



Go Team Defense! Recent FDA Approved Abuse Deterrent Opioids

HYATT REGENCY DENVER & COLORADO CONVENTION CENTER · SEPTEMBER 3-6, 2017

MAD Drugs

Abuse Deterrent Opioids approved in 2016-17



1

- Jennifer Langer PharmD, BCPS
- Heather Smith PharmD, BCPS



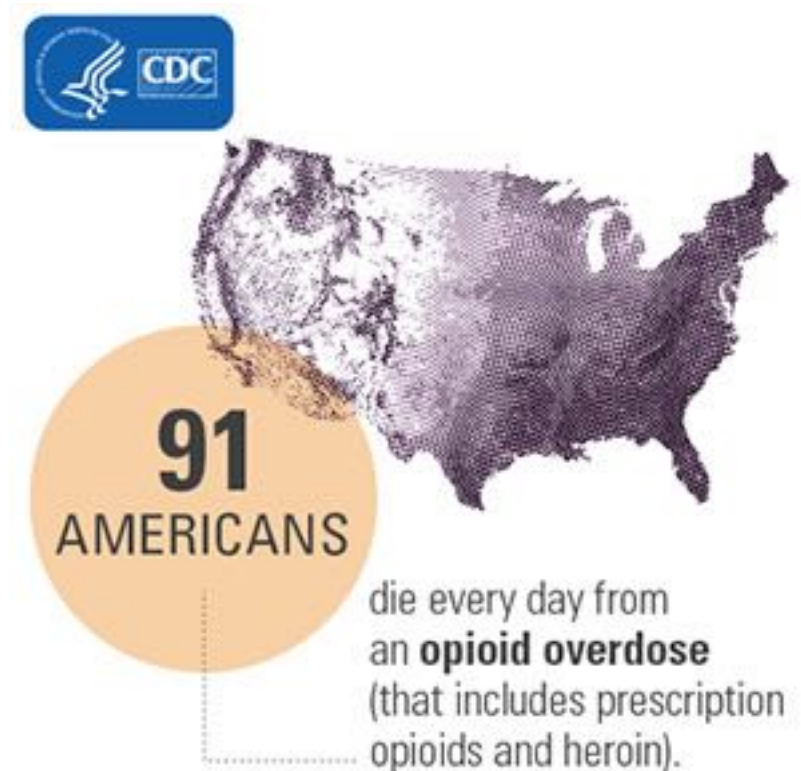
Objectives

1. Define Abuse Deterrent Opioid (ADO).
2. List requirements needed for a medication to obtain ADO labeling.
3. Name 4 new ADO's released in January 2016-July 2017.
4. Describe advantages and disadvantages over others in the market.
5. Be familiar with ADO's impact based on post marketing literature with Oxycontin.

MAD Drugs

Opioid Abuse in the USA

- From 2000 to 2015
 - > 0.5 million people died from drug overdoses²
- Since 1999
 - The amount of opioid prescriptions and deaths from prescription opioids has quadrupled²
- Overdose rates highest among ages 25 to 54 years³



MAD Drugs

Substance Abuse Post TBI and SCI

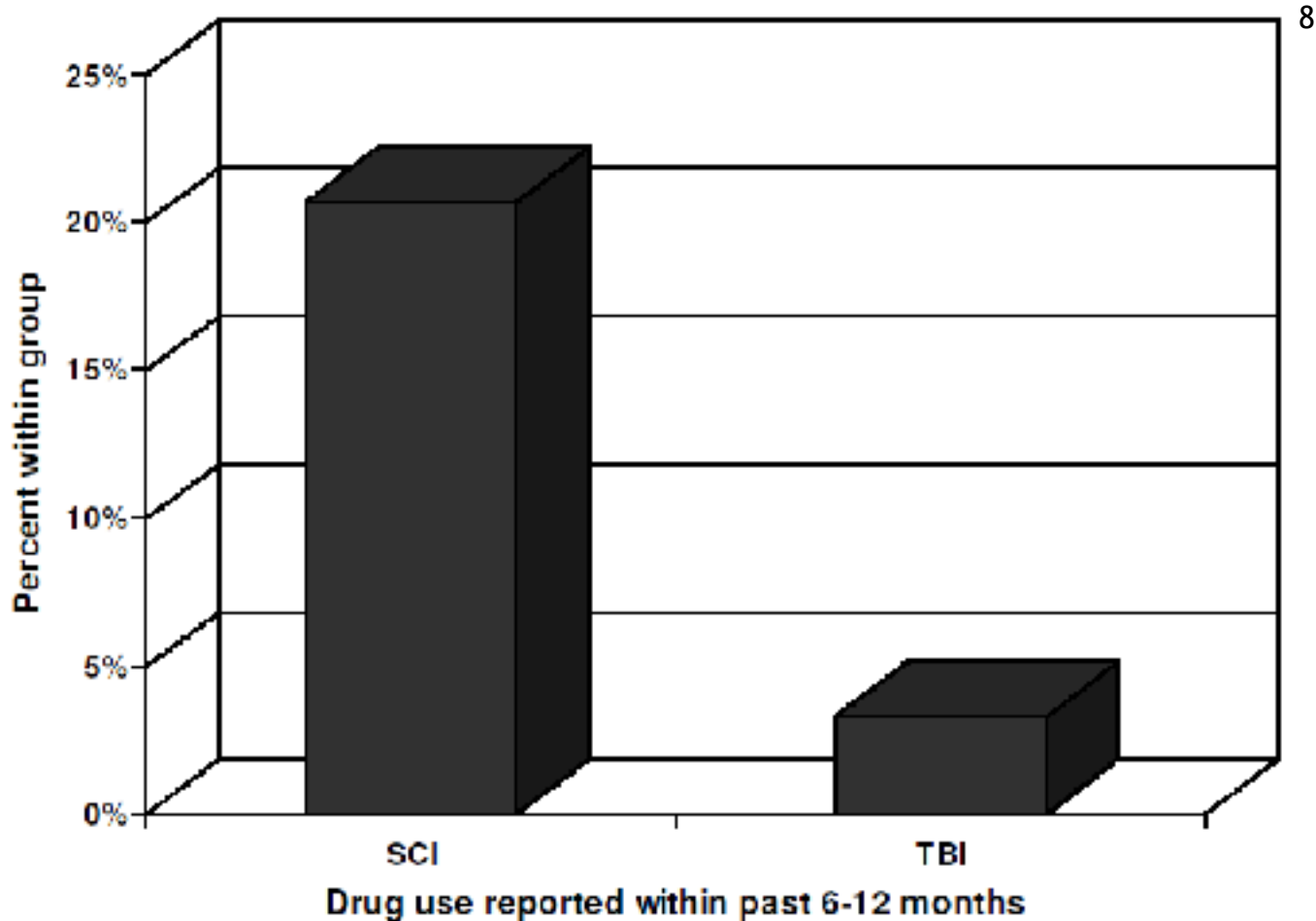
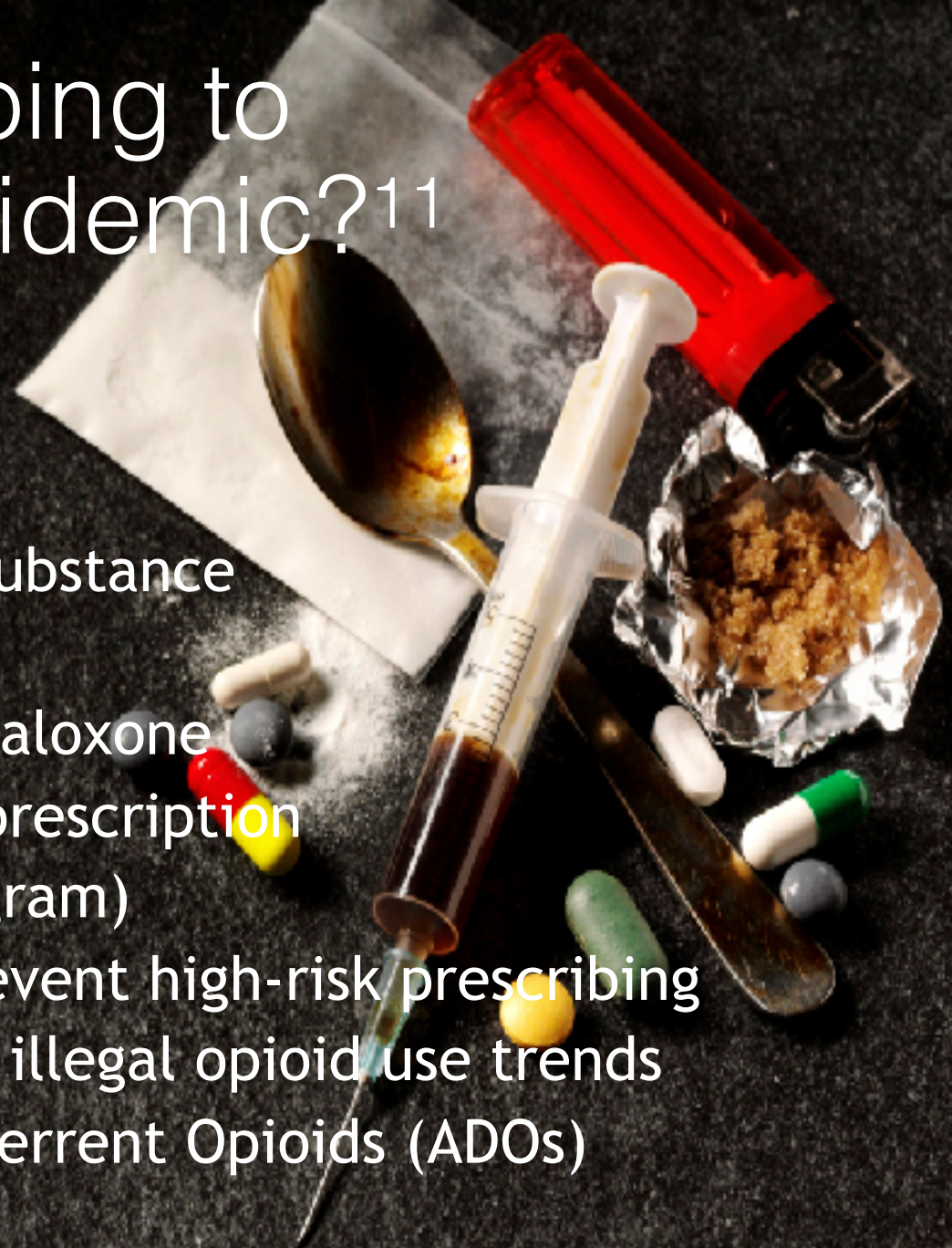


Figure 3. Substance use in persons with TBI and traumatic spinal cord injury 1-year post-injury. SCI = Spinal cord injury
TBI = Traumatic Brain Injury

What are we doing to improve the epidemic?¹¹

- Improving opioid prescribing
- Expanded access to substance abuse treatment
- Expanded access to naloxone
- Promotion of PDMP (prescription drug monitoring program)
- Strategies to help prevent high-risk prescribing
- Improve detection of illegal opioid use trends
- Start using Abuse Deterrent Opioids (ADOs)



Requirements for ADO labeling⁶¹

- Category 1: Laboratory tests to determine how easily AD properties can be compromised
- Category 2: In vivo studies comparing pharmacokinetic profiles before and after manipulation
- Category 3: RCT performed evaluating subjective effects of the formulation
 - Drug liking
 - Whether user would use this product again
- Category 4: Post marketing epidemiological studies
 - assess whether a formulation has been associated with meaningful reductions in adverse clinical outcomes related to abuse and misuse

MAD

Drugs

- Mechanisms to deter opioid abuse¹³
 - Controlled release of drug
 - Sequestered opioid antagonist
 - Tablets that resist crushing and grinding
 - Gelling agents that make injection difficult
 - Reduced amount of intact drug produced by vaporization
 - Increased difficulty extracting pure opioid after dissolution
 - Increased crushed particle size
 - Substances that burn/irritate nasal mucosa
 - Depot/subcutaneous delivery system

MAD

Drugs

Intended Use: Treatment of severe, chronic pain requiring long-term daily, around the clock opioid analgesia in patients with no other adequate treatment options¹³

Lets play

MAD

Drugs

A=BUY

B=Sell

MAD

Drugs

A=BUY

B=Sell

vantrela 
(hydrocodone bitartrate) 
extended-release tablets

14

- Abuse Deterrent Properties¹⁵
 - Resistant to crushing, breaking, and dissolving
 - Retains ER properties when manipulated
 - Forms viscous material when dissolved, which is resistant to needle passage.
- Extended Release Hydrocodone¹⁵
 - How supplied: 15 mg, 30 mg, 45 mg, 60 mg, 90 mg
- Dosing recommendations¹⁵:
 - Opioid Naïve: 15 mg Q12H
 - If converting from other opioid, use conversion table in package insert
 - Single doses of 60 mg or greater or total daily dose of 120 mg are only to be used in those who are considered opioid-tolerant

MAD Drugs

vantrela ER

Approved: January 2017

vantrela ER¹⁴
(hydrocodone bitartrate) (II)
extended-release tablets


Hysingla ER¹⁶
(Hydrocodone Bitartrate) (II)
EXTENDED-RELEASE TABLETS

Zohydro ER⁷
(hydrocodone bitartrate) (II)
EXTENDED-RELEASE CAPSULES
10 mg - 15 mg - 20 mg - 30 mg - 40 mg - 50 mg

Comparisons

Vantrela ER

- Resistant to crushing and breaking; tablet forms a viscous gel when dissolved¹⁸
- When manipulated lower peak conc and lower early exposure vs. Zohydro

Hysingla ER

- Resistant to crushing and breaking; tablet forms a viscous gel when dissolved¹⁸

Zohydro ER

- Initially FDA approved without AD technology¹⁹
- Reformulated with BeadTek technology¹⁹
 - Excipients form viscous gel when crushed or dissolved¹⁸

Comparisons

	Vantrela ER ¹³	Hysingla ER ²⁰	Zohydro ER ²¹
Constipation	12%	3%	8%
Nausea	14%	8%	7%
Vomiting	5%	6%	1%
Somnolence	3%	1%	0%
Headache	6%	2%	1%
Fatigue	2%	1%	1%



vantrela ER

Approved: January 2017

Comparisons

	CO ²²	WY ²³	OH ²⁴	TN ²⁵	NC ²⁶	NY ²⁷	MA ²⁸	Express scripts ²⁹	CVS Caremark ³⁰
Vantrela ER	NP	-	NC	NC	NC	NC	NC	NC	NC
Hysingla ER	NP	NP	NP	PA	NC	NC	PA	Preferred	PA
Zohydro ER	NP	NP	NP	PA	NP	PA	PA	NP	NC

NC= Not covered

NP=Non Preferred

PA= Prior Authorization required

“-” = No information

MAD

Drugs

vantrela ER

Approved: January 2017

Advantages

- ✓ Abuse deterrent technology
- ✓ Purity and peak hydrocodone levels lower than Zohydro when manipulated

Disadvantages

- 😱 Q12H dosing
 - 😱 Alternative: Hysingla Q24H
- 😱 Not covered by many insurances



MAD Drugs

vantrela ER

Approved: January 2017

A=BUY

B=Sell

vantrela 
(hydrocodone bitartrate) 
extended-release tablets

MAD
Drugs

vantrela ER

Approved: January 2017

- POLL RESULTS

MAD
Drugs

vantrela ER

Approved: January 2017

A
B=Sell
]

MAD Drugs

Egalet

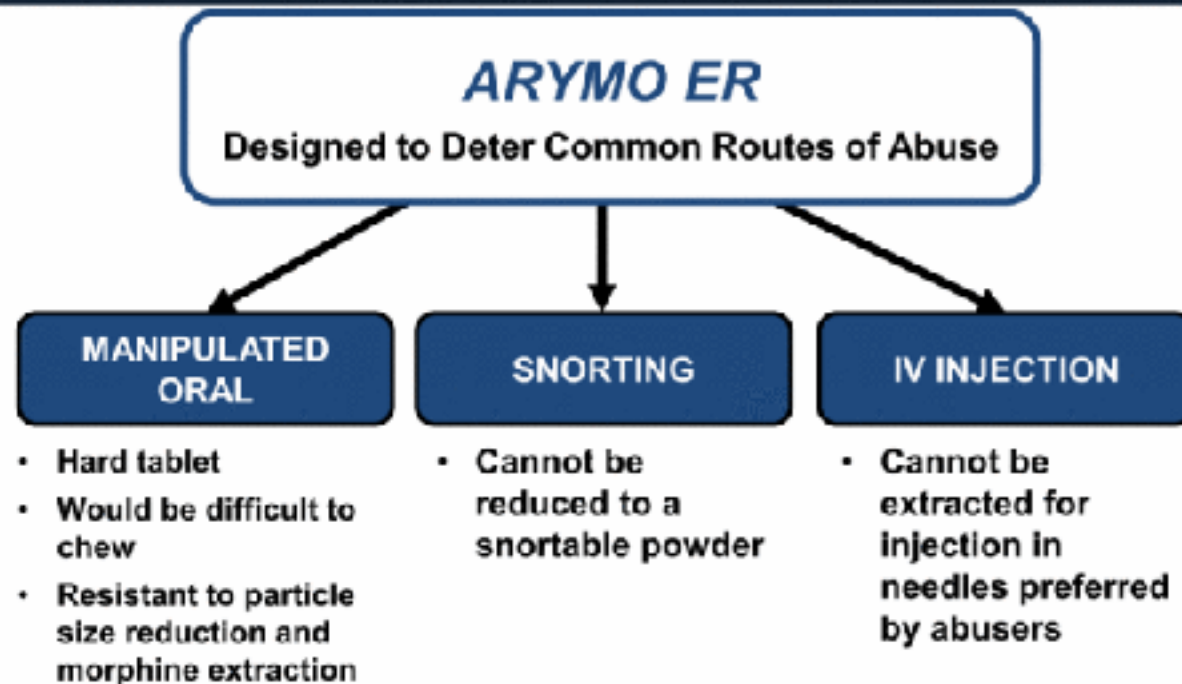
A=BUY

B=Sell

ArymoTM ER
(morphine sulfate)Ⓜ
EXTENDED-RELEASE TABLETS

31

ARYMO ER Provides a Broad Abuse-Deterrent Profile



- Abuse Deterrent Properties³³
 - Resistant to crushing, breaking, and dissolving
 - Retains ER properties when manipulated
 - Forms viscous material when dissolved, which is resistant to needle passage.
- Extended Release Hydrocodone³³
 - How supplied: 15 mg, 30 mg, 60 mg
- Dosing recommendations³³:
 - Opioid Naïve: 15 mg Q8 or 12H
 - If converting from other opioid, use conversion table in package insert

Usual Dosage: Read accompanying prescribing information.

NDC 69344-311-11

34

Arymo™ ER

(morphine sulfate) extended-release

60 mg

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

100 Tablets



Swallow Tablets whole. Do not cut, break, chew, crush, or dissolve.

NDC 65597-303-10

35

MorphaBond™ ER

(morphine sulfate) Extended-release Tablets

60 mg

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

Swallow tablets whole. Do not break, crush, dissolve, or chew.

100 Tablets

Rx Only



Comparisons

Arymo ER

- Guardian technology¹⁸
 - More difficult to crush/chew
 - Gels when trying to dissolve it

Morphabond ER

- Sentrybond technology³⁶
 - Harder to adulterate
 - Designed to maintain intended release profile of extended release product

Comparisons

Arymo ER

- Common Side Effects³³
 - Constipation
 - Dizziness
 - Sedation
 - Nausea/vomiting
 - Sweating
 - Dysphoria
 - Euphoric mood

Morphabond ER

- Common Side Effects³⁷
 - Constipation
 - Dizziness
 - Sedation
 - Nausea/vomiting
 - Sweating
 - Dysphoria
 - Euphoric mood



arymo ER
Approved: January 2017

Comparisons

	CO ²²	WY ²³	OH ²⁴	TN ²⁵	NC ²⁶	NY ²⁷	MA ²⁸	Express scripts ²⁹	CVS Caremark ³⁰
Arymo ER	NC	-	NC	PA	NC	NC	PA	NP	NC
Morphabond	NP	-	NC	PA	NC	NC	NC	NP	NC

NC= Not covered

NP=Non Preferred

PA= Prior Authorization required

“-” = No information

MAD

Drugs

arymo ER
Approved: January 2017

✓ Advantages

- ✓ Has abuse deterrent technology

😱 Disadvantages

- 😱 Will potentially need Q8H dosing
- 😱 Not covered by many insurances



MAD
Drugs

arymo ER
Approved: January 2017

A=BUY

B=Sell

Arymo™ ER
(morphine sulfate)Ⓢ
EXTENDED-RELEASE TABLETS

MAD
Drugs

arymo ER
Approved: January 2017

- POLL RESULTS

A

B=Sell

]

MAD Drugs



A=BUY

TROXYCA[®] ER
(oxycodone hydrochloride
and naltrexone hydrochloride)
extended-release capsules



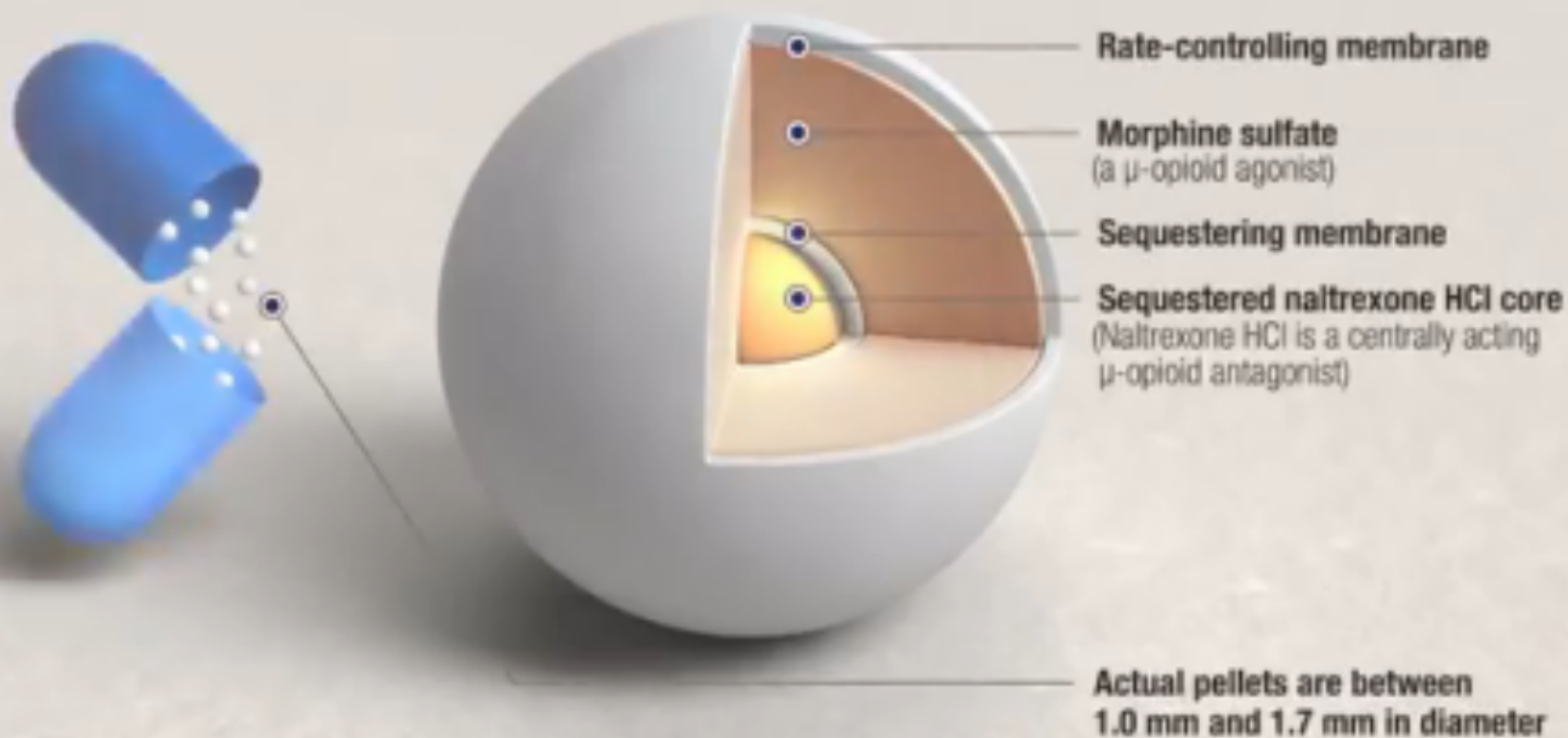
38

20 mg/2.4 mg

B=Sell

THE PELLETS SHOULD NOT BE CHEWED, CRUSHED, OR DISSOLVED.

Troxyca ER: Abuse Deterrent Technology



- Strengths:³⁸

Oxycodone	Naltrexone
10mg	1.2mg
20mg	2.4mg
30mg	3.6mg
40mg	4.8mg
60mg	7.2mg
80mg	9.6mg

- Dose:³⁸

- Opioid Naïve: Oxycodone 10mg/Naltrexone 1.2mg ER PO Q12H
- May adjust dose by oxycodone 20mg/naltrexone 2.4mg Q 2-3 days PRN based on efficacy, safety and tolerability.

- Administration:
 - Should be taken orally. Do not crush, cut or chew
 - May be opened and contents sprinkled on applesauce and swallowed without chewing.
 - DO NOT administer through a feeding tube or nasogastric tube

MAD Drugs

Troxyca ER
Approved: December 2016

Comparisons



47

ALWAYS DISPENSE WITH MEDICATION GUIDE
NDC 60793-430-20

Pfizer

EMBEDA[®]
(morphine sulfate and
naltrexone hydrochloride)
Extended Release Capsules

20 mg/0.8 mg

THE PELLETS SHOULD NOT BE CHEWED, CRUSHED, OR DISSOLVED.

30 Capsules Rx only

48

ALWAYS DISPENSE WITH MEDICATION GUIDE
NDC 60793-531-01

Pfizer

TROXYCA[®] ER
(oxycodone hydrochloride
and naltrexone hydrochloride)
extended-release capsules

20 mg/2.4 mg

THE PELLETS SHOULD NOT BE CHEWED, CRUSHED, OR DISSOLVED.

100 Capsules Rx only

49

Comparison

Troxyca ER

- Same ADO mechanism
- Likely precipitates withdrawal if accidentally chewed.

Embeda ER

- Same ADO mechanism
- Precipitates withdrawal if is accidentally chewed.⁵¹
- Contraindicated with use of MAOI's or use within 14days

	Troxyca ER ¹³	Embeda ER ¹³
Constipation	3.4-21.3%	7-31%
Nausea	14.4-25.3%	11-22%
Vomiting	6.2-13.9%	4-8%
Somnolence	Not Reported	1-14%
Headache	1.4-11.6%	Not Reported
Peripheral Edema	0.7-3.8%	Not Reported

Comparison

Troxyca ER

- Oxycodone + naltrexone
- No ceiling dose ⁴⁵
- Effects on constipation:?
 - 3.4-14.9%¹³

Targiniq

- Oxycodone + naloxone
- Analgesic ceiling: 180-240mg ⁴⁵
- Reduces the side effect of constipation.⁴⁵
 - Bowel Function Index scores improved with Targiniq vs Oxycodone alone after 4 weeks of tx.⁵⁰



Troxyca ER
Approved: December 2016

Comparison

	CO ²²	WY ²³	OH ²⁴	TN ²⁵	NC ²⁶	NY ²⁷	MA ²⁸	Express scripts ²⁹	CVS Caremark ³⁰
Troxyca ER	NC	NC	-	-	-	-	-	-	-
Embeda	PA	NC	PA	Preferred	-	-	PA	-	-
Targiniq	NC	NC	-	-	-	-	-	-	-

NC= Not covered

NP=Non Preferred

PA= Prior Authorization required

“-” = No information

- Advantages
 - ✓ Deter abuse
 - ✓ Can be opened and contents sprinkled on applesauce for ingestion.⁵¹
 - ✓ Is an ADO option opioid switching from morphine
 - ✓ Puts ADO's into public circulation.

MAD Drugs

- Disadvantages

- 🙄 Possible link between withdrawal and serious cardiovascular adverse events in opioids antagonists approved for treating opioid induced constipation.⁵¹

- 🙄 Expense

- 🙄 Not covered by many insurance companies

MAD Drugs

Troxyca ER
Approved: December 2016

Buy or Sell?

A=BUY

B=Sell

TROXYCA[®] ER

(oxycodone hydrochloride
and naltrexone hydrochloride)
extended-release capsules



20 mg/2.4 mg

THE PELLETS SHOULD NOT BE CHEWED, CRUSHED, OR DISSOLVED.

MAD Drugs

Troxycya ER

- POLL RESULTS

MAD
Drugs

Troxycya ER
Approved: December 2016

B=Sell

A

J

MAD
Drugs

Xtampza ER
Oxycodone ER
Approved April 26, 2016

52

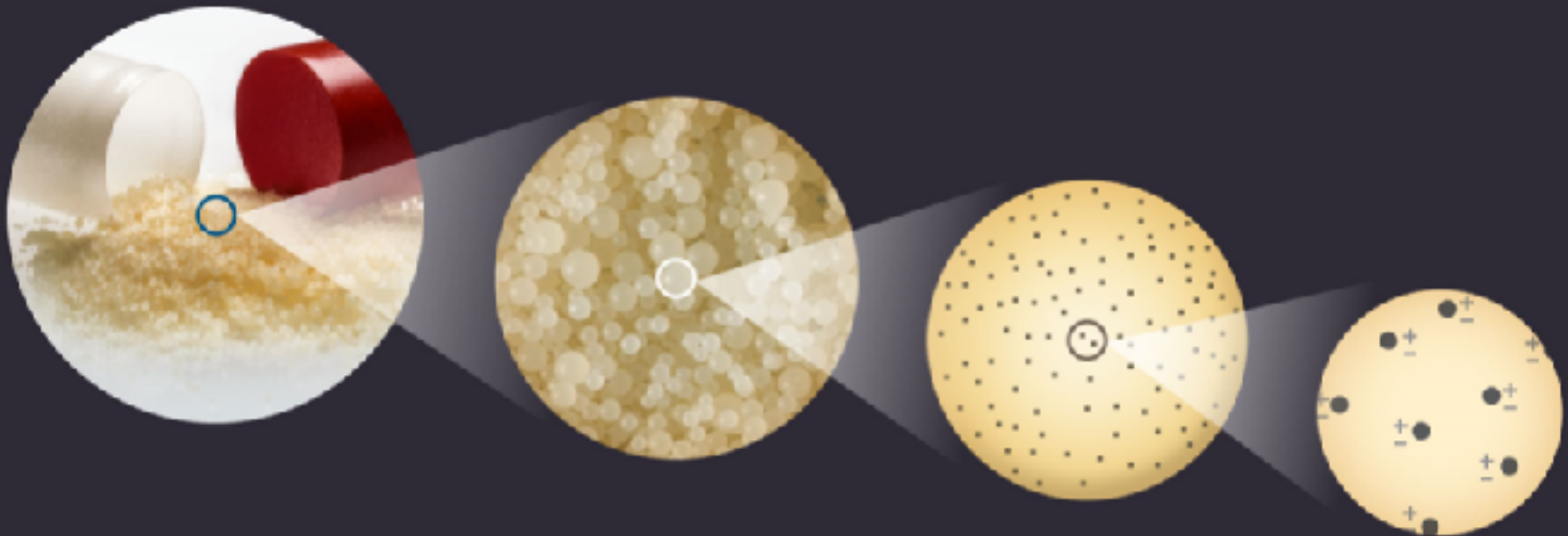
A=BUY

B=Sell



Xtampza[®] ER
(oxycodone) EXTENDED-RELEASE CAPSULES

DETERx[®] Design Elements



Microspheres made of API, fatty acid and waxes impart extended-release properties



Inactive components are made of hydrophobic, waxy materials



Drug is homogeneously dispersed within each microsphere



Drug binds chemically with inactive components

- Strengths:

Xtampza ER	Equivalence to oxycodone HCL
9mg	10mg
13.5mg	15mg
18mg	20mg
27mg	30mg
36mg	40mg

52

- Dose:⁵²

- Opioid Naïve: 9mg PO Q12H
- May adjust dose by 25-50% Q 1-2 days PRN based on efficacy, safety and tolerability.
- Maximum daily dosage 288mg (eight 36mg capsules, equivalent to 320mg oxycodone HCL)

MAD Drugs

Xtampza ER
Oxycodone ER
Approved April 26, 2016

- Administration

- Oral whole capsules or sprinkle capsule contents on soft food or into a cup and administering directly into mouth.
- May be administered via G-tube or nasogastric tube
- Must be given with food
 - Same amount of food at each dose recommended to achieve consistent plasma concentrations.
 - When administered in the fed state, the bioavailability of oxycodone extended-release capsules is 14% greater than that of immediate-release solution. When given while fasted, bioavailability is 25% less than that of the immediate-release solution.

Comparisons

	Oxycontin	Xtampza ER
Formulation	Tablet	Capsule
Abuse deterrent Properties	Physical/chemical barrier Difficult to crush or break Resistent to chemical extraction Forms a viscous gel when dissolved	Physical/Chemical barrier Microspheres are resistant to crushing and chewing Melted or dissolved capsules are difficult to inject
Administration	Oral Do not crush Without regards to food	Oral, G-tube, Nasogastric tube Can be crushed Take with food with every dose

Comparisons

	CO ²²	WY ²³	OH ²⁴	TN ²⁵	NC ²⁶	NY ²⁷	MA ²⁸	Express scripts ²⁹	CVS Caremark ³⁰
Xtampza ER	-	NP	NP**	NP***	-	-	PA	-	-
Oxycontin	PA*	NP	NP**	NP***	NP***	-	PA	Preferred	Preferred

*will be approved for members who've failed treatment with two other preferred products and at least one other opioid in the past year. Failed includes: lack of efficacy, allergy, intolerable side effects, or significant drug-drug interactions.

** For a non-preferred drug, there must have been inadequate clinical response to preferred alternatives, including a trial of no less than one week each of at least two preferred generics or brand

***Approval of NP agents requires trial and failure, contraindication or intolerance of 2 preferred agents, unless otherwise indicated.

NC= Not covered

NP= Non-preferred

PA= Prior Authorization required

"-" = No information

- Advantages
 - ✓ Deter abuse
 - ✓ Will not have the risk of withdrawal and serious cardiovascular adverse events seen with opioid antagonists approved for treating opioid induced constipation.⁵¹
 - ✓ Contents can be opened and sprinkled onto applesauce for ingestion. Can also be given via G-tube or nasogastric tube.
 - ✓ No withdrawal risk if accidentally chewed.

- Disadvantages

- 🤪 Must be taken with food for maximal effect and continue to be taken with food to ensure consistent plasma levels.
- 🤪 Not bioequivalent with current ER Oxycodone, so monitoring for safety and efficacy upon transition is a must.
- 🤪 Not covered by insurance companies at this time

MAD
Drugs

Xtampza ER
Oxycodone ER
Approved April 26, 2016

•

Buy or Sell?

A=BUY

B=Sell



Xtampza[®] ER
(oxycodone) EXTENDED-RELEASE CAPSULES (II)

The logo for Xtampza ER features the brand name 'Xtampza' in a purple, lowercase, sans-serif font, followed by 'ER' in a larger, yellow, uppercase, sans-serif font. Above the 'ER' is a stylized graphic of three curved lines in shades of green and blue. Below the brand name, '(oxycodone)' is written in a smaller, grey, lowercase font. To the right of '(oxycodone)' are the words 'EXTENDED-RELEASE CAPSULES' in a grey, uppercase font. Further to the right is a circular icon containing two vertical bars, representing the imprint on the capsules.

MAD
Drugs

Xtampza ER
Oxycodone ER
Approved April 26, 2016

- POLL RESULTS

MAD
Drugs

Xtampza ER
Oxycodone ER
Approved April 26, 2016

A=


B

B=Sell

MAD Drugs

Effectiveness of ADO's

ADO
formulations
"Oxycontin"



32% reduction ER
oxycodone- related
poison control abuse
cases⁵⁶

15% rate of
poisonings related to
therapeutic use of
ER oxycodone⁵⁶

In 140,496 people
assessed for
substance abuse
problems found that
ER oxycodone abuse
declined by 33%,
non oral abuse
declined by 66% and
frequency of abuse
deceased by 30%⁵⁷

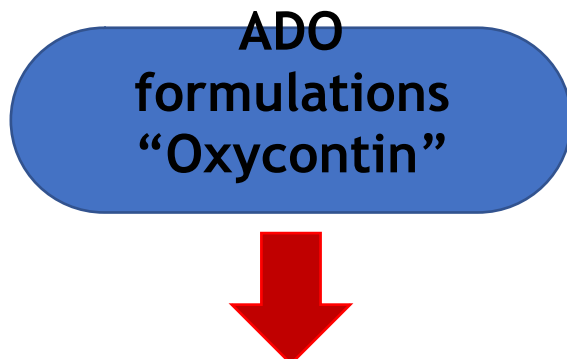
Rate of ER
oxycodone diversion
decline by 50%⁵⁶

Street Price of ER
oxycodone declined
by 22%⁵⁶

MAD
Drugs

Effectiveness of ADO's

ADO
formulations
"Oxycontin"



Estimated prescription overdose rate 20% lower 2yrs after Oxycontin reformulation⁵⁸

But Heroin overdose rate increased by 23%⁵⁸

abuse-deterrent opioids may be related to slightly lower overall healthcare costs for members with ICD-9 codes associated with opioid abuse; this finding was not replicated among members without comorbidities of addiction.⁵⁵

MAD
Drugs

Effectiveness of ADO's

- Post marketing studies for Hyslinga and Embeda are scheduled for completion in 2018 and 2019

MAD Conclusion

Drugs

60

ADO's

- ADO's: opioids formulated with abuse deterrent mechanisms
- There are 4 categories of studies required for ADO labeling
 1. How easily can they be compromised
 2. How different do kinetics behave before and after manipulation
 3. Drug likeability
 4. Post marketing epidemiological studies

MAD Conclusion

Drugs

60

ADO's

- ADO's are opioids formulated with abuse deterrent mechanisms
- There are 4 categories of studies required for ADO labeling
- There were 4 Abuse Deterrent Opioids approved between January 2016 and July 2017
 - Vantrela ER- No advantage over other ADO's
 - Arymo- No advantage over other ADO's
 - Troxyca
 - Same abuse deterrent mechanism as Embeda.
 - Not much advantage over other ADO's
 - Xtampza
 - feeding tube, nasogastric tube requirements and need crushed med for oral consumption
 - Need for consistent food intake at dosing time

MAD Conclusion

Drugs

60

ADO's

- ADO's are one piece of the puzzle.
- There are multiple mechanisms to abuse deterrence in opioid formulations.
- People whom are addicted go to extreme lengths for their fix. ADO's will not stop addiction.
- ADO's help prevent misuse of these products.
- The cost benefit of ADO's are not known yet.
- ADO's do not take the place of vigilant monitoring and follow-up.



THIS IS WAY TOO EASY!

ADDICTS

References

1. <http://www.davegranlund.com/cartoons/2001/09/05/oxycontin-security/> [accessed: 7/25/2017]
2. <https://www.cdc.gov/drugoverdose/epidemic/index.html> [accessed: 7/18/2017]
3. <https://www.cdc.gov/drugoverdose/data/overdose.html> [accessed: 7/18/2017]
4. <https://www.cdc.gov/drugoverdose/data/overdose.html> [accessed: 7/18/2017]
5. <https://www.cdc.gov/drugoverdose/data/overdose.html> [accessed: 7/18/2017]
6. <http://www.drugrehab.org/most-commonly-abused-opiates/> [accessed: 7/26/2017]
7. Past-Month Use of Selected Illicit Drugs. *National Institute on Drug Abuse*. Nationwide Trends. <https://www.drugabuse.gov/publications/drugfacts/nationwide-trends> [accessed: 7/25/2017]
8. Kolakowsky-Hayner SA, Gourley EV, Kreutzer JS, et al. Post-Injury substance abuse among persons with brain injury and persons with spinal cord injury. *Brain Injury*, 16:7, 583-592.
9. <https://www.cdc.gov/drugoverdose/data/heroin.html> [accessed: 7/26/2017]
10. <http://wnpr.org/wnpr-covers-connecticuts-opioid-epidemic> [accessed: 7/25/2017]
11. Understanding the Epidemic. *Centers for Disease Control and Prevention*. Preventing Overdose Deaths. <https://www.cdc.gov/drugoverdose/epidemic/index.html> [accessed: 7/18/2017]
12. Abuse-Deterrent Opioid Formulations. *Med Lett Drugs Ther.* 2015;57(1476):119-120
13. Micromedex [ACCESSED 7/9/17]
14. <https://trademarks.justia.com/865/10/vantrela-er-hydrocodone-bitartrate-cii-extended-release-86510861.html> [accessed: 7/18/2017]

References

15. Vantrela ER ® [Package Insert]. Teva Pharmaceuticals; 2017.
16. <http://www.multivu.com/players/English/7423051-purdue-pharma-launch-hysingla/> [accessed: 7/18/2017]
17. <http://nationalpainreport.com/pills-breakfast-pro-zohydro-8823142.html> [accessed: 7/18/2017]
18. Abuse-Deterrent Opioid Formulations. *Med Lett Drugs Ther.* Jun 5;59(1522):95-6
19. Zohydro Approved Haunts FDA Panelist At Vantrela Meeting. *The Pink Sheet.* June 13;78(24):5-6.
20. Hysingla ER ® {Package Insert}. Stamford, CT: Purdue Pharma LP; 2016.
21. Zohydro ER® [Package Insert]. San Diego, CA: Zogenix, inc: 2015.
22. Colorado Medicaid medication Formulary <https://www.colorado.gov/pacific/sites/default/files/Pharmacy%20-%20PDL%20effective%20July%201%2C%202017%20FINAL.pdf> [ACCESSED 07/09/17]
23. OHIO Medicaid medication formulary: <https://pharmacy.medicare.ohio.gov/sites/default/files/2017-04-01%20PDL.pdf> [ACCESSED 7/9/17]
24. Wyoming Medicaid Medication Formulary: <http://wymedicaid.org/sites/default/files/ghs-files/pdl/2017-05-30/pdleffective-5-30-17.pdf> [ACCESSED 7/9/17]
25. Tennessee Medicaid Medication Formulary: https://tenncare.magellanhealth.com/static/docs/Preferred_Drug_List_and_Drug_Criteria/TennCare_PDL.pdf [Accessed 7/9/17]
26. North Carolina Medicaid Medication Formulary: <https://www.communitycarenc.org/media/related-downloads/mcicaid-preferred-drug-list.pdf> [Accessed 7/9/17]

References

27. New York Medicaid Medication formulary <https://www.uhcommunityplan.com/content/dam/communityplan/plandocuments/findadrug/NY-Medicaid-PDL.pdf> [ACCESSED 7/9/17]
28. Massachusetts Medicaid Medication formulary <https://masshealthdruglist.ehs.state.ma.us/MHDL/pubtheradetail.do?id=543&drugId=5362> [ACCESSED 7/9/17]
29. Express scripts National Preferred <https://www.wvumc.org/wp-content/uploads/2017/04/express-scripts-formulary-1.pdf> [ACCESSED 7/23/17]
30. CVS Caremark medication formulary https://www.caremark.com/portal/asset/caremark_drug_list.pdf [ACCESSED 7/9/17]
31. <http://www.arymoer.com/hcp/patient-savings-and-support> [accessed 7/20/2017]
32. https://www.sec.gov/Archives/edgar/data/1586105/000110465916141503/a16-16190_2ex99d1.htm [accessed: 7/20/2017]
33. Arymo ER ® [package insert]. Wayne, PA: Egalet US inc; 2017
34. <https://www.drugs.com/pro/arymo-er.html> [accessed: 7/25/2017]
35. <https://www.drugs.com/pro/morphabond.html> [accessed: 7/25/2017]
36. <http://inspiriondt.com/our-technology/> [accessed: 7/23/2017]
37. Morphabond ER ® [package insert]. Parsippany, NJ: Daiichi Sankyo, inc; 2016.

References

38. Troxyca(R) ER (Dec 2016)- Micromedex accessed 6/24/17 P&T QUIK® Summary reports on drugs under consideration for inclusion in hospital formularies
39. pictoral description of troxyca ADF technology <https://www.pfizerpro.com/product/embeda/hcp/technology?advert=advert> [ACCESSED 7/23/17]
40. <http://www.womansday.com/health-fitness/womens-health/a1419/everything-you-need-to-know-about-your-meds-104733/> [accessed: 7/23/2017]
41. <https://www.quora.com/Which-powder-is-generally-used-in-Hollywood-movies-as-Cocaine-I-mean-while-shooting-snorting-scenes> [accessed: 7/23/2017]
42. <http://drugabuse.com/library/is-crack-addictive/> [accessed: 7/23/2017]
43. <http://www.alamy.com/stock-photo/overdose.html> [accessed: 7/23/2017]
44. <http://formularyjournal.modernmedicine.com/formulary-journal/news/abuse-deterrent-opioid-pain-drug-approved> [Accessed June 24, 2017]
45. Mellar P. Davis (2016) Pharmacokinetic and pharmacodynamic evaluation of oxycodone and naltrexone for the treatment of chronic lower back pain, Expert Opinion on Drug Metabolism & Toxicology, 12:7, 823-831, DOI: 10.1080/17425255.2016.1191469
46. <http://www.reuters.com/article/us-pfizer-fda-idUSKCN0YS1P9> Pfizer's opioid painkiller can be manipulated for abuse: FDA Reuters 2016 [accessed June 24, 2017]

References

47. Targiniq picture. <http://www.health24.com/Medical/Addiction/News/New-formula-oxicontin-is-mixed-with-naloxone-to-prevent-abuse-20150710> [Accessed 7/31/17]
48. Embeda picture. <https://www.drugs.com/pro/embeda.html> [Accessed 7/31/17]
49. Troxyca picture. <https://www.drugs.com/pro/troxyca-er.html> [Accessed 7/31/17]
50. Burness C, Keating G. Oxycodone/Naloxone Prolonged-Release: A Review of Its Use in the Management of Chronic Pain While Counteracting Opioid-Induced Constipation. *Drugs* [serial online]. March 2014;74(3):353-375. Available from: Academic Search Premier, Ipswich, MA. Accessed July 9, 2017.
51. <http://247wallst.com/healthcare-business/2016/03/15/huge-opportunity-and-risks-in-5-top-abuse-deterrent-er-opioids> [Accessed 07/08/17]
52. <http://www.xtampzaer.com/hcp/> [Accessed 7/23/17]
53. Picture depicting DETERx Design Elements <http://www.collegiumpharma.com/technology/overview> [accessed 7/23/17]
54. Kopecky, E., Fleming, A., Levy-Cooperman, N. Oral Human Abuse Potential of Oxycodone DETERx. *The Journal of Clinical Pharmacology* 2017,57(4) 500-512
55. O'Neill Ryann, Lor Kimberly, and Pruskowski Jennifer. *Journal of Palliative Medicine*. June 2017, 20(6): 676-678. <https://doi-org.hsl-ezproxy.ucdenver.edu/10.1089/jpm.2017.0088>
56. [SG Severtson et al. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. *J Pain* 2013; 14:1122.](#)

References

57. SF Butler et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *J Pain* 2013; 14:351.
58. [MR Laroche et al. Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene. *JAMA Intern Med* 2015; 175:978.](#)
59. Jigsaw puzzle piece picture. <http://igscommunity.com/your-piece-of-the-puzzle/>
[accessed 07/29/17]
60. Puzzle piece picture. <http://www.pinmart.com/silver-puzzle-piece-pin/> [accessed 7/29/17]
61. <https://secure.medicalletter.org/w1476a> [accessed: 7/29/2017]
62. <https://sopwriting.wordpress.com/2011/04/05/regulatory-requirements-differences-between-fda-and-ema/> [accessed: 7/31/2017]
63. http://www.contractpharma.com/issues/20131101/view_features/abuse-deterrent-formulations/53369 [accessed: 7/31/2017]
64. <https://www.rx411.com/category/drug-safety/> [accessed: 7/31/2017]