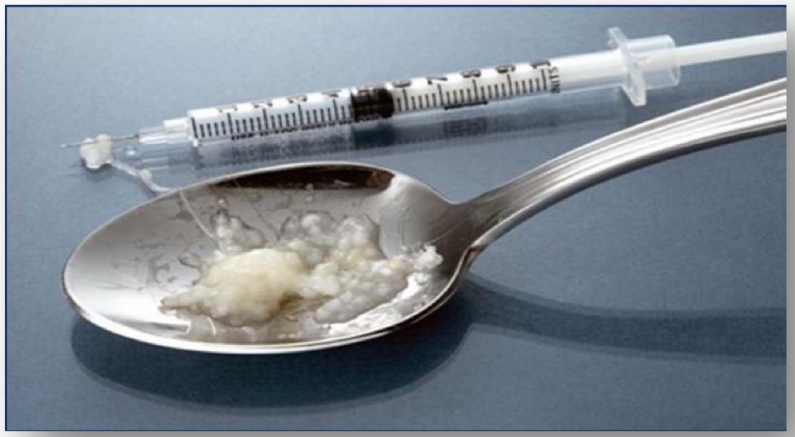
(usually polyethylene oxide-based)

(similar to INTAC / Resistec ADT technologies)

Original formulation

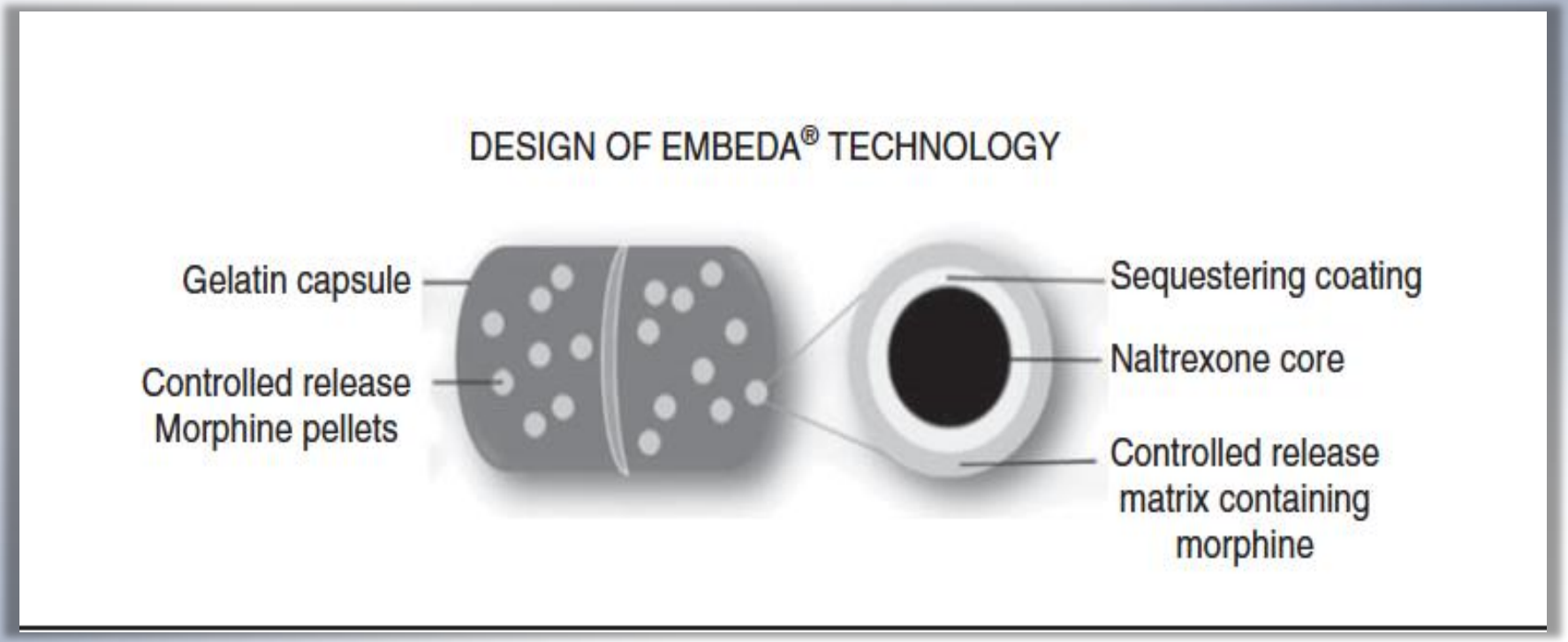


ADF



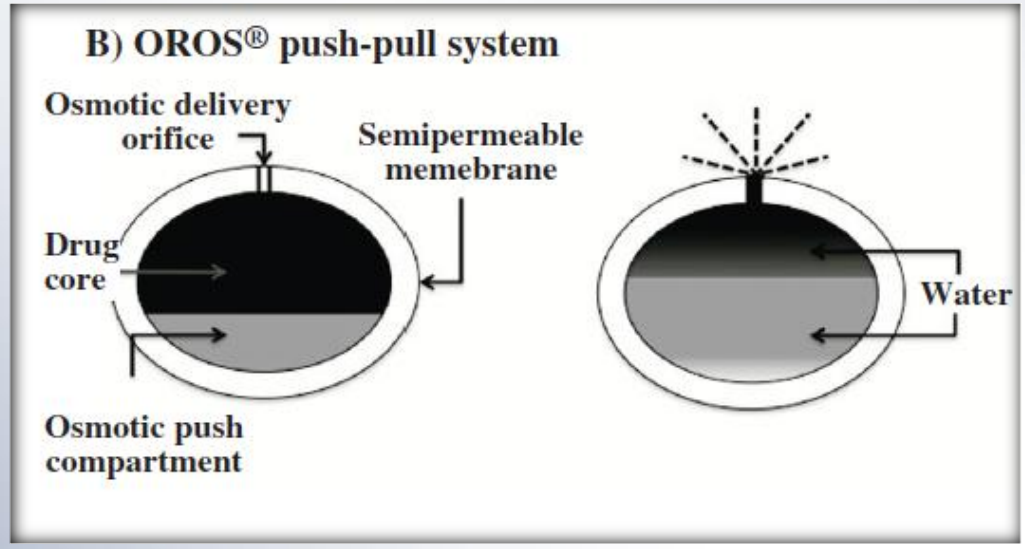
Nguyen V, et al. *J Clin Pharm Therap*. 2015;40:629-34.

Sequestration of Antagonist



Mastropietro DJ and Omidian H. ***Expert Opinion on Pharmacotherapy.*****16:3, 305-323.**

Osmotic Controlled-Release Oral Delivery System (OROS)



Graphic from: Coluzzi P. *Minerva Anestesiol*. 2010;76:1072-84

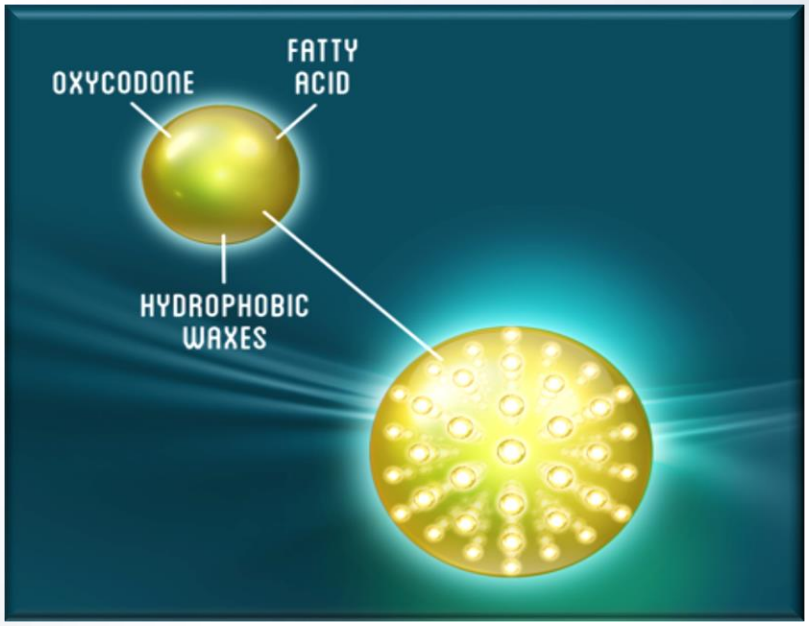
- Semipermeable capsule with a laser-drilled hole in it
- The opioid is placed inside the hollow casing
- Tablet moves through the body, water passes through the case and is absorbed by an expandable chamber, which slowly pushes the drug out through the hole over several hours for an extended effect.

ADT Technology Elements

- The hardened case functions as a barrier to drug abusers, making it extremely difficult to crush.
- Crushing the tablet typically results in large fragments of irregular shape that form a thick solution in small volumes of aqueous solution

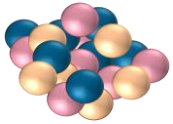
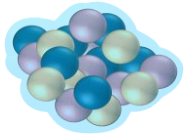
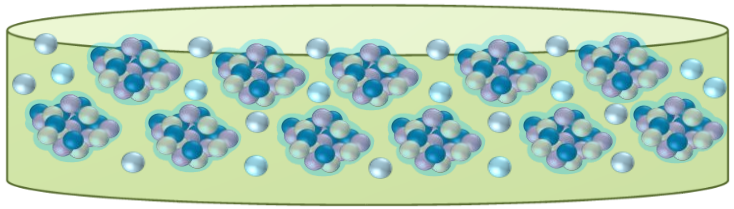
DETERx® ADT Technology

- Oxycodone base + inactive ingredients form a lipophilic salt[1,2]



1. Xtampza ER [prescribing information]. Canton, MA: Collegium Pharmaceutical, Inc; 2016.
2. US Food and Drug Administration. FDA advisory committee briefing document: Xtampza ER (extended-release oxycodone).Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM461640.pdf. Published September 11, 2015.

CIMA ADT: A Multifaceted Approach

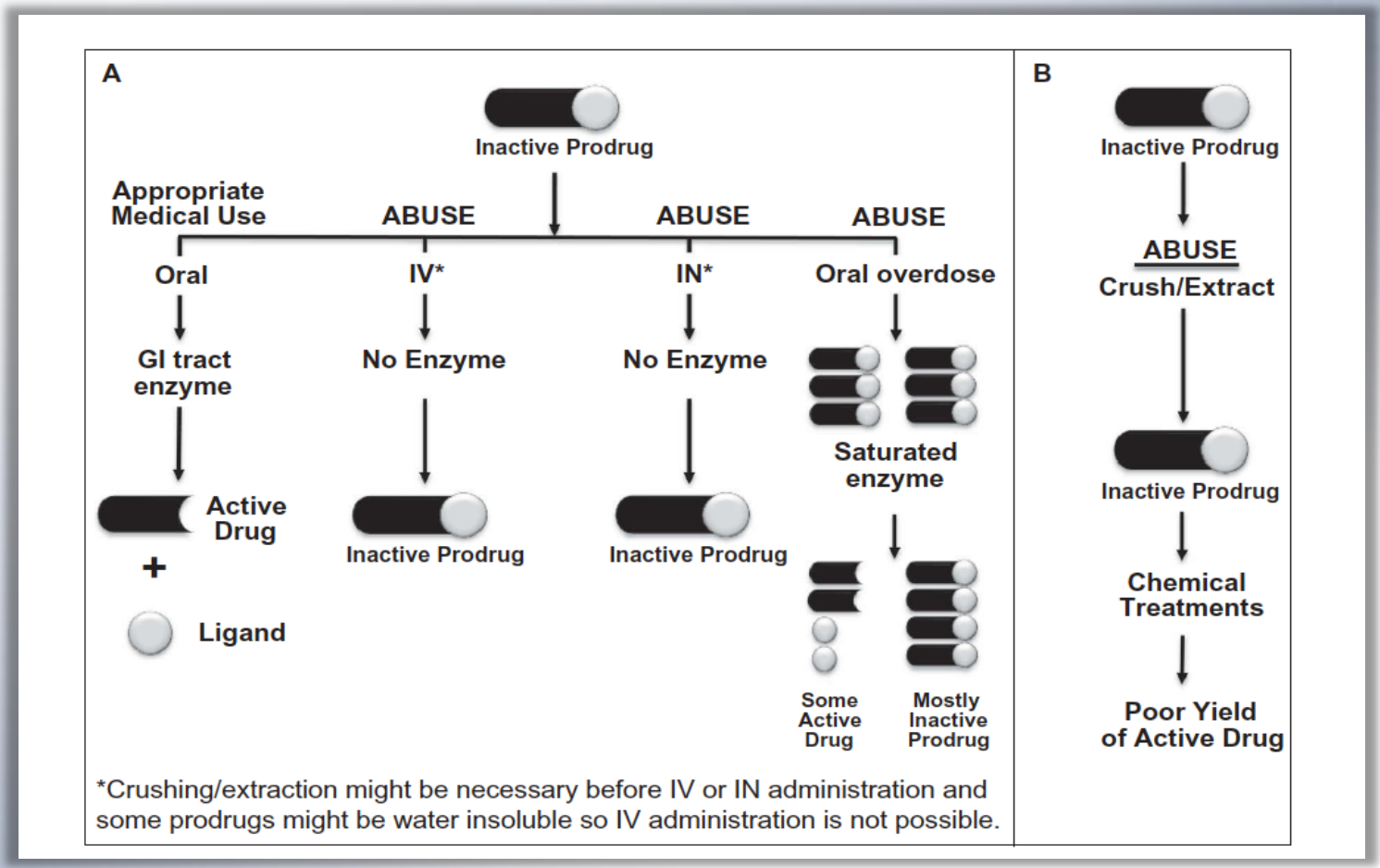
CIMA ADT	
Formulated with 2 polymers: • Polymer 1 is insoluble in alcohol • Polymer 2 is insoluble in water	
Undergoes high shear granulation to resist crushing and small volume solvent extraction	
Fluid bed coating applied to provide an additional barrier to crushing	
Blended with additional polymers and compressed into tablets to add another barrier to alcohol-induced dose dumping and small volume solvent extraction	

Data on file; Teva Pharmaceuticals USA, Inc.

Prodrug Technology for Abuse-Deterrent Opioids

- Prodrugs are chemically-modified versions of pharmacological agents that must undergo transformation in the body to release the active drug
- FOR ADT:
  - Prodrug itself would be inactive at opioid receptors.
  - Only through oral administration would the prodrug become activated as the enzymes necessary to release the active drug are only present in the GI tract.
  - Intravenous and intranasal administration would yield little or no active drug.
  - Overdose protection may be possible if the activating enzyme system is saturable.

Ideal Abuse-Deterrent Prodrug



IN, Intranasal; IV, Intravenous.

Diagram from: Gudin JA, Nalamachu SR. *Postgraduate Medicine*. 2016;128:97-105.

ADT Prodrugs in Development

- KP201: A prodrug of hydrocodone with putative abuse deterrence (benzhydrocodone hydrochloride) is being developed by KemPharm, Inc., Coralville, IA
  - Covalent attachment of a benzoic acid group (ligand) to the active drug, hydrocodone, resulting in benzhydrocodone
  - KP201 is activated by GI tract enzymes that cleave the ligand from the hydrocodone moiety, resulting in the release of active drug
- KP511: A chemically-modified form of hydromorphone, formed by the addition of one or more ligands to hydromorphone
  - Animal data suggests that at high oral supratherapeutic doses, KP511 may only release limited amounts of hydromorphone

Case Study - *continued*

Bill – a patient with chronic low back pain

- Physician calls the pharmacist:
  - Primary care physician asks you if the use of a ER opioid product will eliminate the risk of abuse and/or misuse of the opioid by the patient or his children.

Mythology of ADT Technology

- **MYTH:** ADT prevents all abuse/misuse/diversion
  - Pearls:
    - The right ADT can be an important extra tool to assist providers in preventing misuse / abuse
    - ADT does not prevent the swallowing of supratherapeutic doses of non-manipulated product
    - ADT does not prevent improper prescribing
      - PRN use of extended-release opioids
      - Prescriptions for “half-tablets”

Mythology of ADT Technology

- **MYTH:** All ADT technology is fail-safe
  - Pearls:
    - No FDA-approved product has been proven to 100% resist all extraction methods
      - But some currently available ER opioids with ADT have proven very resistant to both standard tools and solvents as well as advanced extraction techniques

Mythology of ADT Technology

- **MYTH:** ADT technology alone will ensure that my patients will not misuse, abuse or divert their opioids
  - Pearls:
    - Universal precautions are still part of “best practices”

Common Universal Precautions

- Comprehensive pain assessment including opioid misuse risk assessment
- Formulation of pain diagnosis(es)
- Opioid prescriptions should be considered a test or trial; continued or discontinued based on assessment and reassessment of risks and benefits
- Regular face-to-face visits
- Clear documentation

Federation of State Medical Boards. Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain. July 2013. Available at: www.fsmb.org/grpol_policydocs.html.
Gourlay DL, et al. *Pain Med*. 2005;6(2):107-12.
Chou R, et al. *J Pain*. 2009;10(2):147-59.
Franklin GM. *Neurology*. 2014; 83:1277-1284

Common Universal Precautions

- Patient Prescriber Agreements (PPA)
- Informed Consent (goals and risks)
- Plan of Care
- Efficacy not well established but no evidence of a negative impact on patient outcomes
- Monitoring for adherence, misuse, and diversion
  - Urine drug testing
  - Pill counts
  - Prescription Drug Monitoring Program (PDMP) data

FSMB Model Policy 2013. Available at: www.fsmb.org/grpol_policydocs.html
Gourlay DL, et al. *Pain Med*. 2005;6(2):107-12.
Chou R, et al. *J Pain*. 2009;10(2):147-59.
Cheatle MD, Savage SR. *J Pain Symptom Manage*. 2012;44(1):105-16.
Fishman SM, Kreis PG. *Clin J Pain*. 2002;18(4 Suppl):S70-5.
Arnold RM, et al. *Am J Med*. 2006;119(4):292-6.
Starrels J, et al. *Ann Intern Med*. 2010;152(11):712-20.
Franklin GM. *Neurology*. 2014; 83:1277-1284

Mythology of ADT Technology

- **MYTH:** ADT technology has been proven to decrease addiction, abuse, over-dosages, misuse, diversion, etc.
  - Pearls:
    - Category 4 studies have not been completed with any FDA-approved product demonstrating a reduction in these areas.

Case Study - *continued*

Bill – a patient with chronic low back pain

- Physician calls the pharmacist:
  - Primary care physician asks you if all of ADT technologies are relatively the same

Mythology of ADT Technology

- **MYTH:** All ADT technology is the same
  - Pearls:
    - Some ADT use one physical barrier, others use multiple layers of barriers
    - Some ADT use antagonists
      - Could lead to acute withdrawal reactions if manipulated
    - ADT may or may not prevent alcohol dose-dumping, each product needs to be evaluated on the results of their testing.

Mythology of ADT Technology

- **MYTH:** ADT technology ensures that the product will have the best pharmacokinetics in its opioid delivery system.
  - Pearls:
    - This is a separate evaluation that every pharmacist should perform.
      - Will an extended-release product maintain its delivery system in fed and fasted states?
      - Will the product hold to a 12-hour, or 24-hour duration of adequate serum levels of the opioid?

Counseling Tips for All Patients on Extended-Release Opioids

- NEVER……..
  - Drink alcohol while on opioids
  - Crush, chew, snort, smoke, pulverize, inject, etc. ER opioid products
  - Use an external heat source on transdermal opioids
  - Cut, tear, rip open transdermal opioid patches
  - Share with a friend or relative any of your opioid products
  - Take more medication than your physician has prescribed
  - Take illicit drugs while on opioid medications
  - Brag to neighbors, friends, relatives about being on opioids (extended-release or immediate-release formulations)

Counseling Tips for All Patients on Extended-Release Opioids

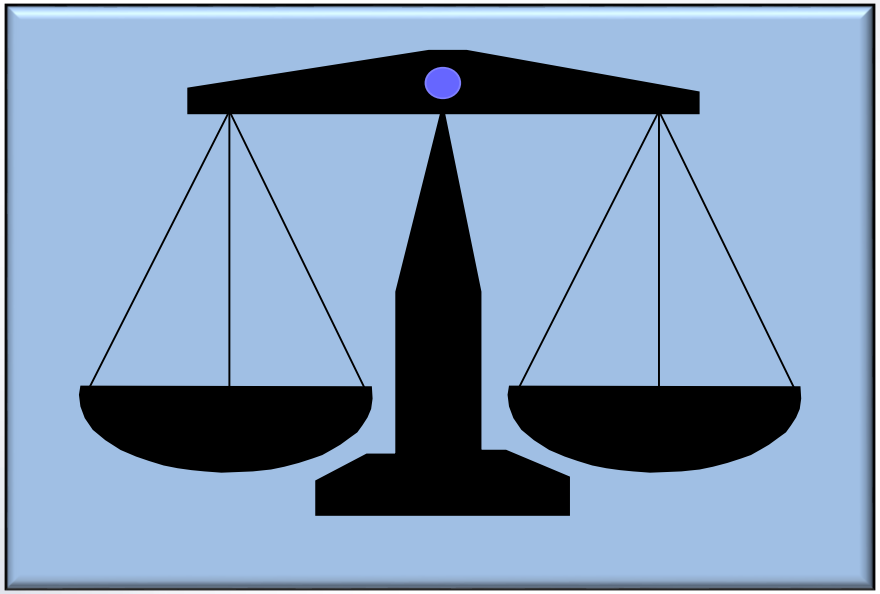
- ALWAYS….
  - Store medication in a safe (preferably locked) place
  - Keep opioids away from children, teens
  - Adhere to the instructions listed on the prescription
  - Adhere to your medication agreement
  - Ask your pharmacist or physician FIRST if you are planning to take any OTC medication or herbal/vitamin product while on LA/ER/IR opioids
  - Call 911 if you experience shortness of breath or have difficulty breathing while on LA/ER/IR opioids

Balancing Medication Use in Patients

√ **Non-pharmacological strategies**

√ **Pain control**

√ **Comfort level**



√ **Improve overall function**

√ **Minimize side effects**

√ **Maximize safety**

√ **Medical / legal guidelines for opioid use**

√ **Use all available tools, including abuse-deterrent technology to diminish risks**