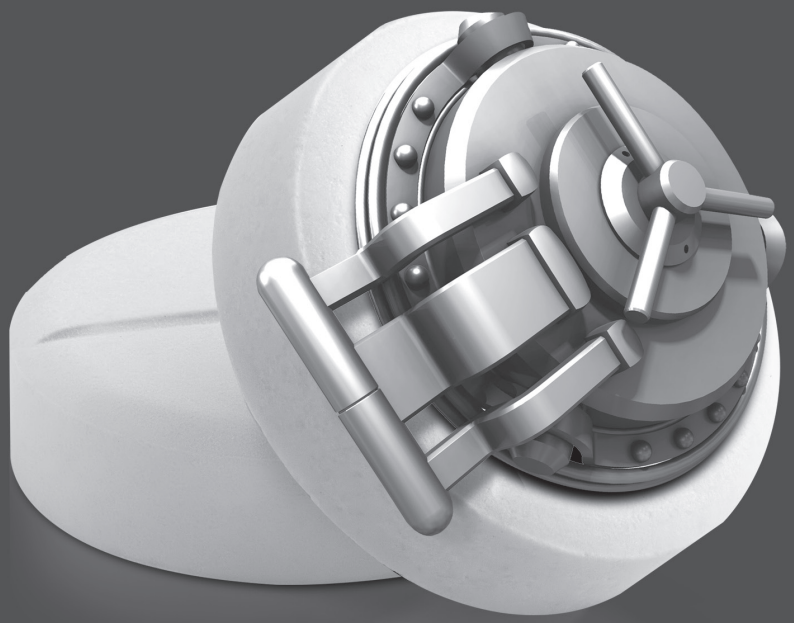


EDUCATIONAL PROGRAM

Which of the following BEST describes your perception of the current state of opioid prescribing for chronic pain?

1. Opioids continue to be over-prescribed and their use is inadequately monitored by the healthcare system.
2. Opioids are still under-prescribed for patients who are truly suffering.
3. Opioid prescribing has reached a nice balance – prescribers are aware of the benefits and of the risks and are neither under- nor over-prescribed.

Opioid Restrictions

- Centers for Disease Control and Prevention (CDC) recommends that chronic pain clinicians "should avoid increasing dosage to ≥90 morphine milligram equivalents (MME) per day or carefully justify a decision to titrate dosage" to that level.
- 19/51 states have enacted a 3–7-day limit on an initial prescription for opioids unrelated to extenuating circumstances.
- The Centers for Medicare & Medicaid Services recently enacted a "hard-stop" for prescriptions of more than 7 days worth of opioid medications for opioid-naïve patients.

CDC. CDC Guideline for prescribing opioids for chronic pain. Available at: https://www.cdc.gov/drugoverdose/pdf/guidelines_at-a-glance-a.pdf
CMS. 2019 Medicare Part D Opioid Policies. Available at: https://www.pharmacist.com/sites/default/files/audience/CMSPartDOpioid%20Pharmacy%20Tip%20Sheet_20181206_508.pdf
AthenaInsight. State-by-state breakdown of opioid regulations. Available at: https://www.athenahealth.com/insight/infographic-opioid-regulations-state-by-state
Whitmore R, Whisenant D. Pharm Times. Feb. 5, 2019. Available at: https://www.pharmacytimes.com/contributor/marilyn-bulloch-pharmd-bcps/2019/02/opioid-prescribing-limits-across-the-states

Do you believe that any of the current opioid restriction policies cause patients to suffer unnecessary pain?

1. YES
2. NO
3. Unsure

How often do patients report difficulty filling their opioid prescriptions?

1. Frequently
2. Sometimes
3. Rarely
4. Never
5. Unsure

The "Opioid Epidemic"

- Missouri, Ohio, Mississippi, counties in California and New York and the cities of Chicago and Dayton (among others) have filed lawsuits alleging "the opioid epidemic is a direct result of a carefully crafted campaign of deception carried out by Defendants (drug companies making pain pills)."
- Physicians have been accused of contributing to opioid abuse, allegedly overprescribing opioids for everything from migraines to post-op hernia repair.
- Kentucky's Attorney General is suing the pharmacy chain Walgreens for allegedly exacerbating the "man-made" opioid crisis, by playing a dual role in the supply chain as both the distributor and dispenser.
  - The lawsuit also asserts the company willfully ignored its own safeguard systems that are designed to protect consumers and monitor their drug consumption.

Has the opioid epidemic affected your practice? Have you ever refused to prescribe or fill prescriptions for opioids?

1. YES
2. NO
3. Does not apply

Has the opioid epidemic affected your practice?

When you have refused to prescribe or fill a prescription for opioids, were you ever fearful about the potential for violence against you by the person requesting the prescription?

1. YES
2. NO
3. Does not apply

Patient Case Study

Larry – a patient with low back pain

- Demographics:
  - 38 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, ballroom dancing
  - Social life – dating, likes to have a glass or two of wine with dinner

Patient Case Study

Larry – a patient with low back pain

- History
  - Diagnosis
    - 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

Patient Case Study

Larry – a patient with 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
  - » Oxycodone 5 mg, 1 tablet up to four times a day. Patient states that he takes on a regular basis 3–4 times a day.
  - » Pharmacist notes that the patient appears to be compliant with his gabapentin and is using about 120 tablets of the oxycodone 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)

Effects of Unmanaged Pain

Physical Functioning

- Ability to perform activities of daily living
- Sleep disturbances

Psychological Morbidity

- Depression
- Anxiety
- Anger
- Loss of self-esteem

Social Consequences

- Relationships with family and friends
- Intimacy/sexual activity
- Social isolation

Societal Consequences

- Healthcare costs
- Disability
- Lost workdays

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 and work
- Patient-centered, multimodal, multidisciplinary treatment approach is the cornerstone of best-practice model
  - Medical, interventional and non-interventional approaches
- Opioids may offer long-term benefit in managing symptoms of pain and may improve 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

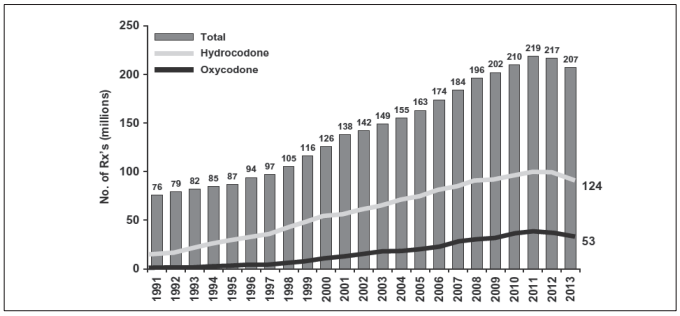
- Sedation, constipation
- Risk of dependency, addiction
- Lack of anti-inflammatory effect
- Tolerance, neuroadaptation, hyperalgesia
- Potential of misuse, abuse and diversion

Prescription Pain Medications… good, bad, ugly?

- Prescription drugs are abused more often than any other drug, except marijuana and alcohol.
- A 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 Jan. 30, 2019).**
Center for Behavioral Health Statistics & Quality, SAMHSA & RTI International. Available at: http://www.samhsa.gov.

Opioid Prescriptions in the US 1991 - 2013



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

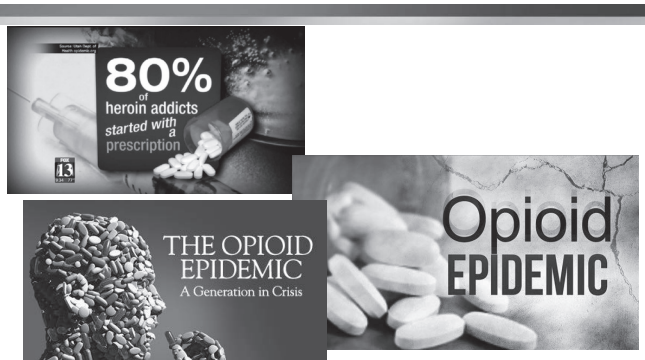
Diagram from: Gudin JA, Nalamachu SR. ***Postgraduate Medicine.*** **2016;128:97-105.**

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.

Opioid Epidemic



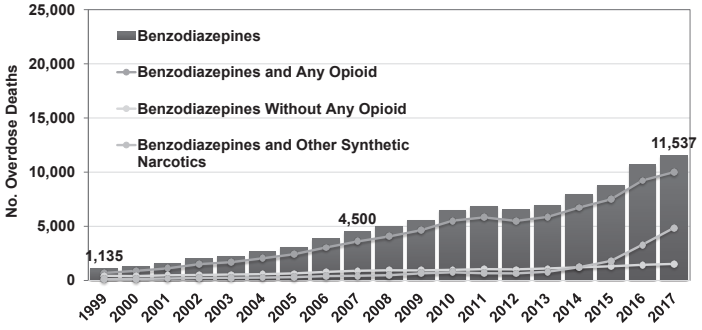
Opioid Abuse

Drug overdoses:

- From 2002–2010, prescriptions for opioids, rates of opioid diversion and opioid-related deaths increased significantly.
  - All three plateaued or decreased from 2011–2013
  - From 2013–2014, rates of opioid overdose deaths increased 14%
- 2015: 33,091 deaths (15.6% increase from 2014)
  - Much of increase due to:
    - Heroin deaths, increased by 20.6%
    - Synthetic opioids deaths, other than methadone (e.g. tramadol, fentanyl) increased by 72.2%
    - Fentanyl mixed with heroin and cocaine
    - Carfentanil – 100× more potent than fentanyl, approved for veterinary use

Dart RC. *NEJM.* 2015;372:241-8.
Brauser D. Prescription opioid abuse warning. Available at: http://www.Medscape.com/viewarticle/838538.
Rudd RA et al. *Morb Mortal Wkly Rep.* 2016; 64;1378-82.
Rudd RA et al. *Morb Mort Wkly Rep.* 2016;65(50-51):1445-52.
CDC. Opioid Overdose. Available at: https:www.cdc.gov/drugoverdose/opioids/fentanyl.html.
Ludden J. http://www.npr.org/sections/health-shots/2016/09/02/492108992/an-even-deadlier-opioid-carfentanil-is-hitting-the-streets.

Opioids and Benzodiazepines



National Institute of Drug Abuse. Overdose death rates. Available at: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates.

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

How Fearful Should We be of Managing Pain with Opioids?

Which of the following BEST describes your perception of the role of a pharmacist in preventing opioid abuse / misuse?

1. Refuse to stock or dispense opioids.
2. Provide in-depth counseling of the patient regarding risks of tampering / manipulating opioids.
3. Report prescribers to medical board if prescriptions exceed greater than 60 pills per month.
4. Recommend to the prescriber an abuse-deterrent formulation opioid for every patient.
5. The pharmacist does not have a role in preventing opioid abuse / misuse as there is barely enough time to dispense prescriptions.
6. Not sure of the best role for a pharmacist in preventing opioid abuse / misuse

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.

Available at: FDA. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm.

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."

Barlas S. *P&T.* 2013;28(9):531–534.

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 expose users to risks of addiction, 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.

Barlas S. *P&T.* 2013;28(9):531–534.

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.

CDC. Available at: https://www.cdc.gov/drugoverdose/pdf/guidelines_at-a-glance-a.pdf.

Misuse, Abuse, Diversion

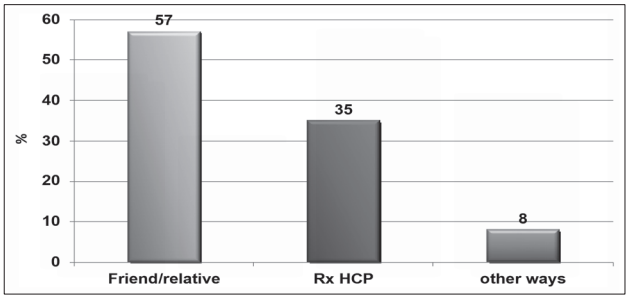
Is there any way to stop this?

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

Smith SM, et al. *Pain*. 2013;54:2287-96.

Pain Relievers Obtained for Nonmedical Use



*Other ways include prescription drugs stolen from a HCP, drugs bought from dealer or other stranger

Han B, et al. *Ann Intern Med*. 2017;167:293-301.

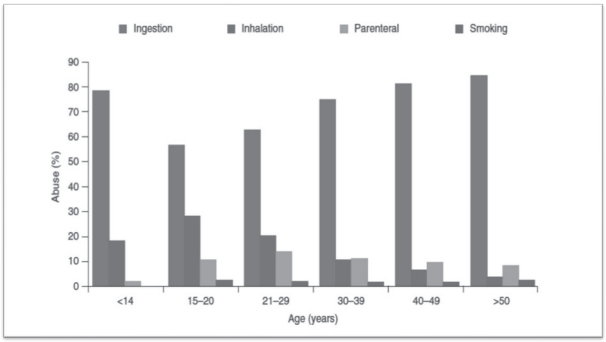
What are Some Common Methods of Abuse?

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.

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

Webster LR. *Drug Alcohol Depend.* 2015;156:e235-236.

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."

Patient Case Study *(continued)*

Larry – a patient with 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 a variety of different extended-release opioids available with many claiming to have some sort of ADT, but are there differences between the products that would help the prescriber make the best decision for Larry?

Which of the following BEST describes your perception on opioids with abuse-deterrent technologies (ADT)?

1. I do not see a place for abuse-deterrent opioids in the care of pain patients.
2. The abuse-deterrent technology utilized doesn't matter to me as long as the opioid contains it.
3. The abuse-deterrent technology utilized is an important consideration that should be evaluated before choosing any opioid.
4. All abuse-deterrent technologies are the same.

Ideal Characteristics of Abuse-Deterrent Technology

- Target both IR and ER opioid formulations.
- Target known or expected routes of abuse by majority of abusers.
- Deter intentional abuse by making manipulation of the opioid product be less "likeable" to abusers.
- Protect patients from rapid release of ER opioids from either innocent / unintentional or from intentional product manipulation.
- Protect patients from dose-dumping with alcohol
- Technology properties ultimate lower street value of products.

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	**Physical/Chemical Barriers** • May prevent chewing, crushing, cutting, grating, or grinding • May resist extraction by solvents
Aversion • Substances may be added to create unpleasant effects when tampered with or taken at higher doses	**Combination** • Use of 2 or more technologies in 1 product to deter abuse
Delivery System • Drug-release designs or method of drug delivery can offer resistance to abuse	**Novel Approaches** • Use of technologies not captured by any of the above
New Molecular Entities and Prodrugs • May require enzymatic activation, different receptor binding profiles, slower CNS penetration, or other novel effects	

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.

With which existing ADT technology are you most familiar?

1. Agonist/Antagonist
2. Aversion
3. Delivery System
4. New Molecular Entities and Prodrugs
5. Physical/Chemical Barrier
6. Not familiar with any of the technologies

Study Categories to Evaluate Abuse-Deterrent Technologies

- Category 1: Laboratory Manipulation and Extraction Studies
- Category 2: Pharmacokinetic Studies
- Category 3: Human Abuse Liability (HAL) Studies*

Premarket

- Category 4: Postmarket Studies

*Also called clinical abuse potential 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

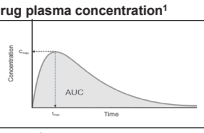
Overview

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. Available at: https://www.rdmag.com/article/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

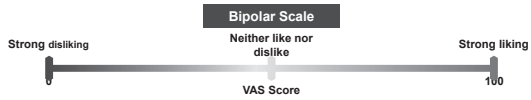
Evaluate impact of manipulation on:

- 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.

Currently Available Extended-Release (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 its crushed and then snorted, or crushed, dissolved and then injected intravenously.

Currently Available ER Opioids with ADT *(continued)*

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.
MorphaBond®	Morphine	SentryBond technology using multiple overlapping abuse deterrent barriers. Retains ER properties if crushed or broken.

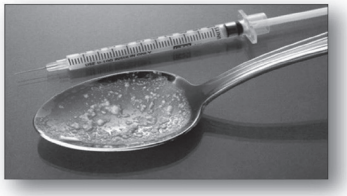
Currently Available Immediate-Release (IR) ADF Opioids

Product Name	Opioid used	Description of technology *(in descending order of date of FDA product approval)*
Oxaydo®	Oxycodone	According to the FDA, product is not a true ADF, more of an irritant. Nasal inhalation leads to burning, discouraging nasal abuse.
RoxyBond®	Oxycodone	First and only immediate-release opioid classified by the FDA as abuse deterrent. Formulated with SentryBond® technology using inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse even if the tablet is subjected to physical manipulation and/or attempts at chemical extraction. Laboratory test data have shown that, compared oxycodone immediate-release tablets, product has increased resistance to cutting, crushing, grinding, or breaking using selected tools. Both intact and manipulated product resisted extraction in selected household and laboratory solvents under various conditions, including selected pretreatments. Compared with oxycodone immediate-release tablets, the product forms a viscous material that resists passage through a needle; it is also more difficult to prepare solutions suitable for intravenous injection. Compared to oxycodone IR, when crushed and snorted nasally, blood levels are lower.

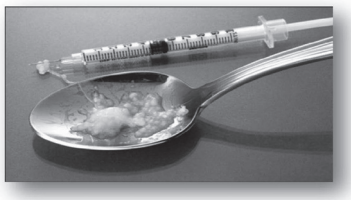
Polymer matrix ADT
(usually polyethylene oxide-based)

(similar to INTAC / Resistec ADT technologies)

Original formulation

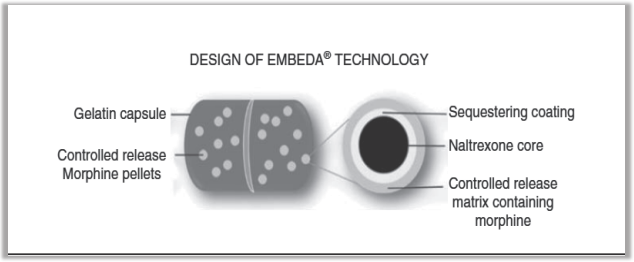


ADF



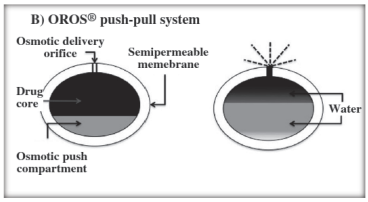
Nguyen V, et al. *J Clin Pharm Therap.* 2015;40:629-34.

Sequestration of Antagonist



Mastropietro DJ, Omidian H. *Expert Opin Pharmacother.* 2015;16:305-323.

Osmotic Controlled-Release Oral Delivery System (OROS)



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

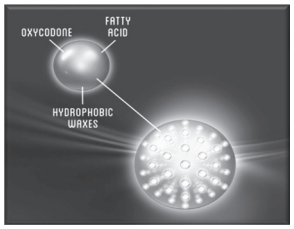
- **Semi-permeable capsule with a laser-drilled hole in it**
- **The opioid is placed inside the hollow casing**
- **Tablet moves through the body, water passes through the case and is absorbed by an expandable chamber, which slowly pushes the drug out through the hole over several hours for an extended 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: https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Pink%20Sheet%20DAILY/2015/September/Collegium_oxycodone_AC_company_brfg.pdf. Published September 11, 2015.

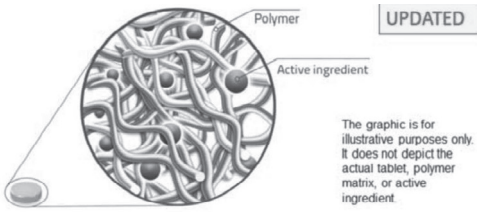
CIMA ADT: A Multifaceted Approach

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.

SentryBond™ Technology

The active ingredient – contained within a polymer matrix of inactive ingredients – **is difficult to visibly distinguish or physically separate** from the polymer matrix[2]



UPDATED

The graphic is for illustrative purposes only. It does not depict the actual tablet, polymer matrix, or active ingredient.

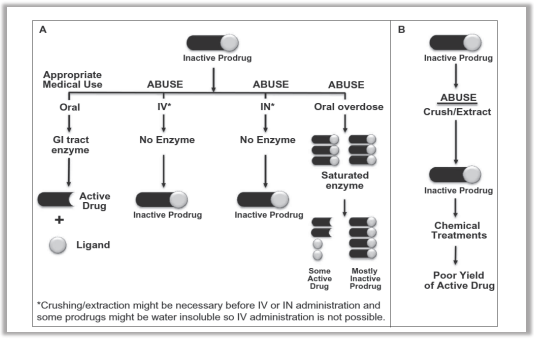
- Retains ER properties when manipulated or crushed
- Forms viscous mass that resists passage through a needle when placed in a liquid environment
- For IR products, when crushed and snorted, blood levels are lower than that obtained with comparable product without abuse-deterrent technology.

Data on file, DSI pharmaceuticals 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.

Patient Case Study - *continued*

Larry – a patient with low back pain

- Physician calls the pharmacist:
  - Primary care physician asks you if the use of an ADT 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 product (ER and IR) 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/IR opioids with ADT have proven very resistant to both standard tools and solvents as well as advanced extraction techniques
      - Some ”next generation” ADT ER products retain their ER properties even if manipulated.

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: https://30qkon2q8eif8wrj03zeh041-wpengine.netdna-ssl.com/wp-content/uploads/2013/10/FSMB-Model-Pain-Policy_July-2013.pdf.
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: https://30qkon2g8eif8wrj03zeh041-wpengine.netdna-ssl.com/wp-content/uploads/2013/10/FSMB-Model-Pain-Policy_July-2013.pdf.
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.

Patient Case Study - *continued*

Larry – a patient with 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 technologies are 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 Opioids

- **NEVER…....**
  - Drink alcohol while on opioids
  - Crush, chew, snort, smoke, pulverize, inject, etc. 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**

Continuing Professional Development
Reflect | Plan | Do | Evaluate

Center for Independent Healthcare Education is committed to supporting pharmacists in their Continuing Professional Development (CPD) and lifelong learning. Please use this form to incorporate the learning from this educational activity into your everyday practice. Continuing Professional Development: a self-directed, ongoing, systematic and outcomes-focused approach to learning and professional development that assists individuals in developing and maintaining continuing competence, enhancing their professional practice, and supporting achievement of their career goals.

CPD Value Statement:

"Pharmacists who adopt a CPD approach accept the responsibility to fully engage in and document their learning through reflecting on their practice, assessing and identifying professional learning needs and opportunities, developing and implementing a personal learning plan, and evaluating their learning outcomes with the goal of enhancing the knowledge, skills, attitudes and values required for their pharmacy practice."

REFLECT

Consider my current knowledge and skills, and self-assess my professional development needs and goals in the area of ADFs.

PLAN

Develop a "Personal Learning Plan" to achieve intended outcomes, based on what and how I want or need to learn.

Develop objectives that are specific for you, measurable, achievable, relevant to the learning/ practice topic, and define the time frame to achieve them.

DO

Implement my learning plan utilizing an appropriate range of learning activities and methods.
List learning activities that you will engage in to meet your goals.
List resources (e.g. materials, other people) that you might use to help achieve your goal.

EVALUATE

Consider the outcomes and effectiveness of each learning activity and my overall plan, and what (if anything) I want or need to do next.

Monitor progress regularly toward achievement of your goal.