PainWeek

**Mirror Mirror on the Wall:**
**Who's the FDA's Fairest ADF of All?**

Mark Garofoli, PharmD, MBA, BCGP, CPE

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## Disclosures

- Advisory Board: DSI
- Expert Witness: U.S. Department of Justice, Consumer Protection Branch

This presentation was not a part of the presenter's official duties at the WVU and does not represent the opinion of WVU

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## Learning Objectives

- Identify the seven current types of abuse-deterrent formulations.
- Recall all of the available abuse-deterrent formulation (ADF) opioid medications, with particular attention to the select few that are both FDA approved specifically as ADF opioid medications and available on the U.S. market.
- Discuss common methods of manipulation of abuse-deterrent formulation (ADF) opioid medications.

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## CDC MME Thresholds & Driving Speed Limits

**Caution**
**50 MEDD**

**Speed Limits**

**Avoid Increasing >/= 90 MEDD**

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## Driving & Opioid Risk Reduction


| |
|---|
| PDMP Review |
| Physical Exam |
| Urine Drug Screening |
| Use Caution with Methadone |
| Short Duration of Initial Opioid |
| Avoid Sedative Co-Prescribing |
| Patient & Provider Agreement/Contract |
| MEDD Cautionary Threshold |
| Gradual Tapering Plan |
| Abuse-Deterrent Formulations |

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Adapted from https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

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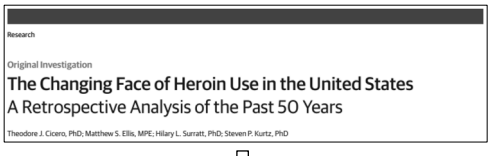
## Opioid Abuse Transition



Research

Original Investigation

The Changing Face of Heroin Use in the United States
A Retrospective Analysis of the Past 50 Years

Theodore J. Cicero, PhD; Matthew S. Ellis, MPE; Hilary L. Surratt, PhD; Steven P. Kurtz, PhD

⇩

75% of Heroin Users Started with Prescription Opioids

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T.J. Cicero, e. a. (2014). The Changing Face of Heroin Use in the United States. *JAMA Psychiatry*, 821-826.

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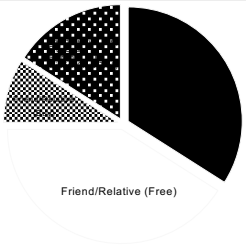
## Where are these opioids coming from…




TRUST
ME
I'M A
HEALTHCARE
PROFESSIONAL

~1/3RD

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2017 DEA National Drug Threat Assessment. https://www.dea.gov/docs/DIR-040-17_2017-NDTA.pdf

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## Opioid Abuse Transition

| Hydrocodone Combo Tablets | Oxycodone Combo IR Products | Oxycodone Sole ER/IR Products | Heroin |
|---|---|---|---|
| $5-10/Tab | $10-15/Tab | $1.50/mg | ($10/Bag) |

ADFs

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Shah A, et al. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use – United States, 2006-2015. Weekly / March 17, 2017 / 66(10); 265–269. www.blueright.org

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## The Early "ADFs"

Phenylpiperidine Opioids (Diarrhea Treatment)

- –Lomotil® (Diphenoxylate & Atropine, 1960)
- –Motofen® (Difenoxin & Atropine, 1978): Metabolite of Diphenoxylate
- –Atropine: Anticholinergic that will produce *dysphoria* in large doses (Aversion)
  - •Blurred Vision, Constipation, Visual Disturbances

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## The Early "ADFs"

Hydrocodone & Homatropine

- –Tussigon Tablets 5mg/1.5mg (FDA 1985)
- –Hydromet Liquid 5mg/1.5mg per 5mL
  - •Hycodan FDA 1943, Generic Hydromet FDA 1983
- –Homatropine: Anticholinergic similar to Atropine (Aversion)

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## The Early "ADFs"

Pentazocine and Naloxone (FDA approved in 1982)

- –Pentazocine Single Product
  - • Single product pentazocine was approved in 1967 (Kappa Agonist, Mu Antagonist)
  - • Observed to be crushed, mixed w/ antihistamine Pyribenzamine, aka "Blues", & injected
  - • 1st DEA Reclassification: pentazocine (single product) to CIV in 1979

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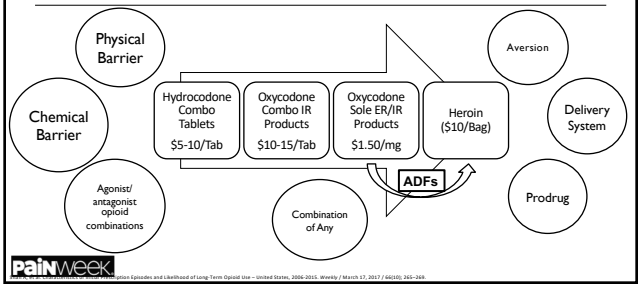
## Opioid Abuse Transition

**ADF Opioid Formulations**

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## Types of Abuse-Deterrent Formulations (ADFs)

| ADF Type | Description |
|---|---|
| 1. **Physical Barrier** | Prevent chewing, crushing, cutting, grating, or grinding |
| 2. **Chemical Barrier** | Resist extraction of the opioid through use of common solvents including water, alcohol or other organic solvents |
| 3. **Agonist/Antagonist Opioid Combinations** | Antagonist is added to the formulation to interfere with release if taken in any other way than it was intended |
| 4. **Aversion** | Substances are added to the dosage form to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or if a higher dosage than directed is used |
| 5. **Delivery System** | Alternative delivery systems that are more difficult to manipulate (such as a depot injectable, an implant, or transdermal application) |
| 6. **Prodrug** | Medication contains a prodrug that lacks opioid activity until it has been transformed in the gastrointestinal tract |
| 7. **Combination of the above** | |

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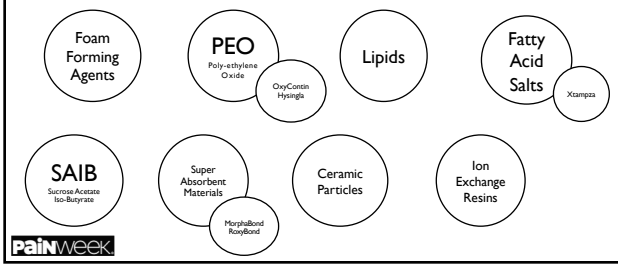
## Physical & Chemical Barriers

**ADF Opioid Formulations**

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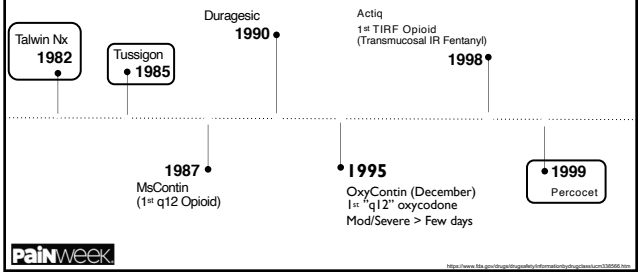
## FDA Opioid Timeline

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https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm

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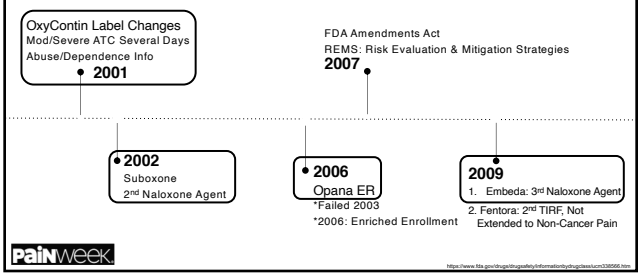
## FDA Opioid Timeline

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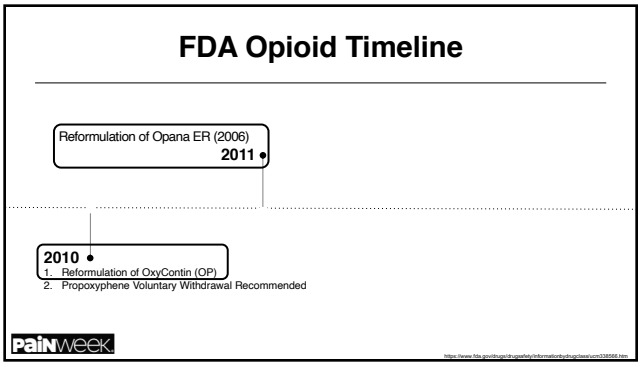
## FDA Opioid Timeline

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## The Opana Story

2011

–FDA approved Opana ER reformulation from Endo Pharmaceuticals, but without ADF Labeling

2012

–Endo submitted a citizen's petition to the FDA to remove original formulation generic oxymorphone products from the market. The petition was denied, and the FDA noted that the rate of IV abuse of the newly designed opioid had been increasing in the months after its introduction to the market

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## The Opana Story

2017 (March)

–Endo presented post-marketing data to the FDA that contained evidence of serious health concerns with IV abuse of the reformulated product, such as thrombotic thrombocytopenic purpura and an outbreak of HIV infections in Indiana

- High molecular weight of the polyethylene oxide (PEO) coating that became lodged in the arterioles of the kidneys of IV abusers

2017 (July)

–FDA recommended Endo remove Opana ER from market, and Endo did so

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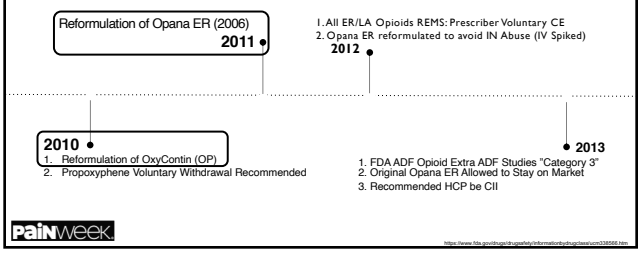
## FDA Opioid Timeline

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https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm

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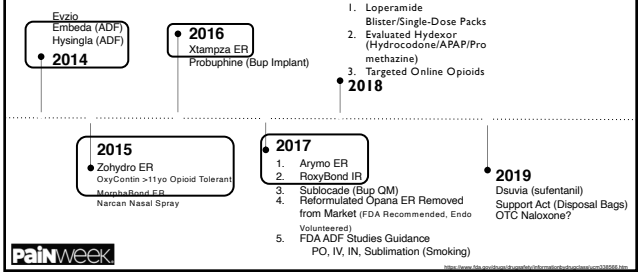
## FDA Opioid Timeline

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https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm

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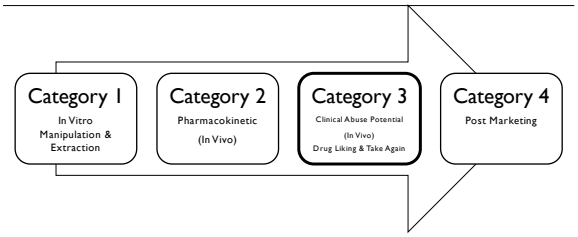
## FDA ADF Studies

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## Category 3: Abuse Potential Studies

- At a minimum, the intact and most effectively manipulated form of a drug should be selected for evaluation
- Physical Manipulation Methods (+/- Heat)
  - –Cutting
  - –Grating
  - –Milling

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https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf

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## Category 3: Abuse Potential Studies

- **Ingestion (oral route)**
  - –Oral bioavailability of physically manipulated or chewed products
- **Injection (parenteral route)**
  - –Extractability and Syringeability of intact and manipulated products
- **Insufflation (nasal route)**
  - –Nasal bioavailability & pharmacodynamic (PD) effects of manipulated & insufflated products
- **Smoking (inhalation route)**
  - –Ability to sublimate intact and manipulated products

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https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf

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## Category 3: Abuse Potential Studies

Comparative In Vitro Studies

–Extractability Studies

–Performed at both Room Temp & Elevated Temp

| Solvent Level | Solvents |
|---|---|
| Level 1 | Deionized Water |
| Level 2 | Vinegar, 0.2% baking soda solution, 40% ethanol, & carbonated drink |
| Level 3 | 100% ethanol, 100% isopropyl alcohol, acetone, 0.1 N HCl, & 0.1 N NaOH |

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https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf

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## Category 3: Abuse Potential Studies

Comparative In Vivo Studies

–Nasal PK

–Oral PK

–Agonist/Antagonist (Both levels tested)

–Multiple Strengths (All tested)

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https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf

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## So who made the cut…pun intended


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FDA Approved ADF Opioids available on US Market
(July 2019)

**Abuse Deterrent Formulation (ADF) Opioids**

| Active Ingredient | Product | FDA ADF Approval | Formulation |
|---|---|---|---|
| oxycodone | **Xtampza ER®** | IN, IV, & PO Chew | ER Capsule |
| | Xartemis ER® (+APAP) | - | IR/ER Tablet |
| | **OxyContin®** | IN & IV | ER Tablet |
| | Troxyca® | IN, IV, PO Crush | ER Capsule |
| | Oxaydo® | - | IR Tablet |
| | RoxyBond® | IN & IV | IR Tablet |
| tapentadol | Nucynta ER® | - | ER Tablet |
| hydromorphone | Exalgo® | - | ER Tablet |
| morphine | **Embeda®** | IN & PO Crush | ER Tablet |
| | **Arymo®** | IV | |
| | **MorphaBond®** | IN & IV | |
| hydrocodone | **Hysingla®** | IN, IV, & PO Chew | ER Tablet |
| | Zohydro ER® | - | ER Capsule |
| | Vantrela ER® | IV | ER Tablet |
| | Hydromet® | - | Liquid |
| | Tussigon® | - | Tablet |
| benzhydrocodone | Apadaz® | - | Tablet |
| pentazocine | Talwin NX® | - | Tablet |

*Targiniq (oxycodone) & Opana (oxymorphone) are Off Market*

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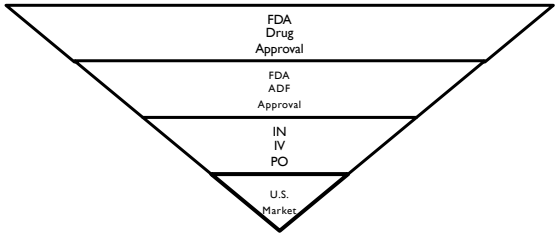
## ADF Opioid Funnel

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## FDA Approved ADF Opioids on US Market

(July 2019)

| Medicine | Product | FDA ADF Approval | | | Formulation |
|---|---|---|---|---|---|
| oxycodone | Xtampza ER® | IN | IV | PO Chew | ER Capsule |
| | OxyContin® | IN | IV | | ER Tablet |
| hydrocodone | Hysingla® | IN | IV | PO Chew | ER Tablet |
| morphine | Embeda® | IN | | PO Crush | ER Tablet |
| | Arymo® | | IV | | |
| | MorphaBond® | IN | IV | | |

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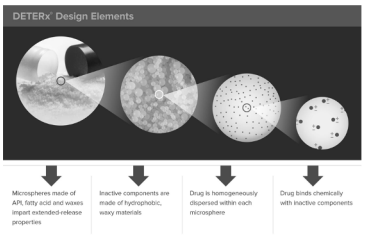
## Xtampza ER®

- DETERx Technology
  - Waxy microspheres solidify in a needle
- FDA ADF Approved
  - IN, IV, & PO
- Take with food
  - GI activated, not pH
- Can be opened and sprinkled into a G-Tube or on food

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| Xtampza ER (oxycodone) Dosage | | Extended-release Oxycodone HCl Dosage |
|---|---|---|
| 9 mg | Equivalent to | 10 mg |
| 13.5 mg | | 15 mg |
| 18 mg | | 20 mg |
| 27 mg | | 30 mg |
| 36 mg | | 40 mg |
| 27 mg + 27 mg | | 60 mg |
| 36 mg + 36 mg | | 80 mg |

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## OxyContin®

- Original formulation (1996-2009): "OC" Imprint
- Newer formulation (2010-present): "OP" Imprint

| Strength | 10 mg | 15 mg | 20 mg | 30 mg | 40 mg | 80 mg |
|---|---|---|---|---|---|---|
| Comparison of original (first) versus reformulated *OxyContin®* tablets (second). | | | | | | |

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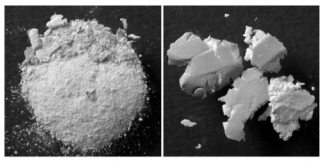
## OxyContin®

- RESISTEC Technology
  - Forms a viscous gel with water
- ADF Category 3 Study (IN/IV)
  - 57% reduction in drug liking
  - 43% no reduction in drug liking
- Phase 4
  - ~50% Decrease in Doctor Chopping, Overdoses, & Poison Center Calls (Heroin Replaced?)
- Q12h Dosing ???



Original OxyContin® | New abuse-deterrent OxyContin®

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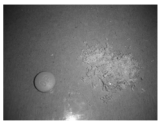
## Oxy-Crisping



### Tools of the Trade

- Grater (PediEgg) (Lemon Zester)
- Ceramic/Glass Plate
- Paper Towel
- Microwave
- Fridge/Freezer

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## FDA Approved ADF Opioids on US Market

(July 2019)

| Medicine | Product | FDA ADF Approval | | | Formulation |
|---|---|---|---|---|---|
| oxycodone | Xtampza ER® | IN | IV | PO Chew | ER Capsule |
| | OxyContin® | IN | IV | | ER Tablet |
| hydrocodone | Hysingla® | IN | IV | PO Chew | ER Tablet |
| morphine | Embeda® | IN | | PO Crush | ER Tablet |
| | Arymo® | | IV | | |
| | MorphaBond® | IN | IV | | |

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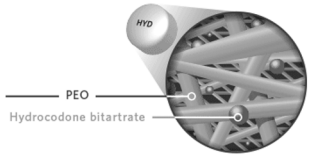
## Hysingla®

- RESISTEC Technology (*Same as OxyContin)
  - –Forms a viscous gel around water
- ADF Category 3 Studies (IN, IV, & PO): ~80% Reduction in Drug Liking

HYdrocodone
SINGle dose
Long Acting

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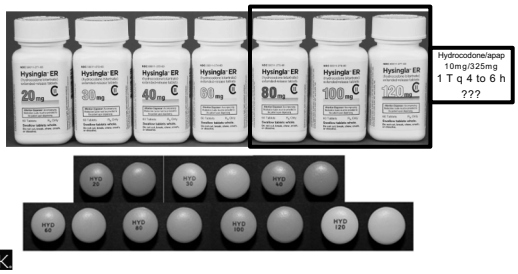
## Hysingla®

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## FDA Approved ADF Opioids on US Market

(July 2019)

| Medicine | Product | FDA ADF Approval | | | Formulation |
|---|---|---|---|---|---|
| oxycodone | Xtampza ER® | IN | IV | PO Chew | ER Capsule |
| | OxyContin® | IN | IV | | ER Tablet |
| hydrocodone | Hysingla® | IN | IV | PO Chew | ER Tablet |
| morphine | Embeda® | IN | | PO Crush | ER Tablet |
| | Arymo® | | IV | | |
| | MorphaBond® | IN | IV | | |

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411218/
https://www.sciencedirect.com/science/article/abs/pii/S0378517312004864
https://www.futuremedicine.com/doi/pdf/10.2217/pmt-2015-0005
https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm

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## Arymo®

- Guardian Technology (Polymer Matrix)
  - Physical & Chemical Barrier
- FDA ADF Approved for IV
- Oxycodone Product in Pipeline



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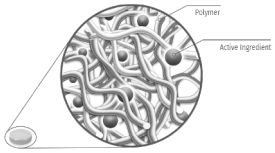
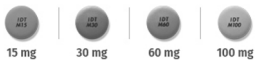
## MorphaBond®

- Sentry Bond Technology
- Dose every 8 to 12 hours
- Can be taken +/- food
- FDA ADF Approved for IV & IN

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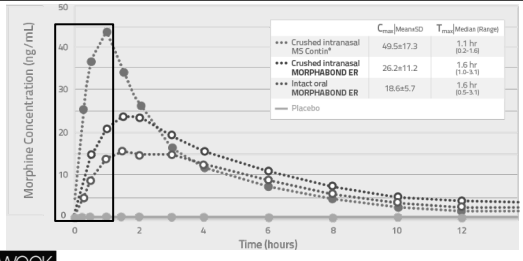
## MorphaBond®

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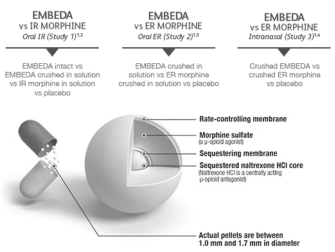
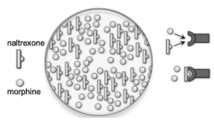
## Embeda®

- Sequestered naltrexone induces withdrawal if abused and ingested
- FDA ADF Approved IN & PO
  - Only FDA ADF Opioid w/o IV
- Morphine:Naltrexone Ratio 100:4







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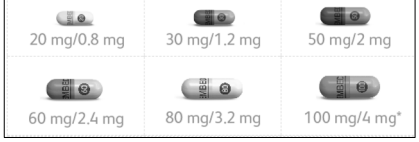
## Embeda®

EMBEDA is available in 6 dosage strengths[1]

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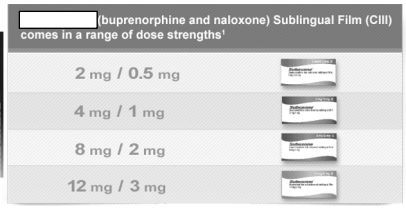
## MAT Buprenorphine Products with naloxone…


[redacted] (buprenorphine and naloxone) Sublingual Film (CIII) comes in a range of dose strengths[1]

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## Buprenorphine vs Naloxone

**Bluelight**

Lazylazyjoe (9/1/2010, 5:57am)
As someone who regularly injects Suboxone, I prefer injecting Suboxone instead of using sublingual mainly because of the efficacy. I can inject 1 to 2mg and be good for an entire day, compared to 4mg sublingual. It also takes affect in 15 minutes instead of 90 minutes.
You do have to be careful though, it is much easier to precipitate withdrawal this way. Wait a little longer for your induction, even longer if coming down off methadone.
The other thing that gets me is that I buy my Suboxone on the street, because between the doc and the pharmacy I'd be paying $150/month & $7.50/pill. If the doc would just prescribe Subtex, I could get it generic and do it legit for about the same cost. It drives me nuts as Suboxone is just as easy to abuse as the Subutex. Not to mention the whole pain management specialist thing is a big scam. There's no reason why a regular doc can't prescribe this schedule 3 drug.

Dread (10/1/2010, 2:08am)
Naloxone was put in there to trick the FDA, and it worked!
It was put in to extend the patent, they had to come up with a "new" product to keep the big bucks coming in.

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## Buprenorphine vs Naloxone

**Package Insert**

**5.2 Risk of Respiratory and Central Nervous System (CNS) Depression**

Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death involved misuse by self-injection or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with SUBOXONE sublingual film *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

In buprenorphine, naloxone tablets may deter injection of buprenorphine, naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-

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Suboxone Full Prescribing Information. February 27, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022410s008lbl.pdf

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## Buprenorphine Battles…

THE UNITED STATES DEPARTMENT of JUSTICE

FOR IMMEDIATE RELEASE — Tuesday, April 9, 2019

**Indivior Inc. Indicted for Fraudulently Marketing Prescription Opioid**

**Company Allegedly Lied to Doctors and Public Health Care Benefit Programs About the Safety and Diversion Risks of Suboxone Film**

CLERK'S OFFICE U.S. DISTRICT COURT
AT ABINGDON, VA
FILED
APR 09 2019
JULIA C. DUDLEY, CLERK
BY: J. C. Clark
DEPUTY CLERK

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF VIRGINIA
ABINGDON

| | | |
|---|---|---|
| UNITED STATES OF AMERICA | ) | |
| | ) | |
| v. | ) | Case No. 1:19CR00016 |
| | ) | |
| INDIVIOR INC. (a/k/a Reckitt Benckiser Pharmaceuticals Inc.) and INDIVIOR PLC | ) | Violations: 18 U.S.C. §§ 2, 1341, 1343, 1347, 1349 |

PainWeek www.painweek.org

https://www.justice.gov/opa/pr/indivior-inc-indicted-fraudulently-marketing-prescription-opioid
https://www.justice.gov/opa/press-release/file/1153305/download

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## FDA Approved ADF Opioids on US Market

July 2019)

| Medicine | Product | FDA ADF Approval | | | Formulation |
|---|---|---|---|---|---|
| oxycodone | Xtampza ER® | IN | IV | PO Chew | ER Capsule |
| | OxyContin® | IN | IV | | ER Tablet |
| hydrocodone | Hysingla® | IN | IV | PO Chew | ER Tablet |
| morphine | Embeda® | IN | | PO Crush | ER Tablet |
| | Arymo® | | IV | | |
| | MorphaBond® | IN | IV | | |

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411218/
https://www.sciencedirect.com/science/article/pii/S0037871910004864
https://www.futuremedicine.com/doi/pdf/10.2217/pmt-2015-0005
https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm




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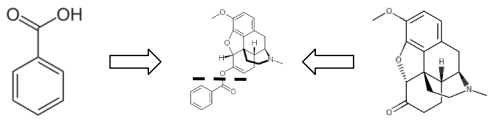
## Benz-hydrocodone/APAP

- Prodrug of Hydrocodone (+APAP) covalently bonded with benzoic acid
  - –Benzoic Acid: Typical food preservative
  - –Ligand-Activated Technology (LAT®): GI Tract Activation
  - –Also being studied with a methylphenidate prodrug



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Clinical Pharmacology Online Database. 2018
Apadaz Package Insert. 2018

## Benz-hydrocodone/APAP

- Controlled Substance Class 2 (just as hydrocodone/apap)
- Indicated for the short-term (*no more than 14 days*) management of *acute* pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
  - NOT FDA approved as an abuse-deterrent formulation (ADF) opioid
  - Benzhydrocodone/APAP 6.12/325mg = hydrocodone/APAP 7.5/325mg

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Clinical Pharmacology Online Database. 2018
Apadaz Package Insert. 2018

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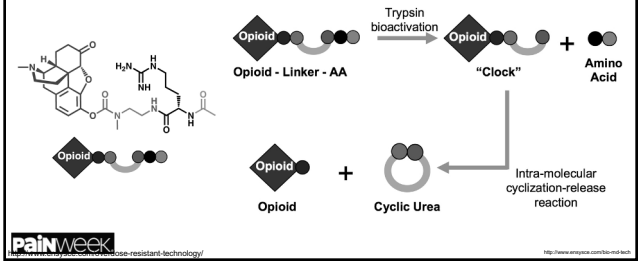
## ADF Opioid Pipeline

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http://www.emyoce.com/bio-md-tech

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## ADF Opioid Pipeline

| Program | Discovery | Preclinical | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|---|
| Oxycodone | PF614 | | | 2018: 4 Clinical Milestones | |
| | PF614-MPAR | | MPAR Preclinical 2 Year Study<br>NIDA Funded $2M through August 2019 | | |
| Hydromorphone | PF329 | | | | |
| | PF329-MPAR | | | | |
| ADHD | PFADHD | | | | |
| | PFADHD-MPAR | | | | |

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https://projectreporter.nih.gov/project_info_details.cfm?aid=9670620&icde=41249723&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&ca=ASC&pball
http://www.ensysce.com/pain-pipeline. Accessed April 2019.

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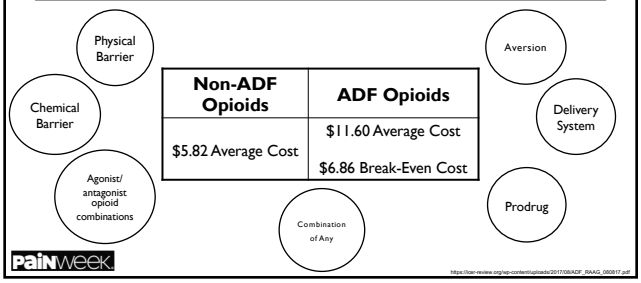
## ADFs, At What Cost?




| Non-ADF Opioids | ADF Opioids |
|---|---|
| $5.82 Average Cost | $11.60 Average Cost<br>$6.86 Break-Even Cost |

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https://icer-review.org/wp-content/uploads/2017/08/ADF_RAAG_080817.pdf

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## Institute for Clinical & Economic Review (ICER)

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

**Abuse-Deterrent Formulations of Opioids: Effectiveness and Value**

Founded in 2006, the Institute for Clinical and Economic Review (ICER) is an independent and non-partisan research organization that objectively evaluates the clinical and economic value of prescription drugs, medical tests, and other health care and health care delivery innovations. ICER

**Conflicts of Interest**
Aetna
Anthem
Blue Cross Blue Shield of Massachusetts
Blue Shield of California
Harvard Pilgrim Health Care
Kaiser Permanente
Partners Healthcare
Premera Blue Cross
United HealthCare
Washington State Health Care Authority

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|---|
| Hysingla® ER (Hydrocodone, Purdue) |
| Vantrela® (Hydrocodone , Teva) |
| Arymo® ER ( Morphine, Egalet) |
| Embeda® (Morphine + naltrexone, Pfizer) |
| Morphabond® (Morphine extended release, Inspirion Delivery Technologies) |
| OxyContin® TR (Oxycodone, Purdue) |
| Xtampza® ER (Oxycodone, Collegium Pharmaceutical Inc.) |
| Targiniq® (Oxycodone + naloxone extended release, Purdue) |
| Troxyca® ER (Oxycodone + naltrexone, Pfizer) |
| RoxyBond™ (Oxycodone immediate release, Inspirion Delivery Technologies) |

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A Look at Abuse-Deterrent Opioids. www.icer-review.org. July 2017. https://icer-review.org/about/

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## Institute for Clinical & Economic Review (ICER)

If ADF opioids reduce risk of diversion by 35%, they would attain cost-neutrality relative to non-ADF opioids.

ADF opioids would still cost the health system an additional $113 million over five years.

The federal government should convene clinical experts, clinical pharmacists, patients, and payers to develop consistent methods to identify patients whose environments represent a high risk for the abuse of opioids.

Given that over 90% of opioid prescriptions are for immediate-release (IR) formulations, and that currently, no IR ADFs are on the market, further investment and development by manufacturers for IR ADFs is critical.

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A Look at Abuse-Deterrent Opioids. www.icer-review.org. July 2017.

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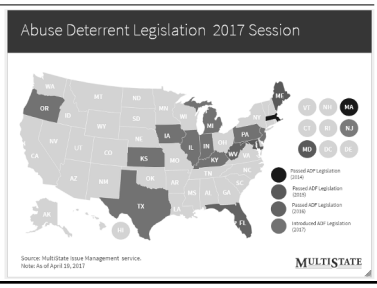
## States Mandating (By Law) ADF Opioid Coverage

- Massachusetts (2014)
- Maine (2015)
- Maryland (2015)
- Florida (2016)
- West Virginia (2016)

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## Audience Question #1

Which of the following are types of abuse-deterrent formulations?

a) Physical and chemical barriers
b) Aversion
c) Prodrug
d) All of the Above

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## Audience Question #2

There are currently more than a dozen Abuse-Deterrent Formulation (ADF) opioid medications available in the United States (US) market that are not only FDA Approved, but also specifically designated by the FDA as an ADF opioid medication.

a) True
b) False

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## Audience Question #3

Which of the following states have legislation mandating the prescription insurance benefit coverage of abuse-deterrent formulation (ADF) opioid medications in at least some manner?

a) Massachusetts
b) Maryland
c) Florida
d) All of the above

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## Discussion

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