Melt in Your Body, Not a Needle: A Review of ADF Opioids

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Antica Casa Vinicola

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Disclosures

- Expert Witness: Cardinal Health
- Consulting Fees/Advisory Board: HealthXL, Speranza

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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Opinions…

I have personal and professional opinions on pain management. However, some things are better left NSAID.

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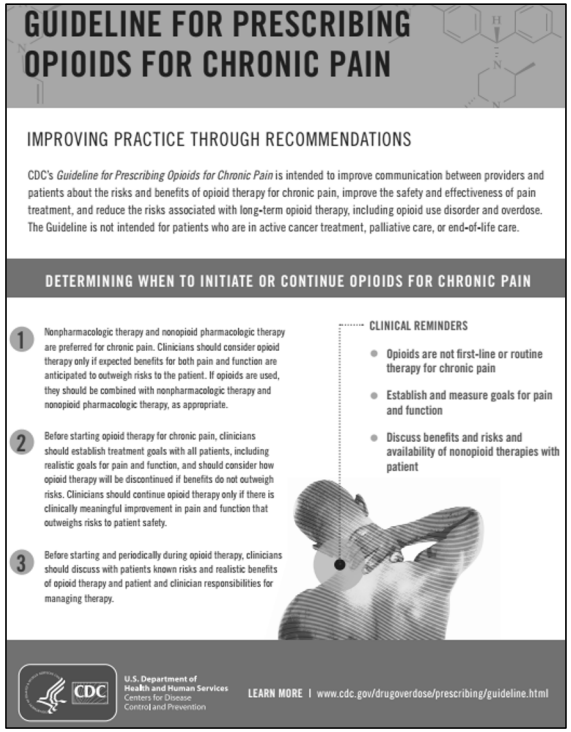
Learning Objectives

- 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.

2016 CDC Chronic Pain Opioid Guidelines



GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

IMPROVING PRACTICE THROUGH RECOMMENDATIONS

CDC's *Guideline for Prescribing Opioids for Chronic Pain* is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose. The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.

DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

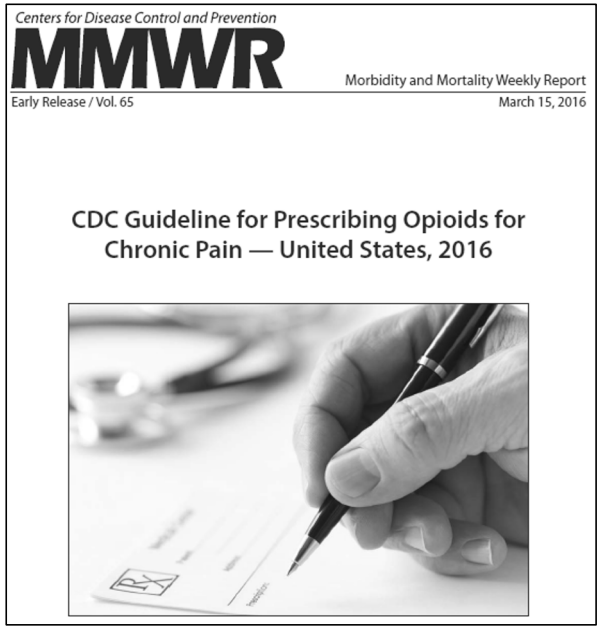
1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

CLINICAL REMINDERS

- Opioids are not first-line or routine therapy for chronic pain
- Establish and measure goals for pain and function
- Discuss benefits and risks and availability of nonopioid therapies with patient

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline.html

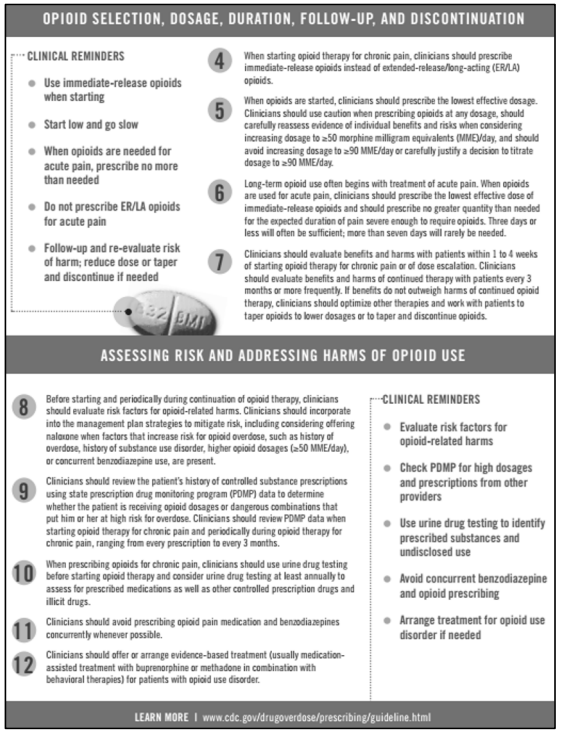


Centers for Disease Control and Prevention

MMWR Morbidity and Mortality Weekly Report

Early Release / Vol. 65 March 15, 2016

CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016



OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION

CLINICAL REMINDERS

- Use immediate-release opioids when starting
- Start low and go slow
- When opioids are needed for acute pain, prescribe no more than needed
- Do not prescribe ER/LA opioids for acute pain
- Follow-up and re-evaluate risk of harm; reduce dose or taper and discontinue if needed

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

ASSESSING RISK AND ADDRESSING HARMS OF OPIOID USE

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

CLINICAL REMINDERS

- Evaluate risk factors for opioid-related harms
- Check PDMP for high dosages and prescriptions from other providers
- Use urine drug testing to identify prescribed substances and undisclosed use
- Avoid concurrent benzodiazepine and opioid prescribing
- Arrange treatment for opioid use disorder if needed

LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline.html

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

2016 CDC Chronic Pain *Opioid* Guidelines

Opioid Use Decision

1. Non-Pharm, Non-Opioid, then Opioid
2. Treatment Goals
3. Risk Assessments & Side Effects

Type/Amount/Time of Opioid

4. IR not ER
5. MME >/= 50/day: Use caution
   No Increasing MME >/= 90 unless justified
6. Acute pain: Short duration
7. Re-evaluate 1 month, then every 3 months.

Risk/Harms of Opioid Use

8. Higher risk → naloxone
9. PDMP initially + every 1-3 months
10. UDT initially + annually
11. Avoid combining opioids & benzos
12. Opioid Use Disorder: Offer MAT

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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

CDC MME Thresholds & Driving Speed Limits

Avoid Increasing >/= 90 MEDD

Speed Limits

Caution 50 MEDD

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CDC MME Thresholds & Driving Speed Limits

Caution
50 MEDD

Avoid
ıcreasing
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

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

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

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75% of Heroin Users Started with Prescription Opioids

Family, Friends, Theft ???

Healthcare Professional(s)

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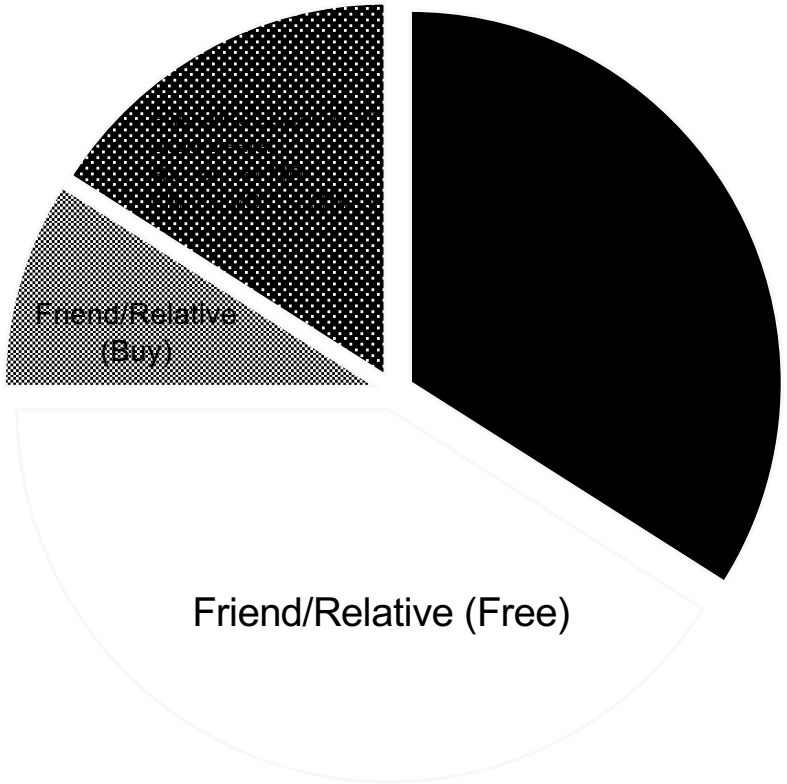
TJ Cicero, e. a. (2014). The Changing Face of Heroin Use in the United States. *JAMA Psychiatry*, 821-826.

Where are These Opioids Coming From?



HEALTHCARE PROFESSIONAL

~1/3rd

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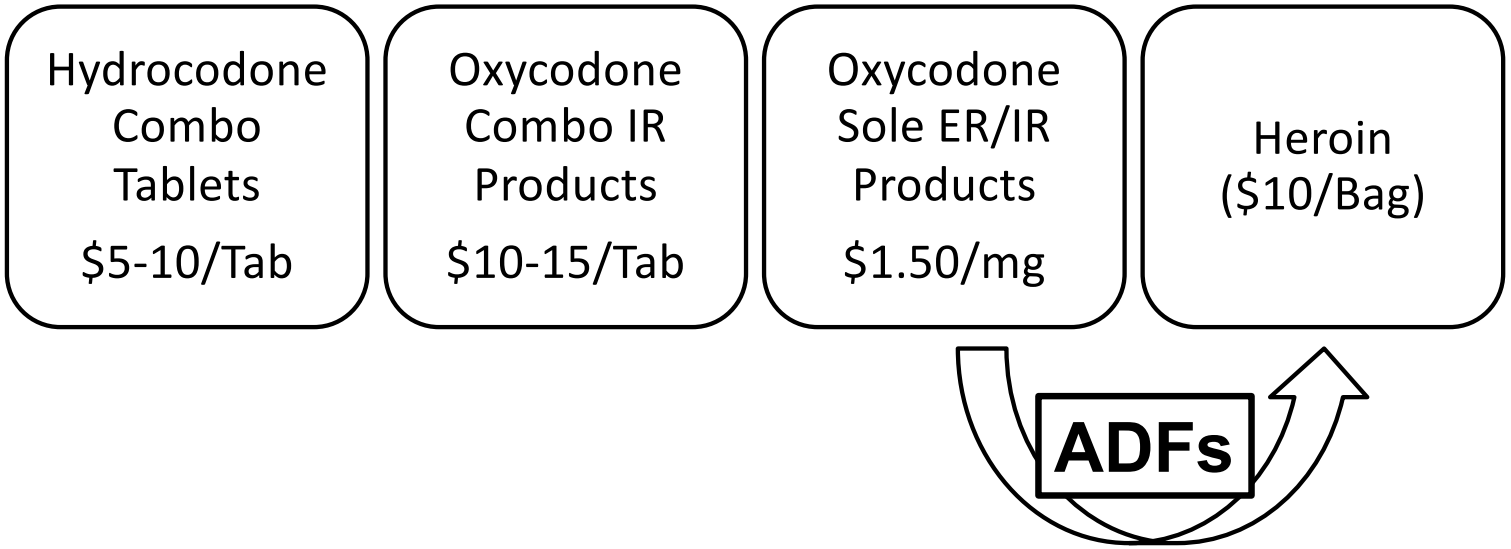
2017 DEA National Drug Threat Assessment. https://www.dea.gov/docs/DIR-040-17_2017-NDTA.pdf

Opioid Abuse Transition



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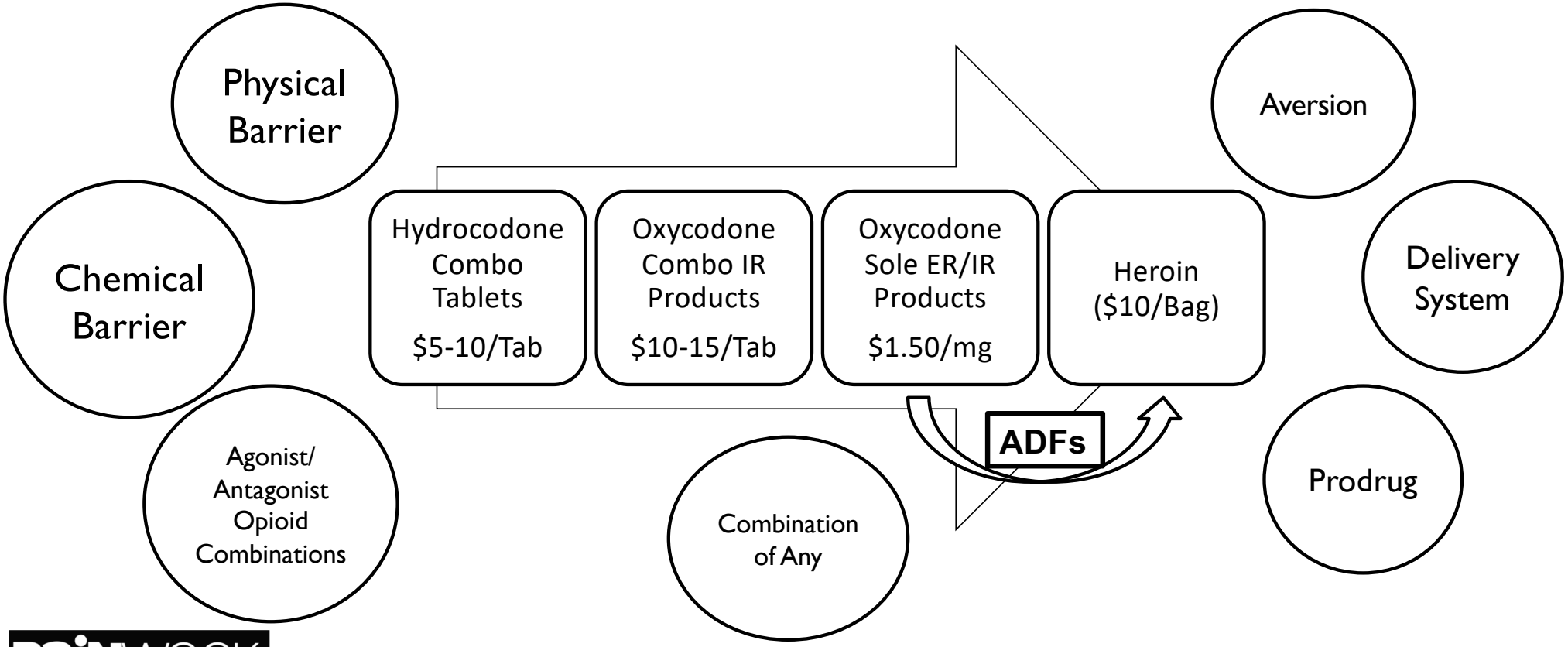
Shah A, et al. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use – United States, 2006-2015. *Weekly* / March 17, 2017 / 66(10); 265–269.
www.bluelight.org

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	

Sophisticated Science?

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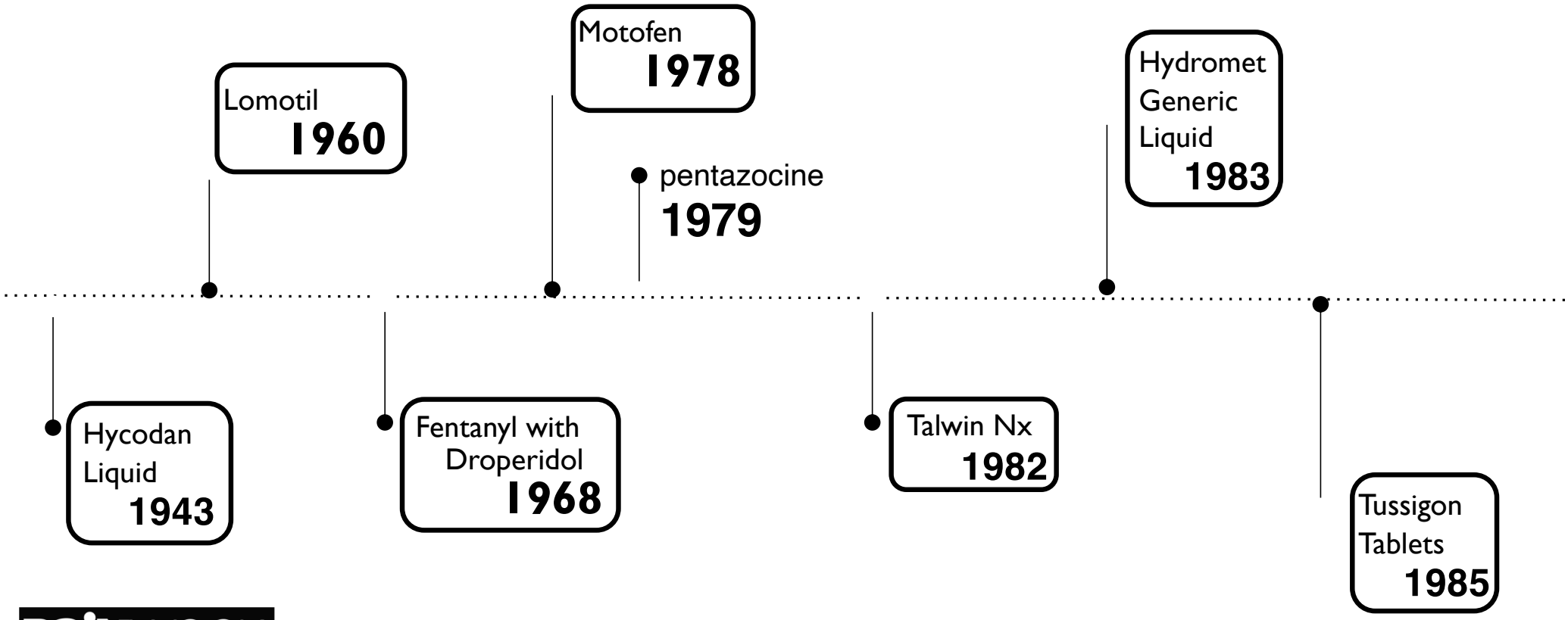
FDA Opioid Timeline



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

The Early "ADFs"

- Hydrocodone & homatropine
  - Tussigon tablets 5mg/1.5mg (FDA 1985)
  - Hydromet liquid 5mg/1.5mg per 5mL (FDA 1943, generic 1983)

  - Homatropine
    - Anticholinergic similar to atropine (aversion)

https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm3

The Early "ADFs"

- Phenylpiperidine opioids (diarrhea treatment)
  - Lomotil® (diphenoxylate & atropine, 1960)
  - Motofen® (difenoxin & atropine, 1978): metabolite of diphenoxylate

  - Atropine
    - Produces dysphoria in large doses (aversion)
    - Anticholinergic: blurred vision, constipation, visual disturbances

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

The Early "ADF's"

Fentanyl with droperidol

- Dr. Robert Dripps (U of Penn) strong opponent due to abuse concerns
- Dr. Janssen (Janssen Pharmaceuticals) & Dr. Dripps developed the combination product of droperidol to fentanyl in a 50:1 ratio (FDA approved 1968)
- Dr. de Castro (Europe) recommended ratio based on his patient treatments including the droperidol to produce dysphoria if abused
- FDA later approved fentanyl as solo products

Stanley, T. The Fentany Story. The Journal of Pain, Vol 15, No 12 (December), 2014: pp 1215-1226.

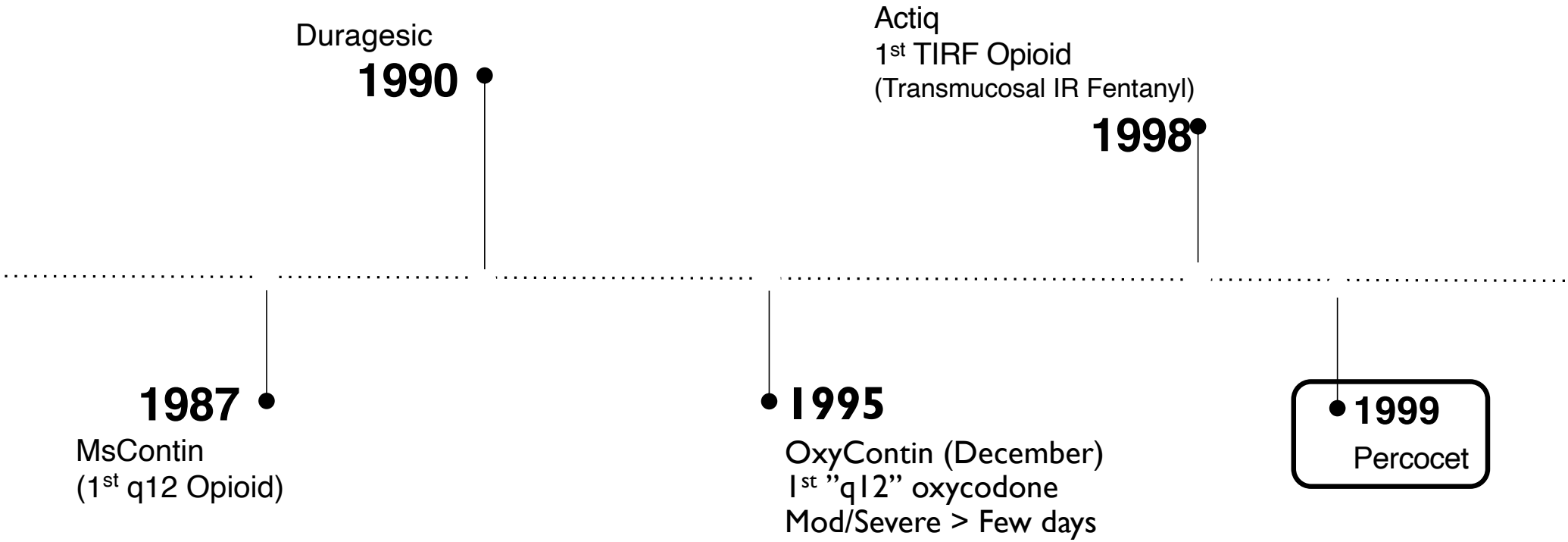
The Early "ADFs"

Pentazocine and naloxone (FDA approved in 1982)

- –Pentazocine single product
  - •Kappa agonist, mu antagonist
  - •Single product pentazocine FDA approved 1967
  - •Observed to be crushed, mixed w/ antihistamine pyribenzamine, & injected
    - –"Pinks & Blues"
  - •1st DEA reclassification: pentazocine (single product) to CIV in 1979

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

FDA Opioid Timeline



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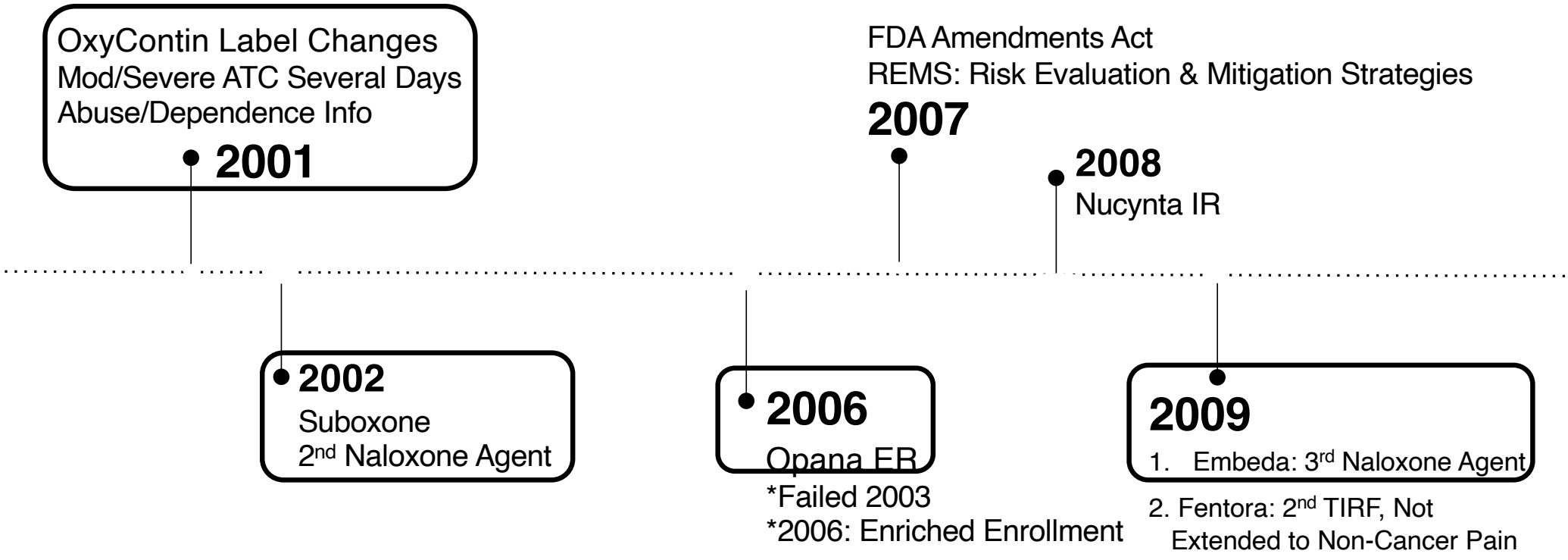
FDA Opioid Timeline



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

FDA Opioid Timeline

2010

1. Reformulation of OxyContin (OP)
2. Propoxyphene Voluntary Withdrawal Recommended

Nucynta ER
Reformulation of Opana ER (2006)

2011

1. All ER/LA Opioids REMS: Prescriber Voluntary CE
2. Opana ER reformulated to avoid IN Abuse (IV Spiked)

2012

2013

1. FDA ADF Opioid Extra ADF Studies "Category 3"
2. Original Opana ER Allowed to Stay on Market
3. Recommended HCP be CII

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

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

2017 (March)

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

  • Polyethylene oxide (PEO) coating lodged in the arterioles of the kidneys of IV abusers

2017 (July)

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

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

FDA Opioid Timeline

2014
1. Evzio
2. Embeda (ADF)
3. Hysingla (ADF)

2015
1. Zohydro ER
2. OxyContin >11yo Opioid Tolerant
3. ~~MorphaBond ER~~
4. Narcan Nasal Spray

2016
1. Xtampza ER
2. Probuphine (Bup Implant)

2017
1. Arymo ER
2. ~~RoxyBond IR~~
3. Sublocade (Bup QM)
4. Ref Opana ER Removed from Market
5. FDA ADF Studies Guidance

2018
1. Loperamide Blister/Single-Dose Packs
2. Apadaz (Benzhydrocodone/APAP)

2019
1. Dsuvia (sufentanil)
2. Generic Narcan NS

2020
Olinvyk (Olinceridine) IV

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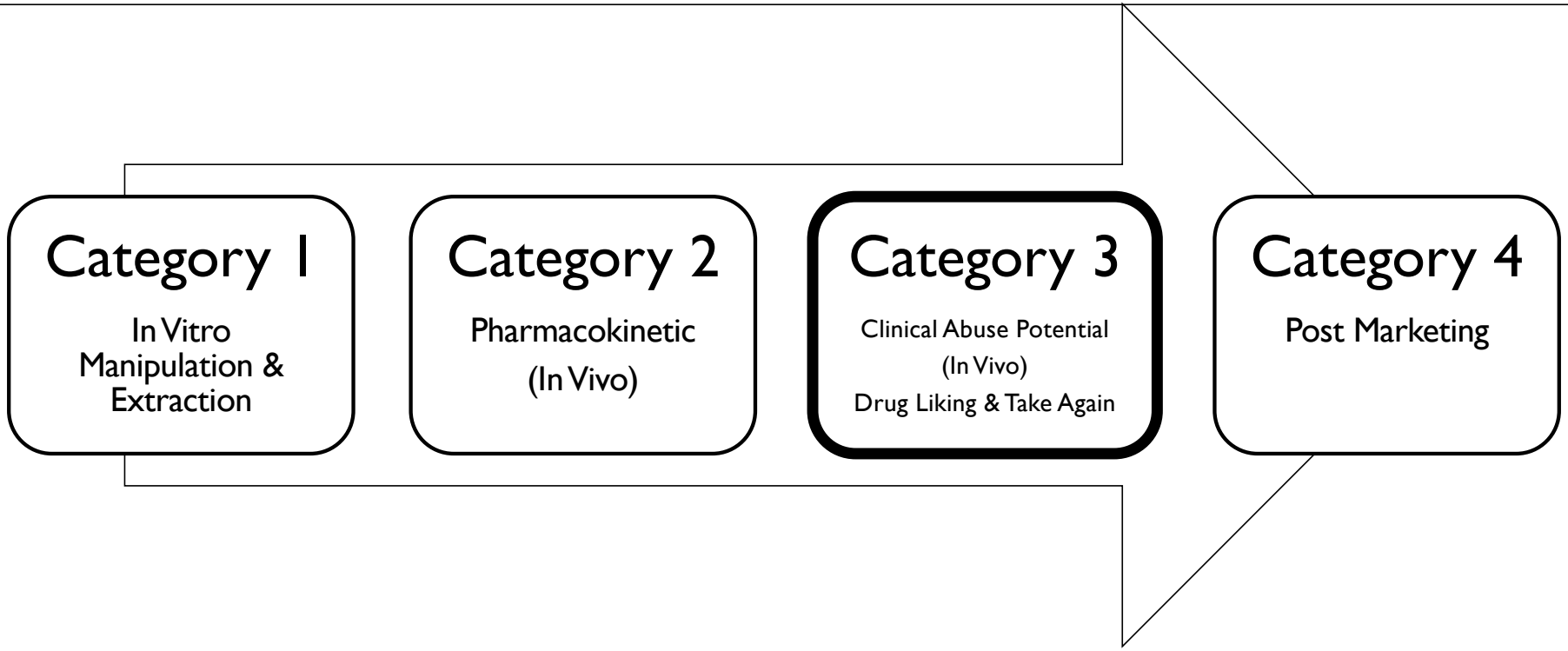
https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm

FDA ADF Studies



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

Category 3: Abuse Potential Studies

Physically manipulated products compared to regular product

- Cutting
- Grafting
- Milling
- Chewing
- +/- Heat

Routes of Administration

–Ingestion (Oral Route)

- Oral bioavailability

–Injection (Parenteral Route)

- Extractability and Syringeability

–Insufflation (Nasal Route)

- Nasal bioavailability & PD effects

–Smoking (Inhalation Route)

- Ability to sublimate

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

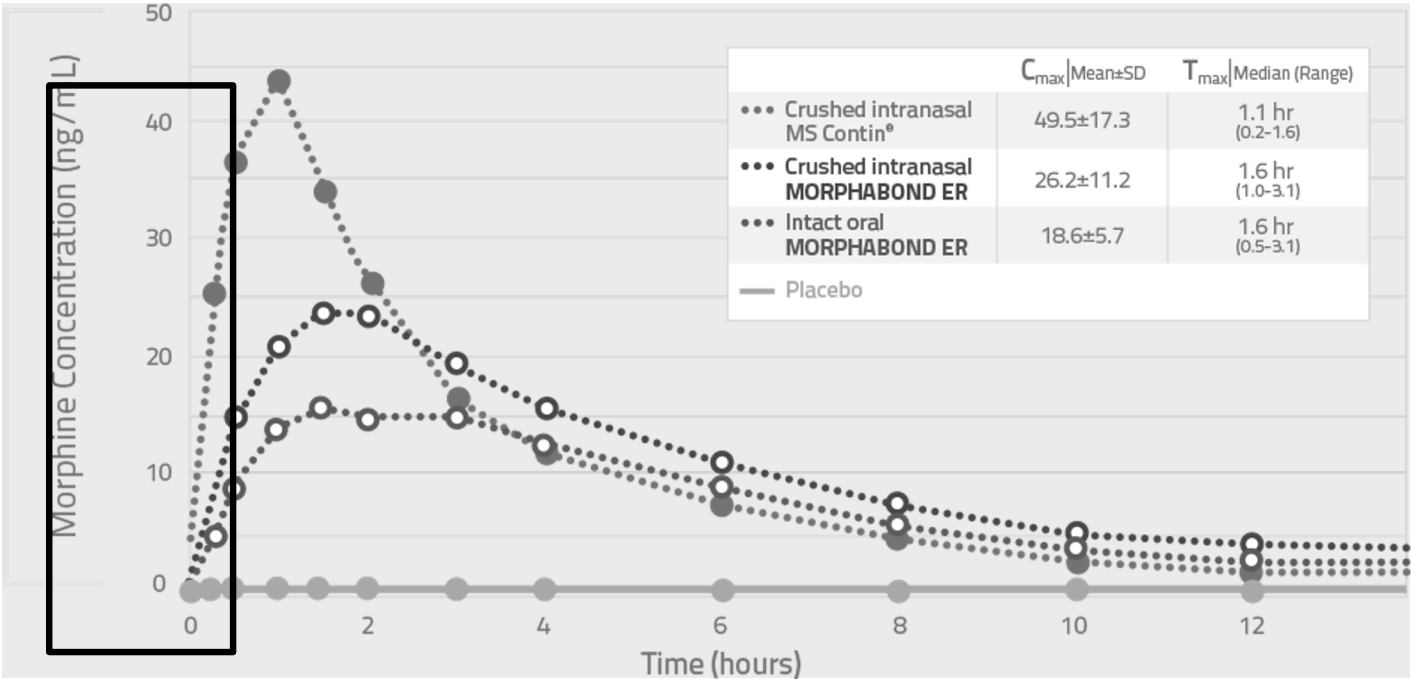
Category 3: Abuse Potential Studies

In Vitro Studies	In Vivo Studies
Extractability Studies	Nasal & Oral PK
Performed at Both Room Temp & Elevated Temp	Multiple Strengths Tested
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, & 0.1N NaOH	Agonist/Antagonist Levels

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

ADF Pharmacokinetics

Derived from Original MorphaBond Data



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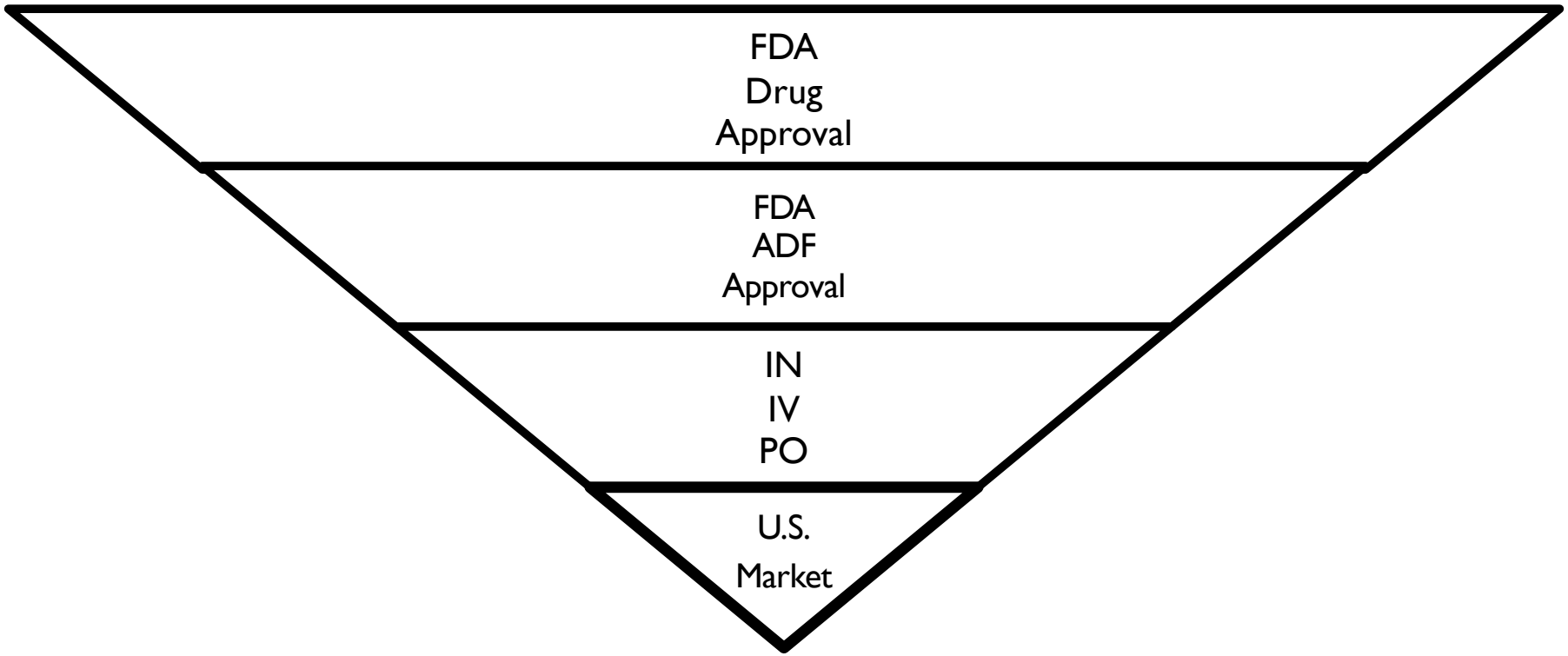
https://morphabondhcp.com/clinical-studies-intranasal-pk-data

ADF Opioid Funnel



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So who made the cut…pun intended

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Abuse Deterrent Formulation (ADF) Opioids "Attempts"

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

Medicine	Product	FDA ADF Approval			Formulation	Generic Available
oxycodone	Xtampza ER®	IN	IV	PO Chew	ER Capsule	No
	OxyContin®	IN	IV		ER Tablet	Yes
hydrocodone	Hysingla®	IN	IV	PO Chew	ER Tablet	Yes

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411218/
https://www.sciencedirect.com/science/article/pii/S0378517316304884
https://www.futuremedicine.com/doi/pdf/10.2217/pmt-2015-0005
https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm

FDA Approved ADF Opioids on US Market (2021)

Medicine	Product	FDA ADF Approval			Formulation	Generic Available
hydrocodone	Hysingla®	IN	IV	PO Chew	ER Tablet	Yes
oxycodone	OxyContin®	IN	IV		ER Tablet	Yes
	Xtampza ER®	IN	IV	PO Chew	ER Capsule	No

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411218/
https://www.sciencedirect.com/science/article/pii/S0378517316304884
https://www.futuremedicine.com/doi/pdf/10.2217/pmt-2015-0005
https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm

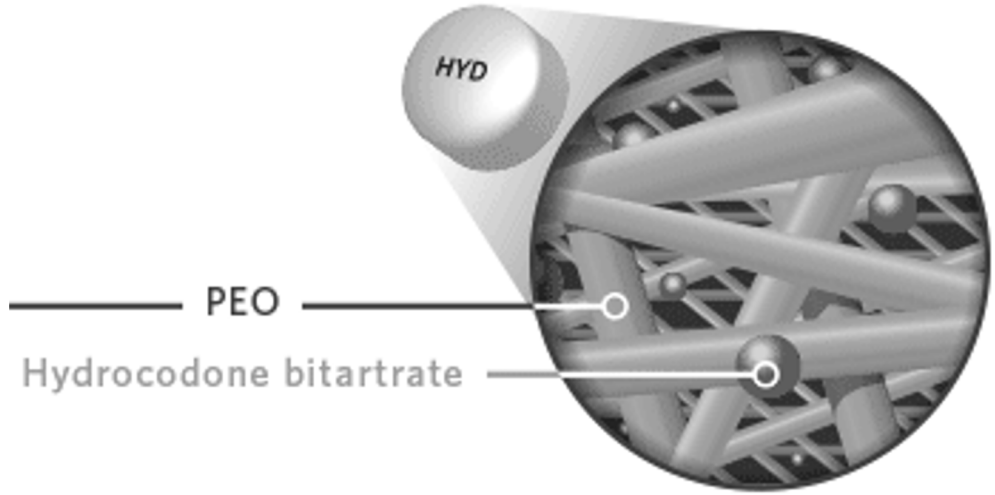
Hysingla®

- 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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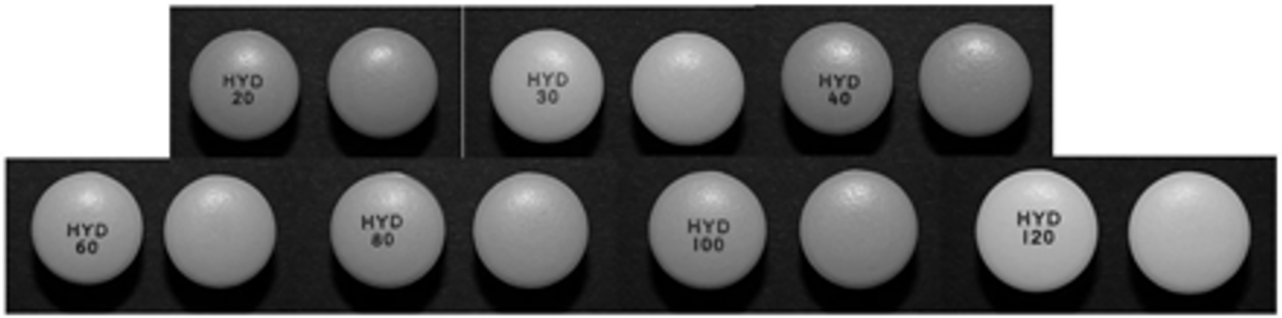
Hysingla®

Available
Generic

Hydrocodone/apap
10mg/325mg
1 T q 4 to 6 h
???



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Clinical Pharmacology Online Database

FDA Approved ADF Opioids on US Market (2021)

Medicine	Product	FDA ADF Approval			Formulation	Generic Available
hydrocodone	Hysingla®	IN	IV	PO Chew	ER Tablet	Yes
oxycodone	OxyContin®	IN	IV		ER Tablet	Yes
	Xtampza ER®	IN	IV	PO Chew	ER Capsule	No

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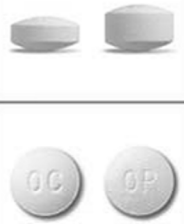
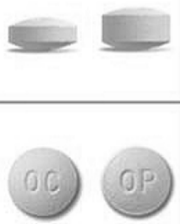
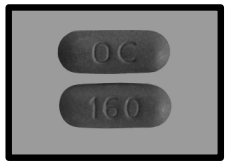
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411218/
https://www.sciencedirect.com/science/article/pii/S0378517316304884
https://www.futuremedicine.com/doi/pdf/10.2217/pmt-2015-0005
https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm

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 shopping, overdoses, & poison center calls (heroin replaced?)
- Q12h dosing ???

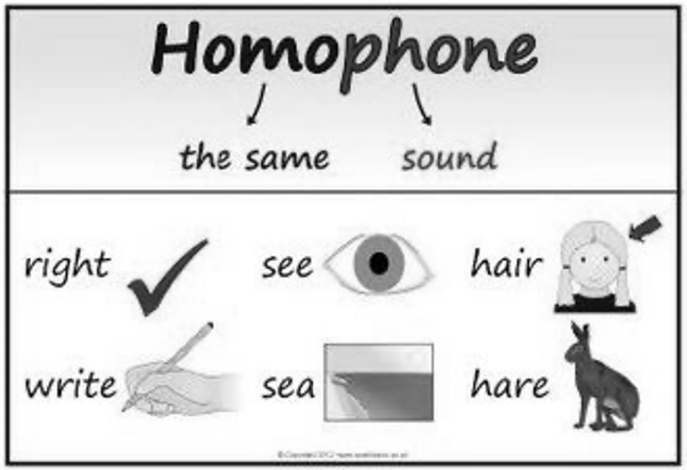
Original OxyContin®

New abuse-deterrent OxyContin®

PAINWEEK®


PURDUE


PERDUE®


Homophone
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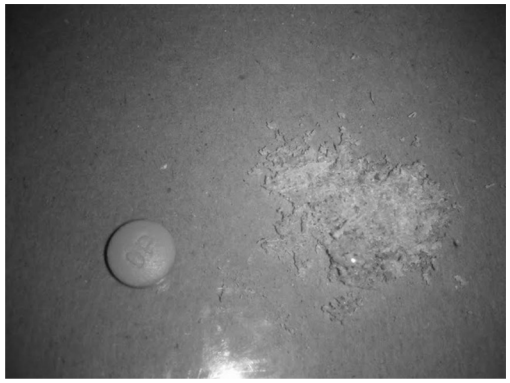
PainWeek®

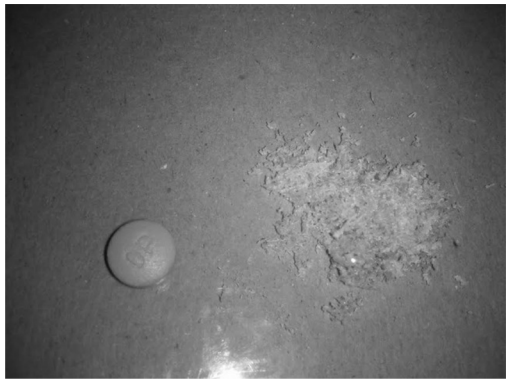
Oxy-Crisping



Tools of the Trade

- Grater (PediEgg)
- Ceramic/glass plate
- Paper towel
- Microwave
- Fridge/freezer

Oxy-Crisping



Tools of the Trade

- Grater (~~Pedi Egg~~) (lemon zester)
- Ceramic/glass plate
- Paper towel
- Microwave
- Fridge/freezer

PAINWEEK

FDA Approved ADF Opioids on US Market (2021)

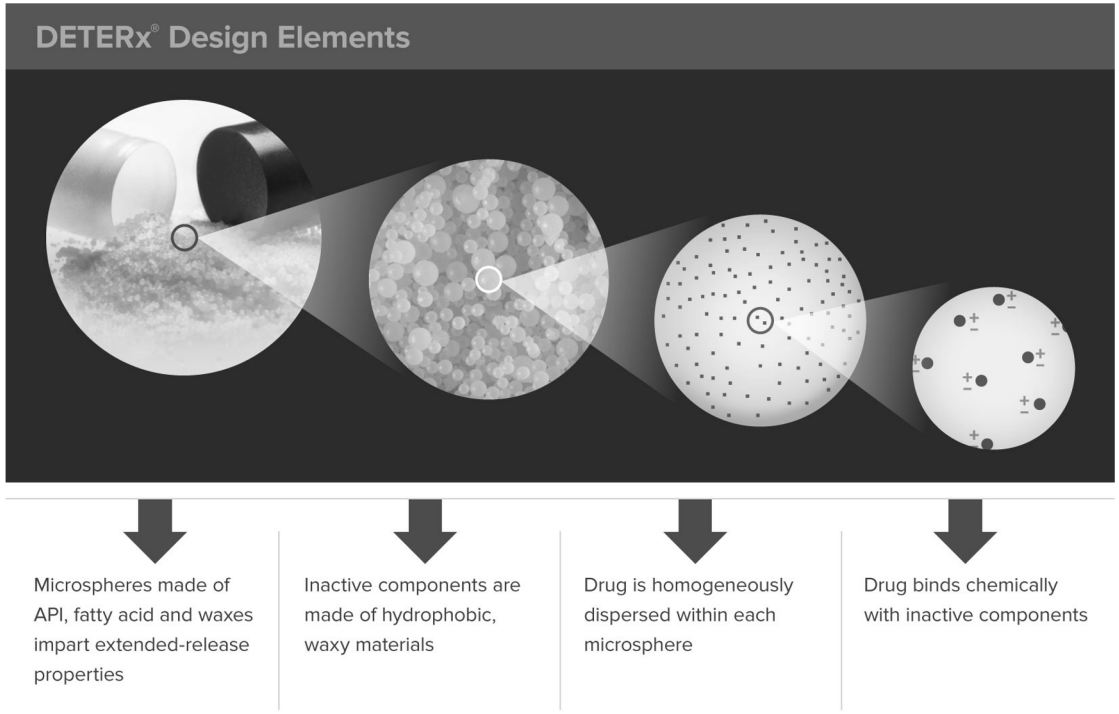
Medicine	Product	FDA ADF Approval			Formulation	Generic Available
hydrocodone	Hysingla®	IN	IV	PO Chew	ER Tablet	Yes
oxycodone	OxyContin®	IN	IV		ER Tablet	Yes
	Xtampza ER®	IN	IV	PO Chew	ER Capsule	No

PAINWEEK®

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411218/
https://www.sciencedirect.com/science/article/pii/S0378517316304884
https://www.futuremedicine.com/doi/pdf/10.2217/pmt-2015-0005
https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm

Xtampza ER®

- DETERx technology
  - Waxy microspheres solidify in a needle

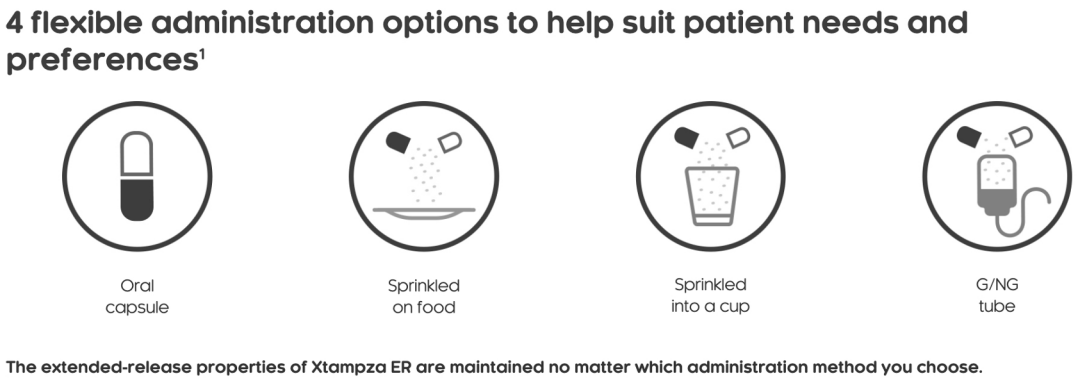


PAINWEEK®

https://www.xtampzaer.com/hcp/

Xtampza ER®

- 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

PAINWEEK®

https://www.xtampzaer.com/hcp/

Oxycodone to Xtampza ER® Comparison

OxyContin® (oxycodone HCl) Dosage		**Xtampza ER** (oxycodone) Dosage
10 mg		**9 mg** 
15 mg		**13.5 mg** 
20 mg		**18 mg** 
30 mg	Equivalent to	**27 mg** 
40 mg		**36 mg** 
60 mg		**27 mg + 27 mg** 
80 mg		**36 mg + 36 mg** 

PAINWEEK®

https://www.xtampzaer.com/hcp/dosing-and-administration/#default

Xtampza ER®

Dosing Considerations

- Hepatic impairment
  - Begin at 1/3rd to ½ usual starting dose, followed by careful dose titration
- Renal Impairment (CrCl < 60mL/min)
  - Oxycodone concentrations approximately 50% higher
  - Conservative Initiation Dosage
  - Use of alternative analgesics for patients requiring <9mg Xtampza ER®
- Opioid Naïve Patients
  - Initiate treatment with one 9 mg capsule orally every 12 hours with food

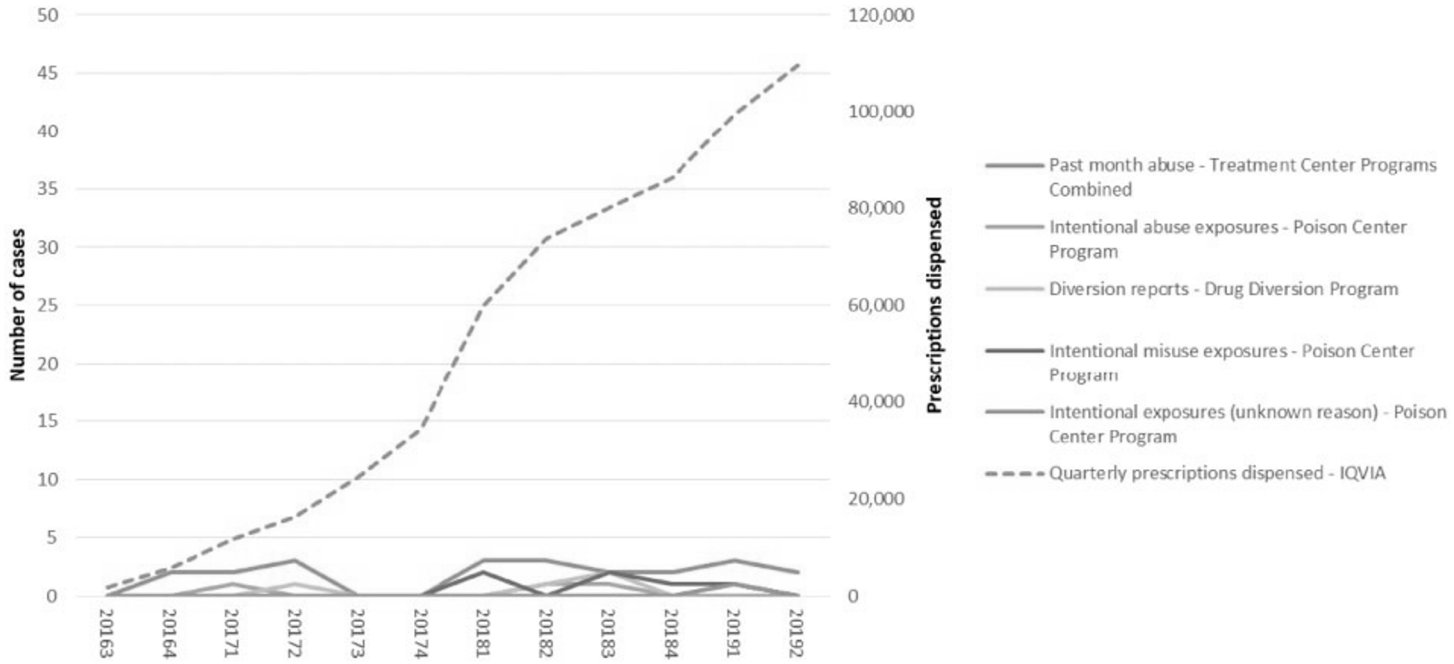
Xtampza ER®

Transition from Other Rx Opioids

- Other Oral Oxycodone Formulations May Be Converted
  - Using the same total daily dose of oxycodone, by administering one-half of the patient's total daily oral oxycodone dose as Xtampza ER® every 12 hours with food
- Transdermal (TD) Fentanyl
  - 18 hours following the removal of the TD fentanyl patch, treatment can be initiated
  - No systematic assessment of such conversion, thus use a conservative Xtampza ER® approximate 9 mg dose every 12 hours as initial substitution for each 25 mcg/hr dosage of TD fentanyl

Xtampza ER®

2020 Post Marketing Analysis (Rx's to Abuse)



July 1, 2016, through June 30, 2019 (1st 3-Years Initial Marketing)

PainWeek®

Severtson SG, et. al. Postmarketing Analysis of Misuse, Abuse, and Diversion of Xtampza ER. Pain Medicine, 21(12), 2020, 3660–3668

Xtampza ER®

2020 Post Marketing Analysis (Abuse Cases)

Table 2. Cumulative abuse and misuse cases by program, drug group, and route of administration, 2016-Q3 through 2019-Q2

	Poison Center Program, Total Intentional Abuse/Misuse/Unknown Exposures			Treatment Center Programs Combined, Past-Month Abuse			Drug Diversion Program, Total Events
Drug Group	Cases, No.	Cases Involving Injection, No. (%)	Cases Involving Inhalation, No. (%)	Cases, No.	Cases Reporting Injection, No. (%)	Cases Reporting Snorting, No. (%)	Cases, No.
Xtampza ER	10	0 (0)	0 (0)	21	2 (9.5)	3 (14.3)	5
IR oxycodone	5,292	59 (1.1)	307 (5.8)	4,113	473 (11.5)	1,550 (37.7)	4,360
Other ADF ER opioids	817	31 (3.8)	76 (9.3)	2,158	343 (15.9)	672 (31.1)	313
Non-ADF ER opioids	486	9 (1.9)	10 (2.1)	628	185 (29.5)	113 (18.0)	418

ADF = abuse-deterrent formulation; ER = extended-release formulation; IR = immediate-release formulation.

July 1, 2016, through June 30, 2019 (1st 3-Years Initial Marketing)

PainWeek®

Severtson SG, et. al. Postmarketing Analysis of Misuse, Abuse, and Diversion of Xtampza ER. Pain Medicine, 21(12), 2020, 3660–3668

Xtampza ER®

2021 Post Marketing Analysis (Abuse Cases)

Table 3 Prevalence of Nonmedical Use (NMU) for Xtampza ER and Comparators by Route of Administration (7/1/2016–12/31/2019)

	Past 30-Day Xtampza ER NMU		Past 30-Day Other Oxycodone ER NMU		Past 30-Day Oxycodone IR NMU	
	n	%	n	%	n	%
Total NMU Mentions*	**73**	**100.0**	**4114**	**100.0**	**31,281**	**100.0**
Route of Administration**						
Any Oral**	**45**	**61.6**	**3261**	**79.3**	**21,977**	**70.3**
Swallow whole	38	52.1	2262	55.0	15,498	49.5
Chew then swallow	5	6.8	658	16.0	4287	13.7
Dissolve like a cough drop	2	2.7	230	5.6	1489	4.8
Dissolved in liquid then drank	0	0.0	111	2.7	703	2.2
Any non-oral**	**21**	**28.8**	**2380**	**57.9**	**18,787**	**60.1**
Chi-square, Any Non-Oral (p-value)	**Index Group**		**18.57 (*<0.001*)**		**52.47 (*<0.001*)**	
Snort	13	17.8	1314	31.9	12,696	40.6
Smoke	3	4.1	165	4.0	1250	4.0
Inject	5	6.8	901	21.9	4841	15.5
Other	8	11.0	189	4.6	685	2.2

PainWeek®

Green JL, et. al. Nonmedical Use of Xtampza® ER and Other Oxycodone Medications in Adults Evaluated for Substance Abuse Treatment: Real-World Data from the Addiction Severity Index-Multimedia Version (ASI-MV®). *J Pain Res*. 2021;14:1773-1783

Xtampza ER®

2020 Post Marketing Analysis (Street Pricing)

Table 3. Geometric mean price per milligram by drug group and API, unadjusted and adjusted ratio of geometric mean prices per milligram

Value	Value	No.	Geometric Mean Price per mg (95% CI)	Unadjusted Ratio of Geometric Mean Price per mg (95% CI)	Adjusted Ratio of Geometric Mean Price per mg[a] (95% CI)
Drug Group	Xtampza ER	157	$0.59 ($0.51–$0.69)	Ref	Ref
	IR oxycodone	9,027	$0.99 ($0.97–$1.01)	1.67 (1.43–1.94), $P < 0.001$	1.08 (0.93–1.25), $P = 0.335$
	Other ADF ER opioids	2,012	$0.50 ($0.48–$0.52)	0.84 (0.72–0.98), $P = 0.030$	1.11 (0.95–1.29), $P = 0.176$
	Non-ADF ER opioids	745	$0.33 ($0.31–$0.35)	0.59 (0.51–0.69), $P < 0.001$	1.18 (0.97–1.45), $P = 0.103$
API	Oxycodone	10,729	$0.90 ($0.89–$0.92)	Ref	Ref
	Hydrocodone	503	$0.37 ($0.34–$0.40)	0.41 (0.37–0.44), $P < 0.001$	0.69 (0.63–0.77), $P < 0.001$
	Morphine	709	$0.31 ($0.29–$0.33)	0.34 (0.32–0.37), $P < 0.001$	0.57 (0.50–0.66), $P < 0.001$
mg strength	Natural log of mg strength		—	0.59 (0.58–0.61), $P < 0.001$	0.63 (0.61–0.65), $P < 0.001$

ADF = abuse-deterrent formulation; API = active pharmaceutical ingredient; ER = extended-release formulation; IR = immediate-release formulation.

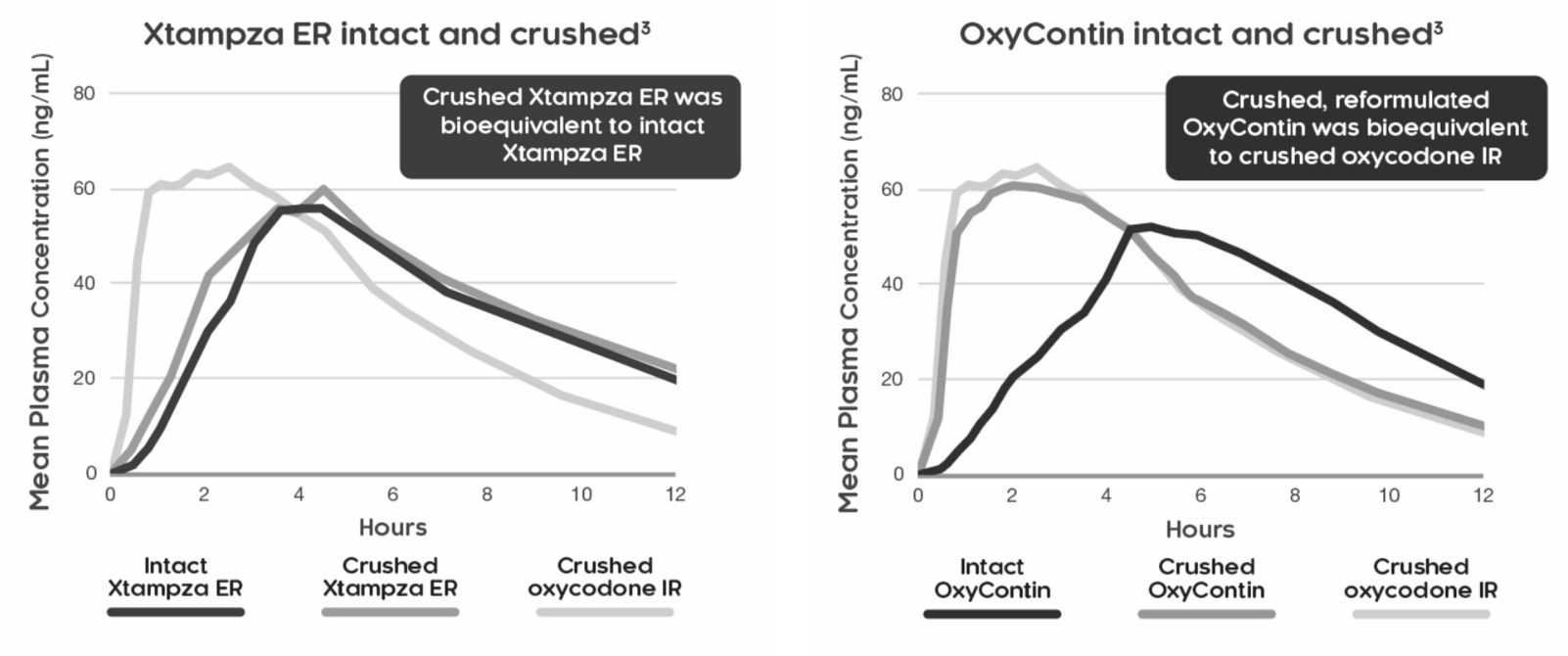
*Drug group ratios are adjusted for variables associated with price per milligram, specifically active pharmaceutical ingredient and pill dosage strength in milligrams.

July 1, 2016, through June 30, 2019 (1st 3-Years Initial Marketing)

PainWeek®

Severtson SG, et. al. Postmarketing Analysis of Misuse, Abuse, and Diversion of Xtampza ER. Pain Medicine, 21(12), 2020, 3660–3668

Xtampza ER® vs OxyContin



In a randomized, open-label, active-controlled, 5-treatment crossover study, Gudin et al compared the PK of crushed oxycodone IR to Xtampza ER (crushed and intact) and reformulated OxyContin (crushed and intact) taken orally in 42 healthy subjects.[3]

PAINWEEK®

https://www.xtampzaer.com/hcp/

FDA Approved ADF Opioids on US Market (2021)

Medicine	Product	FDA ADF Approval			Formulation	Generic Available
hydrocodone	Hysingla®	IN	IV	PO Chew	ER Tablet	Yes
oxycodone	OxyContin®	IN	IV		ER Tablet	Yes
	Xtampza ER®	IN	IV	PO Chew	ER Capsule	No

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411218/
https://www.sciencedirect.com/science/article/pii/S0378517316304884
https://www.futuremedicine.com/doi/pdf/10.2217/pmt-2015-0005
https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm

Institute for Clinical & Economic Review (ICER)

ADF Opioids: Effectiveness & Value (2006)

ADF Products in Study
Hysingla ER (hydrocodone, Purdue)
Vantrela (hydrocodone, Teva)
Arymo ER (morphine, Egalet)
Embeda (morphine + naltrexone, Pfizer)
Morphabond ER (morphine, Inspirion)
OxyContin (oxycodone, Purdue)
Xtampza ER (oxycodone, Collegium)
Targiniq (oxycodone + naloxone, Purdue)
Troxyca ER (oxycodone + naloxone, Pfizer)
RoxyBond (oxycodone, Inspirion)

Non-ADF Opioids	ADF Opioids
$5.82 Average Cost	$11.60 Average Cost $6.86 Break-Even Cost

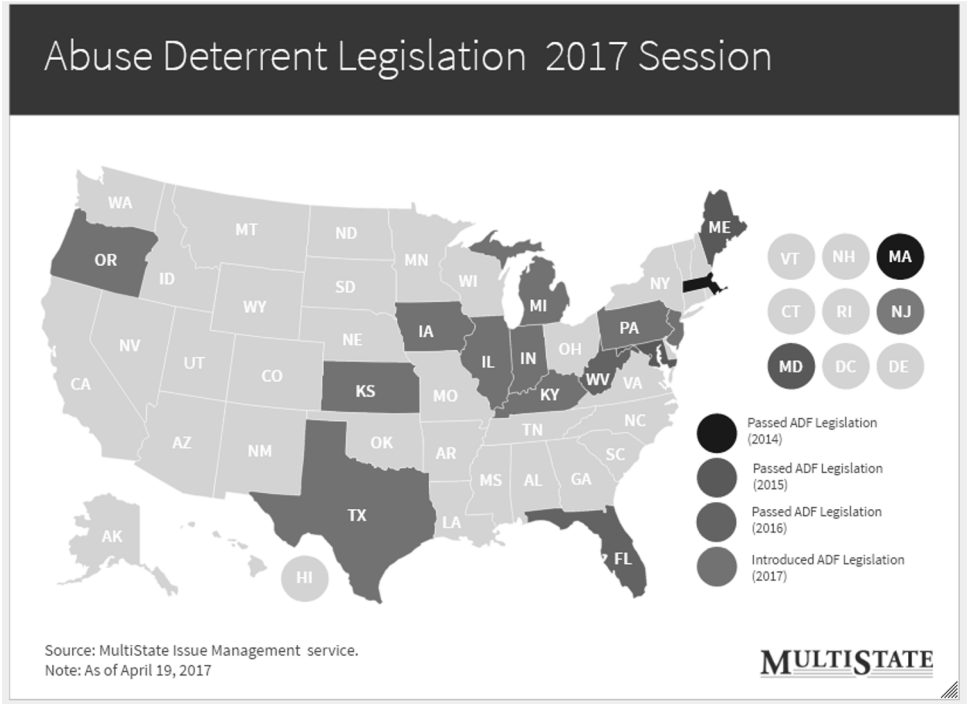
Conflicts of Interest

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

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

States Mandating ADF Opioid Coverage

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



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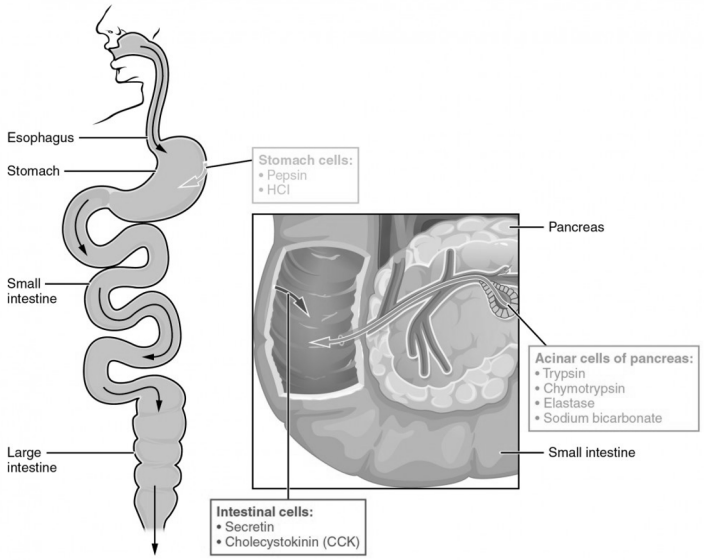
ADF Opioid Pipeline
TAAP/MPAR

- TAAP (Trypsin Activated Abuse Protection)
  - Trypsin is found only in the small intestine
- MPAR (Multi-Pill Abuse Resistance)
  - A small amount of trypsin inhibitor (soybeans & egg whites) added to each pill not affecting opioid release
  - If multiple pills are purposefully/accidentally ingested, the trypsin inhibitor blocks the prodrug activation

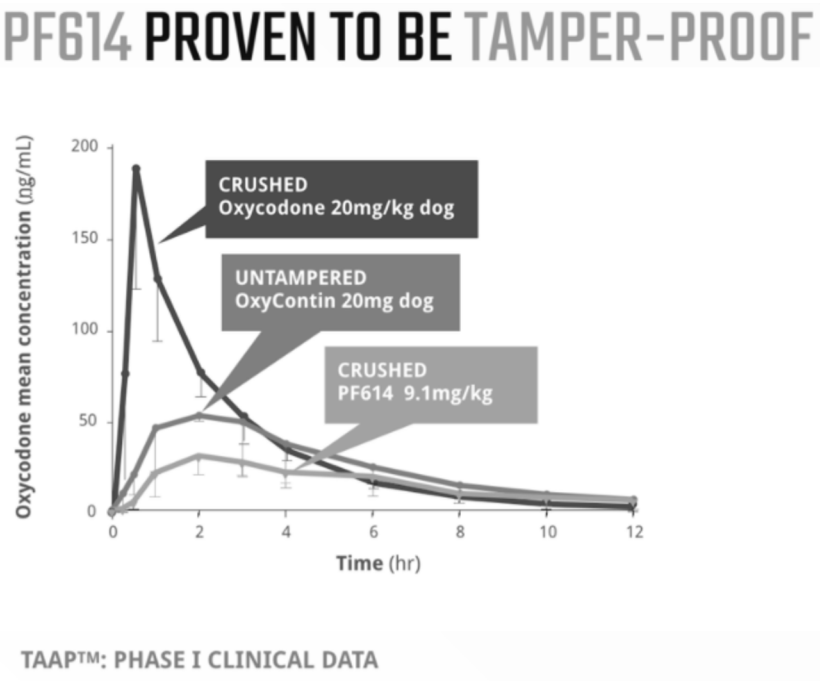


http://www.ensysce.com/bio-md-tech
http://www.ensysce.com/overdose-resistant-technology/
http://www.physiologymodels.info/digestion/proteins.htm

ADF Opioid Pipeline

TAAP/MPAR

- Oxycodone (PF614)
  - 12-hour t ½ (true BID dosing)
- Hydromorphone ER (PF329)
- Amphetamine (PF8001/8026)
  - ADHD
- R-Methadone (PF26810)
  - Medication Assisted Treatment (MAT)



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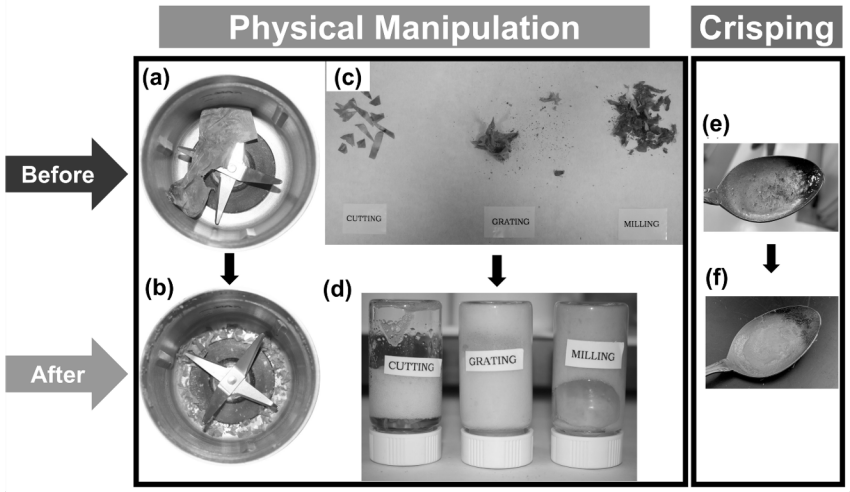
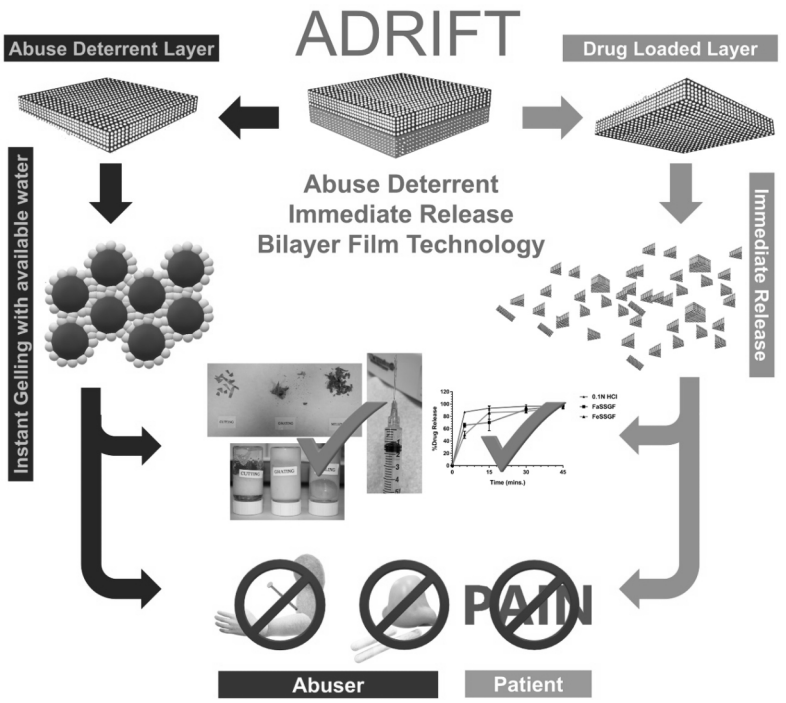
https://ensysce.com/our-pipeline
http://www.ensysce.com/overdose-resistant-technology/

ADF Opioid Pipeline

ADRIFT





PAINWEEK

Palekar S, et. al.Abuse deterrent immediate release film technology (ADRIFT): A novel bilayer film technology for limiting intentional drug abuse, International Journal of Pharmaceutics (2020),

Audience Question #1

While performing an opioid risk assessment for a 45yo patient with chronic lower back pain (utilizing hydrocodone/apap 10/325mg QID), you find out that the patient lives in a house with a spouse who has a substance-use disorder. Which of the following FDA approved ADF ER opioids is readily available on the US market and most appropriate for this patient?

a) Hysingla ER 40mg QD
b) Hysingla ER 60mg QD
c) Zohydro ER 20mg BID
d) Zohydro ER 30mg BID

Audience Question #1 (ANSWER)

While performing an opioid risk assessment for a 45yo patient with chronic lower back pain (utilizing hydrocodone/apap 10/325mg QID), you find out that the patient lives in a house with a spouse who has a substance-use disorder. Which of the following FDA approved ADF ER opioids is readily available on the US market and most appropriate for this patient?

a) **HYSINGLA ER 40MG QD [CORRECT]**
b) Hysingla ER 60mg QD
c) Zohydro ER 20mg BID
d) Zohydro ER 30mg BID

Medicine	Product	FDA ADF Approval			Formulation	Generic Available
oxycodone	Xtampza ER®	IN	IV	PO Chew	ER Capsule	No
	OxyContin®	IN	IV		ER Tablet	Yes
hydrocodone	Hysingla®	IN	IV	PO Chew	ER Tablet	Yes

Audience Question #2

While performing an opioid risk assessment for a 55yo patient with chronic lower back pain (utilizing oxycodone ER 20mg BID), you find out that the patient has a history of marijuana addiction, and that the patient would prefer to sprinkle his medication on his food instead of swallowing the pill whole. Which of the following FDA approved ADF ER opioids is readily available on the US market and most appropriate for this patient?

a) Troxyca ER 30mg QD
b) Troxyca ER 40mg QD
c) Xtampza ER 20mg BID
d) Xtampza ER 18mg BID

Audience Question #2 (ANSWER)

While performing an opioid risk assessment for a 55yo patient with chronic lower back pain (utilizing oxycodone ER 20mg BID), you find out that the patient has a history of marijuana addiction, and that the patient would prefer to sprinkle his medication on his food instead of swallowing the pill whole. Which of the following FDA approved ADF ER opioids is readily available on the US market and most appropriate for this patient?

a) Troxyca ER 30mg QD
b) Troxyca ER 40mg QD
c) Xtampza ER 20mg BID
d) XTAMPZA ER 18MG BID [CORRECT]

Medicine	Product	FDA ADF Approval			Formulation	Generic Available
oxycodone	Xtampza ER®	IN	IV	PO Chew	ER Capsule	No
	OxyContin®	IN	IV		ER Tablet	Yes
hydrocodone	Hysingla®	IN	IV	PO Chew	ER Tablet	Yes

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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

PAINWEEK

Audience Question #3 (ANSWER)

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 [CORRECT ANSWER]

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

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Discussion

PAINWEEK

LinkedIn: Mark Garofoli