

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

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Faculty





- Family of 8 Pharmacists
 Wife, In-Laws, & Cousins
- Family Vineyard in the Marche Region of Italy

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Disclosures

Nothing to disclose

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 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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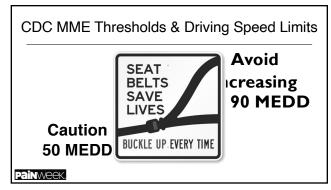
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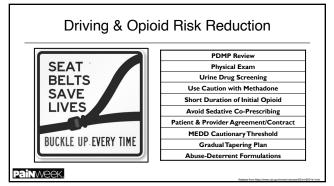
CDC MME Thresholds & Driving Speed Limits

Avoid
Increasing
Speed >/= 90 MEDD
Limits

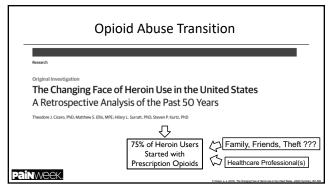
Caution 50 MEDD

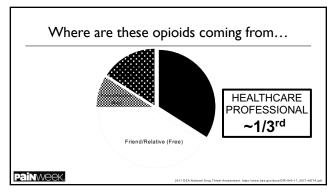
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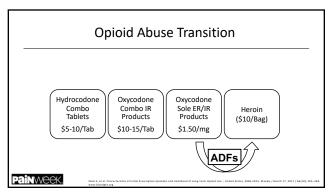


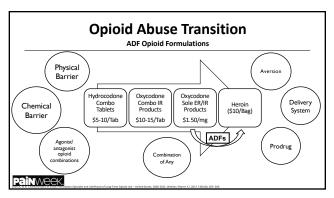


	Opioid Abuse Transition	
l	Research	
l	Original Investigation	
	The Changing Face of Heroin Use in the United States A Retrospective Analysis of the Past 50 Years	
l	Theodore J. Cicero, PhD; Matthew S. Ellis, MPE; Hilary L. Surratt, PhD; Steven P. Kurtz, PhD	
l	$lue{lack}$	
	75% of Heroin Users Started with Prescription Opioids	
1	Pain Week.	





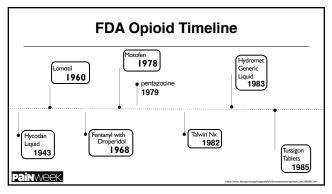




Types of Abuse-Deterrent Formulations (ADFs) ADF Type Description I. Physical Barrier Prevent chewing, crushing, cutting, grating, or grinding Resist extraction of the opioid through use of common solvents including water, alcohol or other organic solvents 2. Chemical Barrier Antagonist is added to the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

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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)

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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

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

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The Early "ADFs"

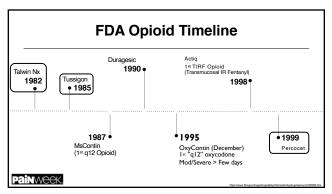
Pentazocine and naloxone (FDA approved in 1982)

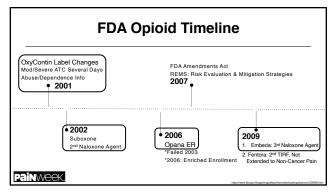
- -Pentazocine single product
 - •Kappa agonist, mu antagonist
 - •Single product pentazocine FDA approved 1967
 - •Observed to be crushed, mixed w/ antihistamine pyribenzamine, & injected --"Pinks & blues"
- •1st DEA reclassification: pentazocine (single product) to CIV in 1979

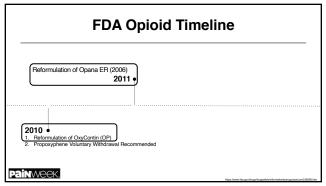
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https://www.fds.gov/drugs/drugsafety/informationbydrugclassa/ucm338566.htt

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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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https://www.tds.gov/drugs/drugsafety/informationbydrugclass/ucm338565.htm

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.

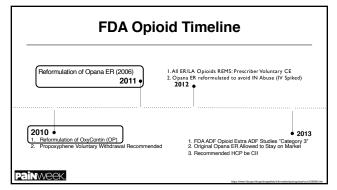
 High molecular weight of the polyethylene oxide (PEO) coating that became lodged in the arterioles of the kidneys of IV abusers

2017 (July)

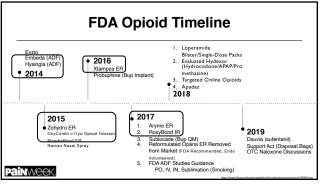
-FDA recommended Endo remove Opana ER from market, and Endo did so

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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 O O O Contribution Online Painweck

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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

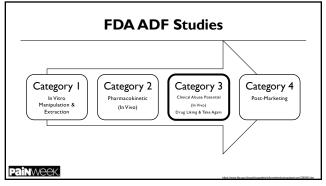
ightharpoonupNOT FDA approved as an abuse-deterrent formulation (ADF) opioid

➤ Benzhydrocodone/APAP 6.12/325mg = hydrocodone/APAP 7.5/325mg

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Clinical Pharmacology Online Data Apadaz Package Insert. 2018

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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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Category 3: Abuse Potential Studies

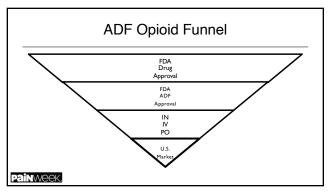
In Vitro Studies	In Vivo Studies
Extractability Studies	Nasal & Oral PK
Performed at Both Room Temp & Elevated Temp	Multiple Strengths Tested
Solvents Level 1: Deionized water Level 2: vinegar, 0.2% baking soda solution, 40% ethanol, & carbonated drink Level 3: 100% ethanol, 100% isopropyl alcohol, acetone, 0.1 N HCI, & 0.1 N NaOH	Agonist/antagonist levels

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So who made the cut...pun intended

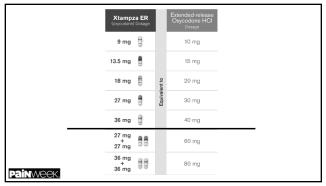


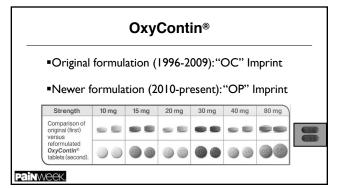
	Abuse	Deterrent Formu	lation (ADF) O	pioids			
	Active Ingredient	Product	FDA ADF Approval	Formulation			
		Xtampza ER®	IN, IV, & PO Chew	ER Capsule			
		Xartemis ER® (+APAP)	-	IR/ER Tablet			
	oxycodone	OxyContin [®]	IN & IV	ER Tablet			
	Oxycodone	Troxyca®	IN, IV, PO Crush	ER Capsule			
		Oxaydo®		IR Tablet			
FDA Approved ADF Opioids available on US Market (July 2020)		RoxyBond®	IN & IV	IR Tablet			
	tapentadol	Nucynta ER®	-	ER Tablet			
	hydromorphone	Exalgo®		ER Tablet			
	morphine	Embeda®	IN & PO Crush				
		morphine	morphine	morphine	Arymo®	IV	ER Tablet
		MorphaBond®	IN & IV				
		Hysingla®	IN, IV, & PO Chew	ER Tablet			
		Zohydro ER®		ER Capsule			
	hydrocodone	Vantrela ER®	IV	ER Tablet			
		Hydromet®		Liquid			
		Tussigon®		Tablet			
	benzhydrocodone	Apadaz®	-	Tablet			
	pentazocine	Talwin NX®		Tablet			
	Targini	iq (oxycodone) & Opana (o	xymorphone) are Off Ma	arket			



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

*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 **Base of the second of t





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?)

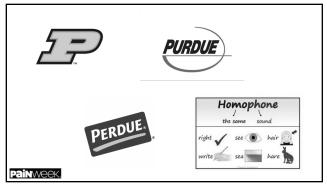






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Oxy-Crisping Tools of the Trade • Grater (PediEgg) • Ceramic/glass plate • Paper towel • Microwave • Fridge/freezer

Oxy-Crisping Tools of the Trade Grater (lemon zester) Ceramic/glass plate Paper towel Microwave Fridge/freezer

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FDA Approved ADF Opioids on US Market

(July 2020)

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

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Hysingla[®]

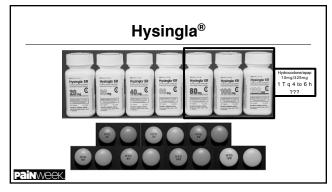
- RESISTEC Technology (*Same as OxyContin)

 —Forms a viscous gel around water
- ■ADF Category 3 studies (IN, IV, & PO): ~80% reduction in drug liking

HYdrocodone SINGle dose Long Acting



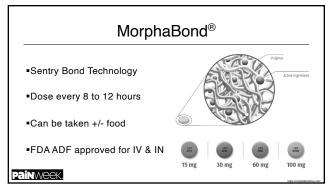
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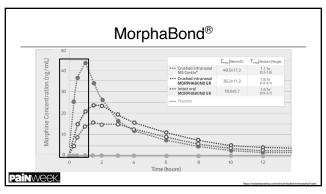


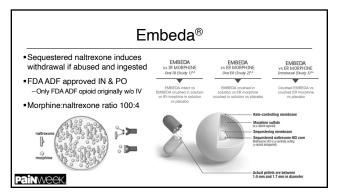
	FDA	ADF	Approval	Formulation
Xtampza ER®	IN	IV	PO Chew	ER Capsule
OxyContin [®]	IN	IV		ER Tablet
	IN	IV	PO Chew	ER Tablet
Embeda®	IN		PO Crush	
Arymo [®]		IV		ER Tablet
MorphaBond®	IN	IV		
	Xtampza ER® OxyContin® Hysingla® Embeda® Arymo®	Xtampza ER® IN OxyContin® IN Hysingla® IN Embeda® IN Arymo®	Xtampza ER® IN IV OxyContin® IN IV Hysingla® IN IV Embeda® IN Arymo® IV	Xtampza ER® IN IV PO Chew

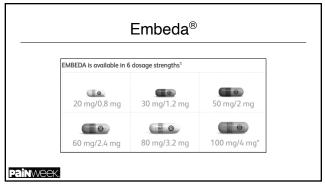
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MAT Buprenorphine Products with Naloxone...

FORMULATION	STRENGTH					
Sublingual Tablet	2mg BUP 0.5mg NX	-	8mg BUP 2mg NX	-		
Sublingual Film	2mg BUP 0.5mg NX	4mg BUP Img NX	8mg BUP 2mg NX	12mg BUP 3mg NX		

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Buprenorphine vs Naloxone

Bluelight

Lazylazyjoe (91/2010, 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 2 mg and be good for an entire day, compared to 4 mg sublingual. It also takes affect in 15 minutes instead of 90 minutes. You do have to be careful though, it is much easier to graciolate withdrawal this way. Walt 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/pil. 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 <u>Suboxone is uisal as asy to abuse as the Subutex.</u> 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.

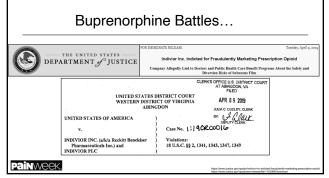
Dread (10/1/2010, 2:08am)

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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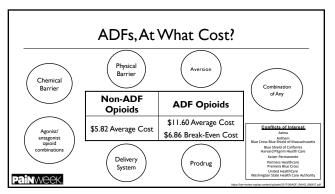
	Buprenorphine vs Naloxone			
Package Insert				
5.2	Risk of Respiratory and Central Nervous System (CNS) Depression			
post-i	norphine has been associated with life-threatening respiratory depression and death. Many, but not all, marketing reports regarding coma and death involved misuse by self-injection or were associated with the mitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Warn sto of the potential danger of self-administration of benzodiazepines or other CNS depressants while treatment with SUBOXONE sublingual film [see Warnings and Precautions (5.3), Drug Interactions (7)].			
opioi whos	substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some 1-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those e opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone inations by the intravenous or intranasal route. In methadone-maintained patients and heroin-			
i n w	Selection Full Proceeding Information, February 27, 2718, http://www.accessedin.file.gov/frequenties_accessbasis/2010/222410000			





FDA Approved ADF Opioids on US Market (July 2020) Product Xtampza ER® OxyContin® Medicine oxycodone IN IV Hysingla® Embeda® ER Tablet hydrocodone IN IV PO Chew IN PO Crush Arymo[®] MorphaBond[®] morphine **ER** Tablet IV IN IV Painweek.

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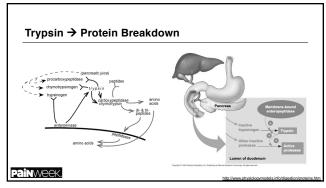
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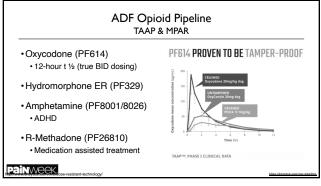
ADF Opioid Pipeline

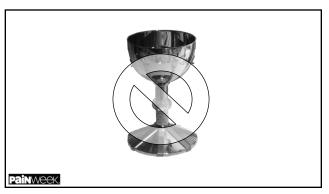
- •TAAP (Trypsin Activated Abuse Protection)
- •Trypsin is found only in the small intestine
- •MPAR (Multi-Pill Abuse Resistance)
 - •A small amount of trypsin inhibitor (soybeans & egg whites) added to each pill not affecting opioid release
 - •If multiple pills are ingested (on purpose or accidentally)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

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http://www.ensysce.com/bio-md-te







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ΔΙ	unier	ICE	CJITE	noite	# 1

A 45yo female patient with chronic lower back pain and hypertension presents to your practice as a new patient already having utilized https://hydrocodone. for many years. While performing an opioid risk assessment, you find out that she is living in a house with a spouse who has a substance-use disorder. You would like to convert the patient's current non-abuse-deterrent formulation (ADF) ER opioid to an FDA approved ADF ER opioid formulation that is readily available on the US market. Which of the following is the most appropriate selection based on this intention?

- a) Zohydro ER
- b) Hysingla
- c) Vantrela
- d) Xtampza ER

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Audience Question #1

- a) Zohydro ER
- b) HYSINGLA [CORRECT ANSWER]
- c) Vantrela
- d) Xtampza ER

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Medicine	Product
	Xtampza ER®
oxycodone	OxyContin®
hydrocodone	Hysingla®
	Embeda®
morphine	Arymo®
	MorphaBond®

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Audience Question #2

A 55yo male patient with chronic lower back pain and DM2 presents to your practice as a new patient already having utilized oxcoding for many years. Upon performing an opioid risk assessment, you find that he is of high risk for opioid abuse. He also states that he would prefer an opioid medication that can be sprinkled on his food instead of swallowing the pill whole. You would like to convert the patient's current non-abuse-deterrent formulation (ADF) ER opioid to an FDA approved ADF ER opioid formulation that is readily available on the US market, Which of the following is the most appropriate selection based on this intention?

- a) Embeda
- b) Zohydro ER c) OxyContin
- d) Xtampza ER

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٨ı	annaihı	Question	#2
Αl		QUESTION	#/

A 55yo male patient with chronic lower back pain and DM2 presents to your practice as a new patient already having utilized oxycordone for many years. Upon performing an opioid risk assessment, you find that he is of high risk for opioid abuse. He also states that he would prefer an opioid medication that can be sprinkled on his food instead of swallowing the pill whole. You would like to convert the patient's current non-abuse-deterrent formulation (ADF) ER opioid to an EDA approved ADE ER opioid formulation that is readily available on the US market. Which of the following is the most appropriate selection based on this intention?

- a) Embeda
- b) Zohydro ER
- d) XTAMPZA ER [CORRECT ANSWER]
- Product Xtampza ER⁶ oxycodone OxyContin[®] hydrocodone Hysingla[®] Embeda[®] Arymo[®] MorphaBond

Medicine

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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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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 [CORRECT ANSWER]
- ■Massachusetts (2014)
- ■Maine (2015)
- ■Maryland (2015) ■Florida (2016)
- ■West Virginia (2016)

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