



# Long Acting Opioids

## ECHO

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FAMILY MEDICINE RESIDENCY  
OF IDAHO

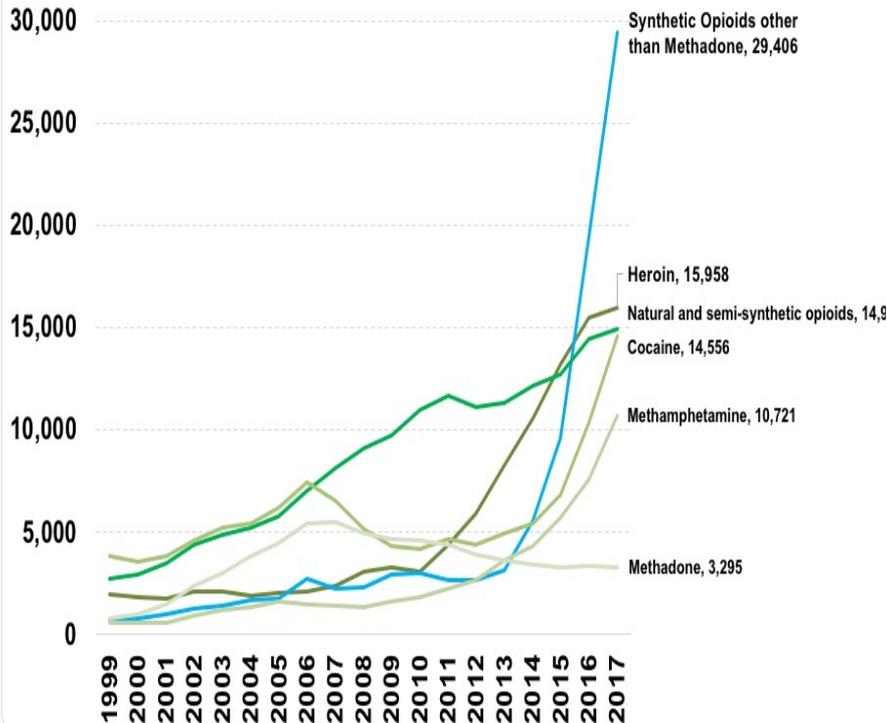


# Disclaimer/ Objectives:

- I am not receiving any compensation from an outside entity for the delivery of this material
- Upon the completion of this brief overview and discussion the participant should be able to:
  - List opioid agents that are available in abuse deterrent long acting formulations
  - Identify patients that may be candidates for these products
  - Advocate for appropriate use of these medications

# Opioid Deaths

Drugs Involved in U.S. Overdose Deaths, 1999 to 2017



Everyone knows that patients are dying from opioid overuse/abuse: intentional or unintentional

– Intentional- pain not controlled?

- Suicide?

– Unintentional-

- Benzos plus opioids-
  - “I forgot I took it 5 times”
- Diversion
- Children- access to the product
- Street medications adulterated



# Concern of Opioids: SA and LA

**Table 1** The 10 principles of Universal Precautions

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1. Diagnosis with appropriate differential
2. Psychological assessment including risk of addictive disorders
3. Informed consent (verbal or written/signed)
4. Treatment agreement (verbal or written/signed)
5. Pre-/post-intervention assessment of pain level and function
6. Appropriate trial of opioid therapy  $\pm$  adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the “Four As” of pain medicine: *Analgesia, Activity, Adverse Reactions, and Aberrant Behavior*
9. Periodically review pain and comorbidity diagnoses, including addictive disorders
10. Documentation

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Adapted from Gourlay et al. [1].

GourlayDL,HeitHA,AlmahreziA.Universal precautions in pain medicine: A rational approach to the management of chronic pain. Pain Med 2005; 6(2):107–12

# CDC Guideline: 12 main points

- 1- Nonpharmacologic and non opioid preferred in chronic pain
- 2- Establish treatment goals
- 3- Discuss risks and benefits
- 4- Immediate should be prescribed not LA/SR
- 5- Prescribe lowest dose possible (Avoid >90 MME/day)
- 6- Long term use begins with txt of acute pain
- 7- Evaluate at 1-4 weeks
- 8- Before continuing establish plans to mitigate risk (naloxone)
- 9- Review PDMP for use every 3 months
- 10- Consider urine drug testing
- 11- Avoid benzos with opioids
- 12- Offer txt for patients with opioid use disorder



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

TO LEARN MORE

[WWW.CDC.GOV/DRUGOVERDOSE/PRESCRIBING/GUIDELINE](http://WWW.CDC.GOV/DRUGOVERDOSE/PRESCRIBING/GUIDELINE)

March 2016

# Who is a candidate for Opioids?

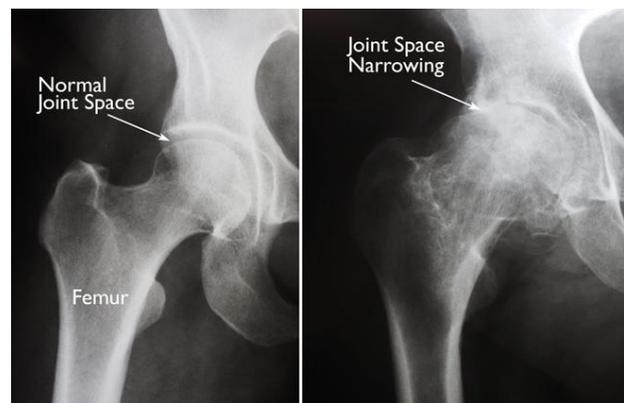
MODERATE

## *ii. Assessment of Effectiveness of Long-Term Opioid Therapy*

11. Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring. (Evidence: Level II; Strength of Recommendation: Moderate)
12. Consider up to 40 morphine milligram equivalent (MME) as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose. (Evidence: Level II; Strength of Recommendation: Moderate)
13. Avoid long-acting opioids for the initiation of opioid therapy. (Evidence: Level I; Strength of Recommendation: Strong)
14. Recommend methadone only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within FDA recommended doses. (Evidence: Level I; Strength of Recommendation: Strong)
15. Understand and educate the patients of the effectiveness and adverse consequences. (Evidence: Level I; Strength of Recommendation: Strong)
16. Similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids. (Evidence: Level I-II; Strength of recommendation: Moderate to strong)
17. Periodically assess pain relief and/or functional status improvement of  $\geq 30\%$  without adverse consequences. (Evidence: Level II; Strength of recommendation: Moderate)
18. Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain. (Evidence: Level I; Strength of Recommendation: Strong)

# Appropriate patient:

- Rheumatoid Arthritis?
- Osteoarthritis?
- Ankylosing spondylitis?
- Fibromyalgia?
- Back Pain?
- Chronic Noncancer Pain CNCP



**FIGURE 1.** Left to right: A, Lateral radiograph (standing) of a 15-year-old female synchronized figure skater with low back pain and bilateral L4 spondylolysis with a grade 1 anterolisthesis of L4 on L5. B, Increased spondylolysis and spondylolisthesis occurred when the athlete returned to sport after 7 months of conservative treatment. C, Athlete was referred to orthopedic surgery for posterior fusion of L4-L5, after which she returned to synchronized figure skating.



# Who should get Long Acting Opioids?

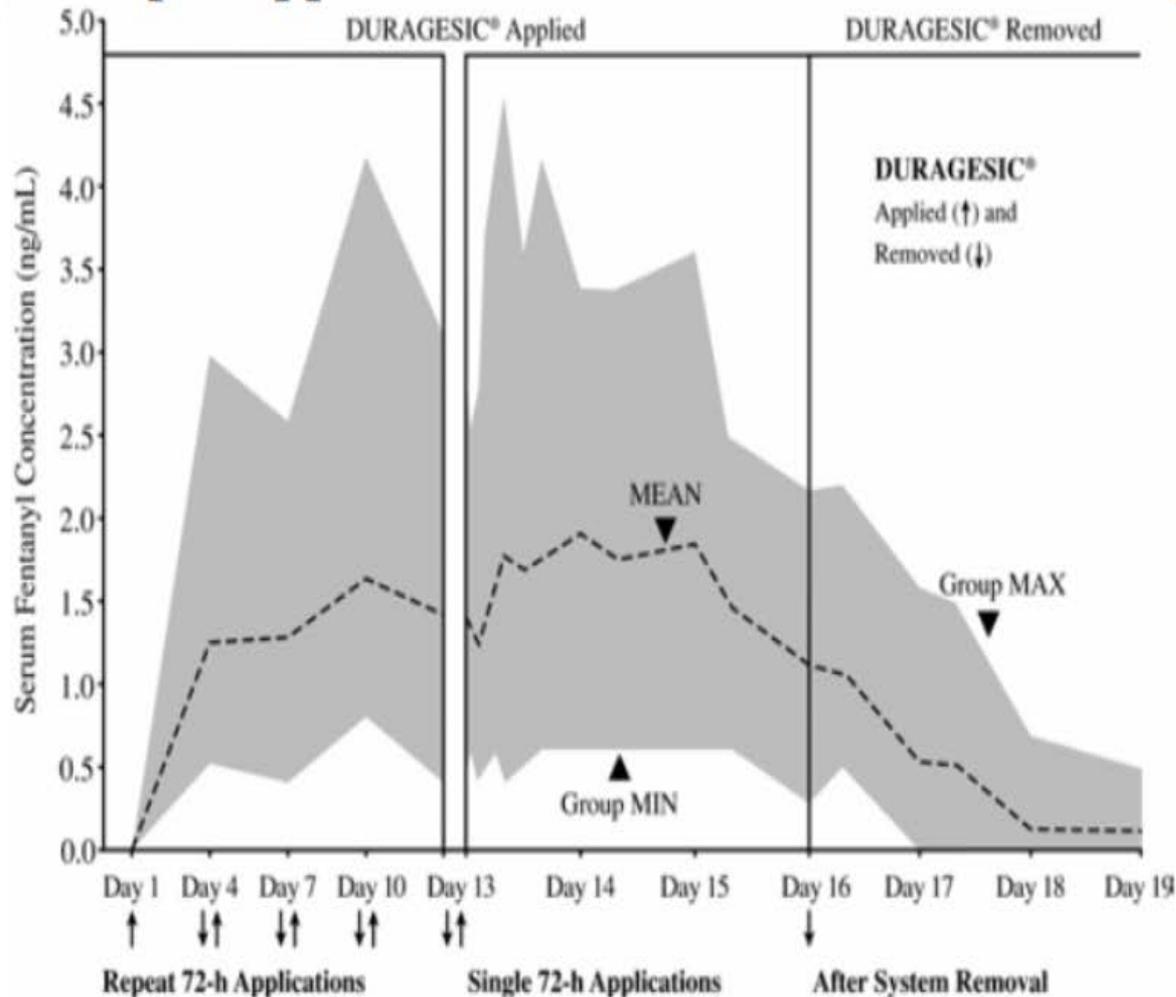
## Who Should get Chronic Opioid Therapy

- Only after IR medications are around clock
  - Start low and escalate if needed
- Only after physical multimodality therapies
- Optimized adjunctive medications:
  - Amine uptake inhibitors
  - Gabapentinoids
  - Topical, TENS units
- No “Aberrant drug-related behaviors”
- Focus on ***Functionality***

# Rationale:

## Serum Fentanyl Concentrations

Following Multiple Applications of DURAGESIC® 100 mcg/h (n=10)



# Hydrocodone Abuse Deterrent

## Zohydro: BeadTek®

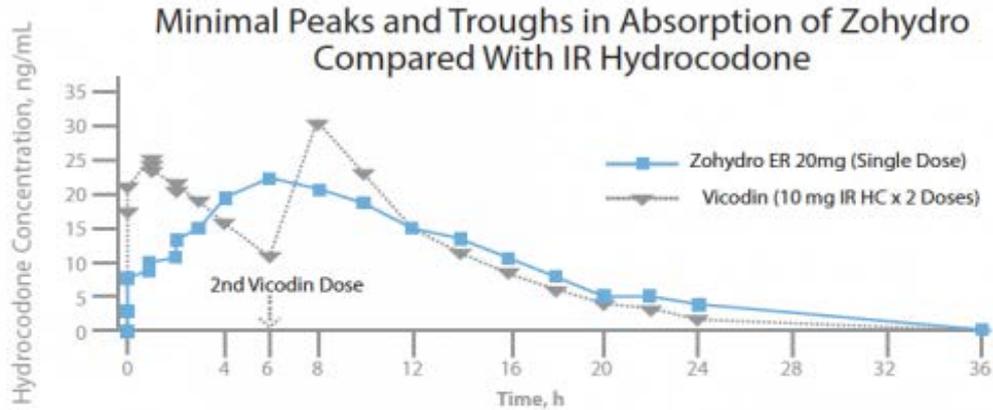


Figure 2. Graphic illustration of the bioavailability difference between Zohydro ER compared ER, extended release; IR HC, immediate-release hydrocodone combination ©Pernix Therapeutics. Reproduced with permission of Pernix Therapeutics.

## Hysingla® Resistec

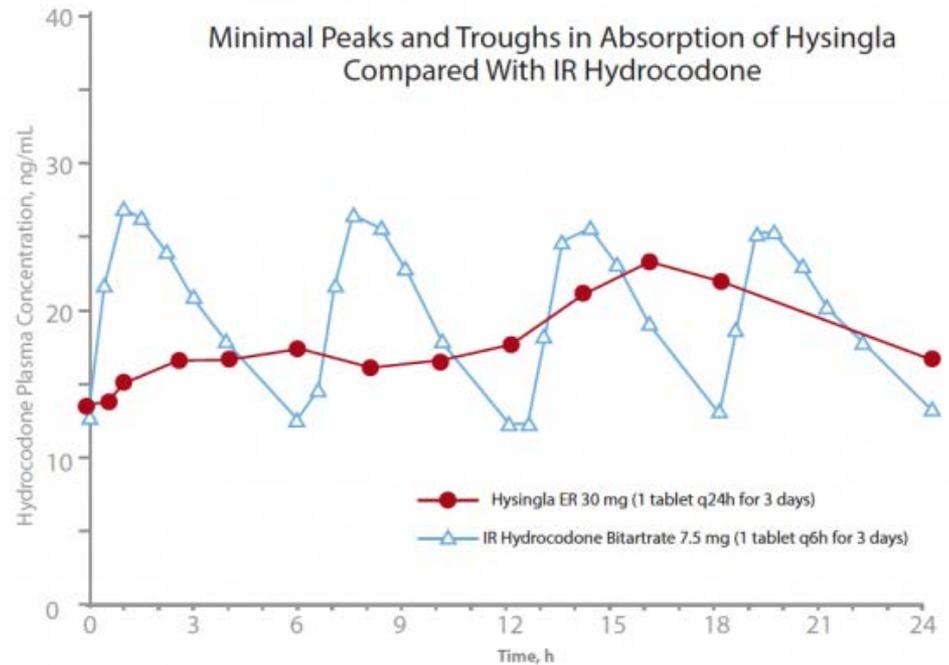
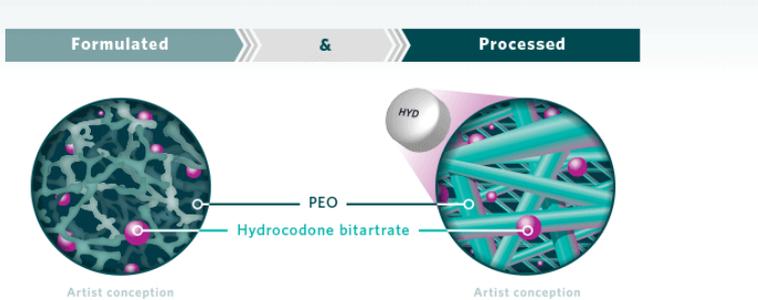
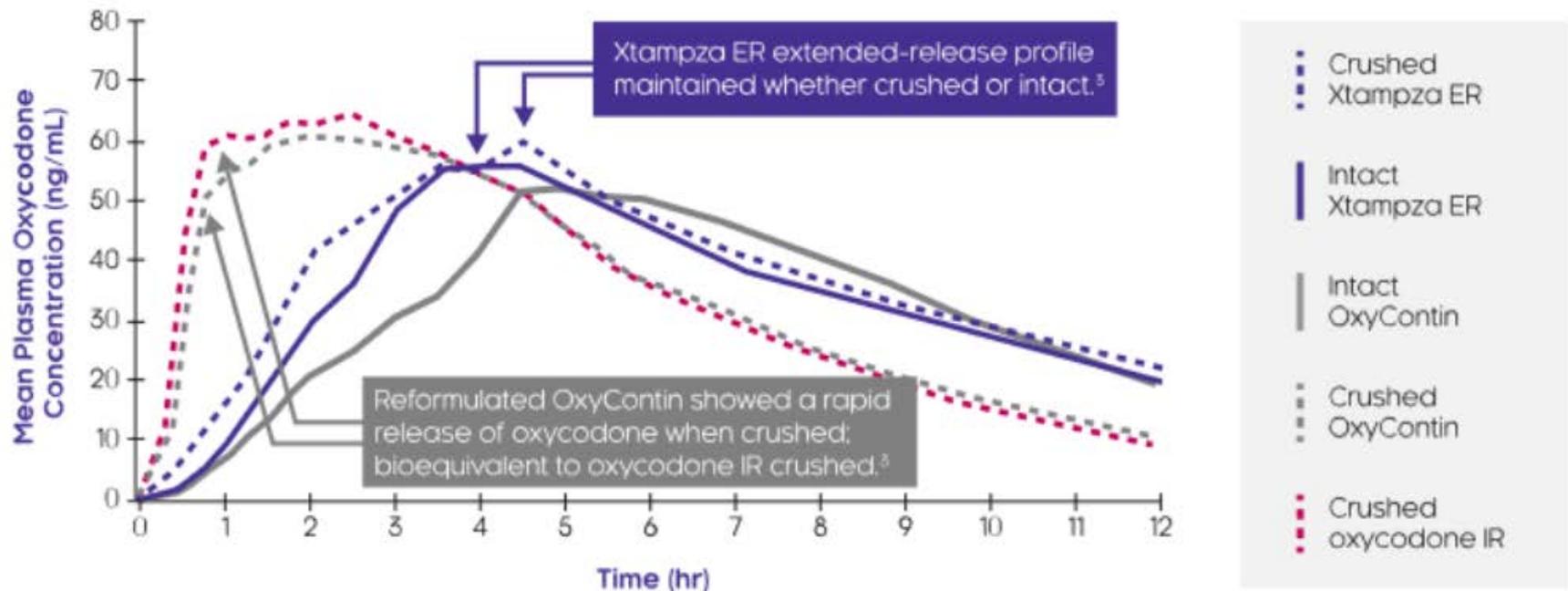


Figure 3. Graphic illustration of the bioavailability of Hysingla ER compared with immediate-release hydrocodone bitartrate. ER, extended release; IR, immediate release ©Purdue Pharma L.P. Reproduced with permission of Purdue Pharma L.P.

# Oxycodone Long Acting

- Oxycotin<sup>®</sup>, (Generics?), Xtampza<sup>®</sup>
  - 10,15,20,30,40,60,80 mg Q 12
  - 9, 13.5, 18, 27, 36 mg Q 12

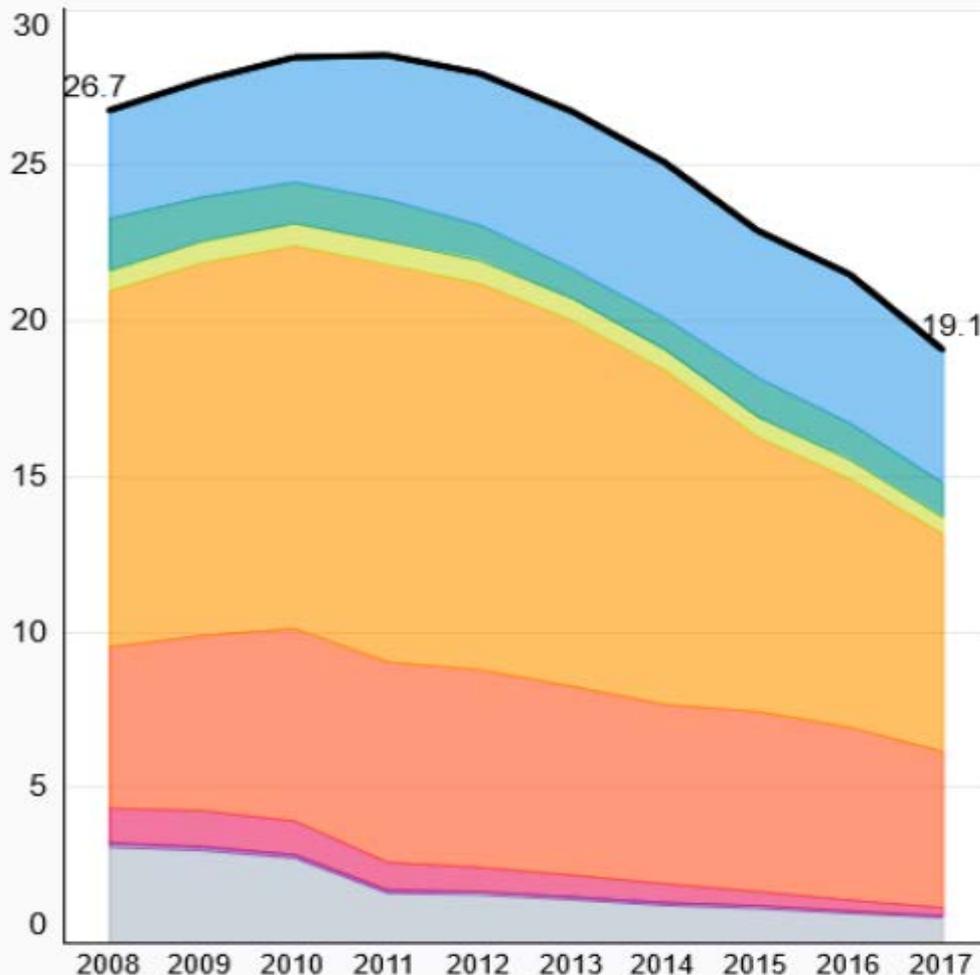


# Opioid Use Last Ten Years

Figure 2: 10 Year Trends in Prescription Opioid Use in the Commercially Insured



## Pills per Person - National



### Measure

Pills per Person

### State

National

### Drug

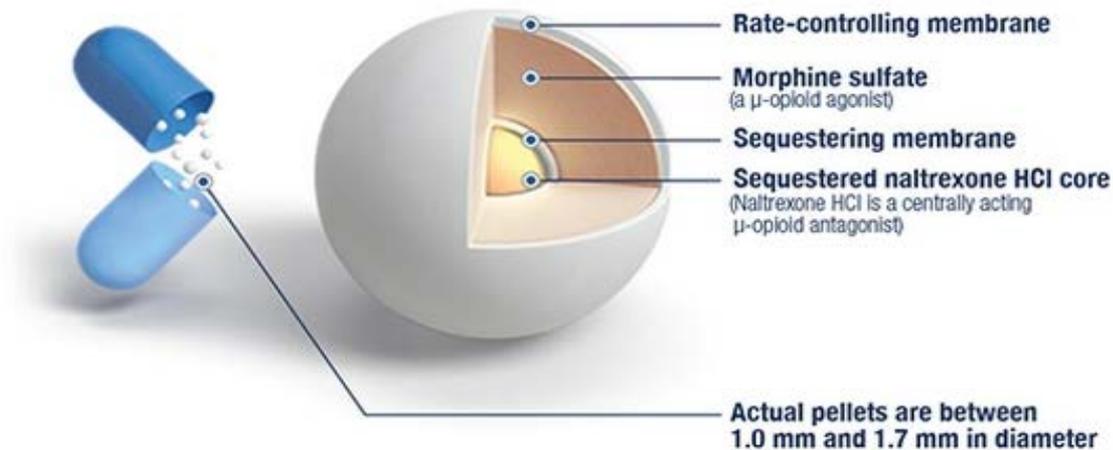
- Tramadol
- Codeine
- Morphine
- Hydrocodone
- Oxycodone SA
- Oxycodone LA
- Fentanyl
- Other

<https://www.healthcostinstitute.org/blog/entry/opioid-10yr-trends>

# Abuse Deterrent Technologies: Morphine plus Naltrexone:

**EMBEDA is specifically designed with sequestered naltrexone HCl, which is released with manipulation by crushing <sup>1</sup>**

EMBEDA capsules contain pellets of ER morphine sulfate and sequestered naltrexone HCl



Oxycodone plus  
naltrexone:  
Troxyca ER®  
Approved 8/19/16  
Pfizer stopped  
sales  
8/16/19 Elite Pharm  
Looking to obtain  
rights to market

## **The role of sequestered naltrexone HCl in EMBEDA <sup>1</sup>**

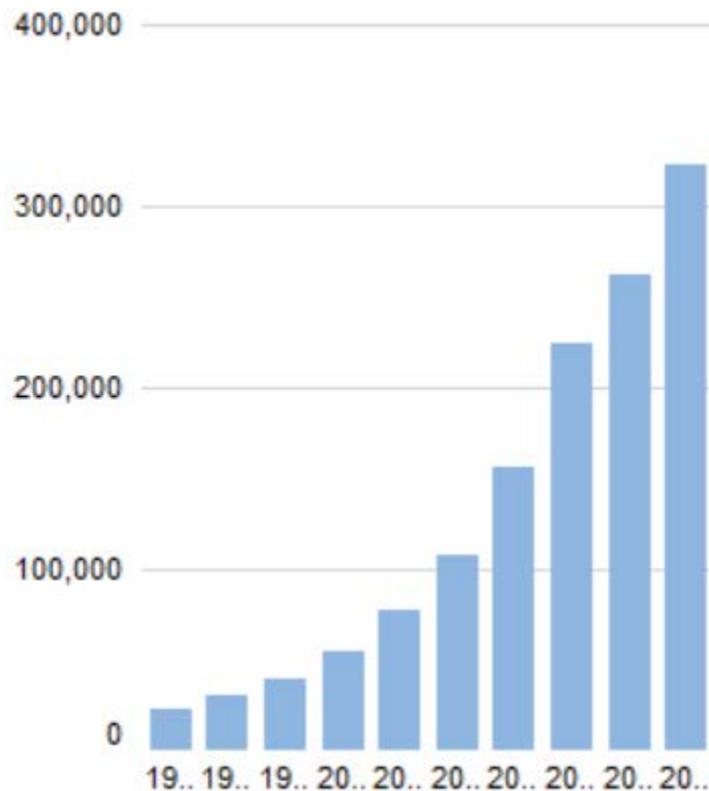
When taken as directed, the sequestered naltrexone is intended to have no clinical effect.

# Methadone:

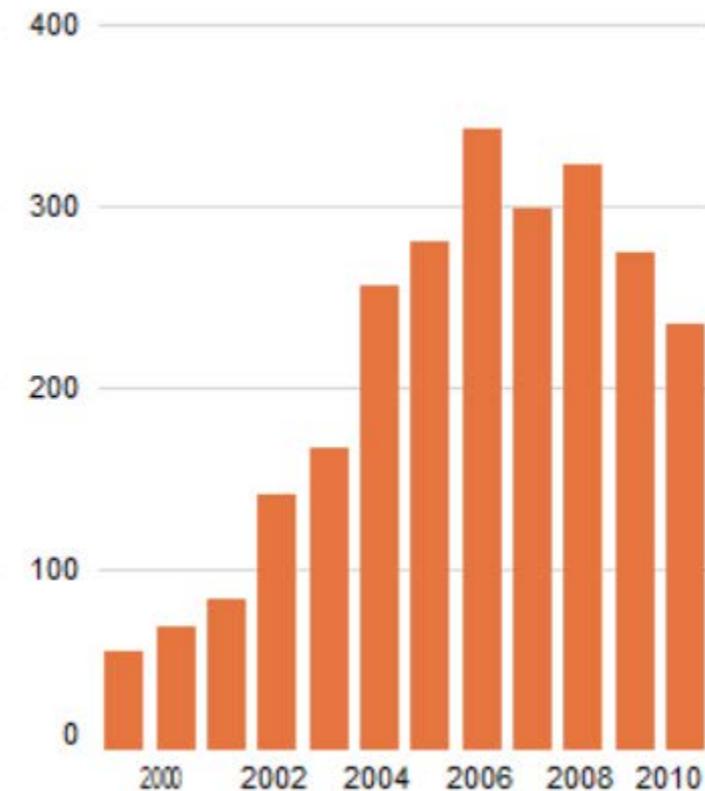
- CAN be prescribed for pain!
- VERY long t  $\frac{1}{2}$  half
- 5,10mg (40mg) tablets
- Figure out dose-
- Give  $\frac{1}{2}$  for 1 week
- “Document that you told them and they understand NOT to take methadone for BT pain!”
  - BT = Break Through
- Give whatever for that
- Up your basal after week
- **Conversion Ratio of Oral Morphine to Oral Methadone**
- <100 mg - 3:1 (*i.e.*, 3 mg morphine:1 mg methadone)
- 101-300 mg - 5:1
- 301-600 mg - 10:1
- 601-800 mg - 12:1
- 801-1000 mg - 15:1
- >1001 mg - 20:1
- Due to incomplete cross-tolerance, it is recommended that the initial dose is 50-75% of the equianalgesic dose.

# Seattle Times Methadone Deaths

Consumption of methadone in Washington state, in grams, from 1997 to 2006



Accidental methadone deaths in Washington from 1999 to 2010



**Cost comparison**  
*OxyContin costs the state more than 12 times as much as a comparable amount of methadone.*



Source: U.S. Drug Enforcement Administration; Seattle Times analysis of Washington death-certificate data; Department of Social and Health Services

*The End*

Completeness slides and interesting data if time permitting:

# Fentanyl: Topical Good, Buccal Bad

- Duragesic<sup>®</sup>, Generics
  - 12,25,50,75,100 mcg/hour- 72 hour patch
  - Disposal!

**TABLE 1: DOSE CONVERSION GUIDELINES**

Current Analgesic	Daily Dosage (mg/day)			
Oral morphine	60-134	135-224	225-314	315-404
Intramuscular or Intravenous morphine	10-22	23-37	38-52	53-67
Oral oxycodone	30-67	67.5-112	112.5-157	157.5-202
Oral codeine	150-447			
Oral hydromorphone	8-17	17.1-28	28.1-39	39.1-51
Intravenous hydromorphone	1.5-3.4	3.5-5.6	5.7-7.9	8-10
Intramuscular meperidine	75-165	166-278	279-390	391-503
Oral methadone	20-44	45-74	75-104	105-134
	↓	↓	↓	↓
Recommended DURAGESIC Dose	25 mcg/hour	50 mcg/hour	75 mcg/hour	100 mcg/hour

Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table 1, use the conversion methodology outlined above with Table 2.

<sup>1</sup> Table 1 should not be used to convert from DURAGESIC to other therapies because this conversion to DURAGESIC is conservative. Use of Table 1 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible [see *Dosage and Administration (2.3)*].

Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table 1, use the following methodology:

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using a reliable reference.

**TABLE 2: RECOMMENDED INITIAL DURAGESIC DOSE BASED UPON DAILY ORAL MORPHINE DOSE**

Oral 24-hour Morphine (mg/day)	DURAGESIC Dose (mcg/hour)
60-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

NOTE: In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to DURAGESIC.

<sup>1</sup> Table 2 should not be used to convert from DURAGESIC to other therapies because this conversion to DURAGESIC is conservative. Use of Table 2 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible [see *Dosage and Administration (2.3)*].

# Tapentadol Nucynta®



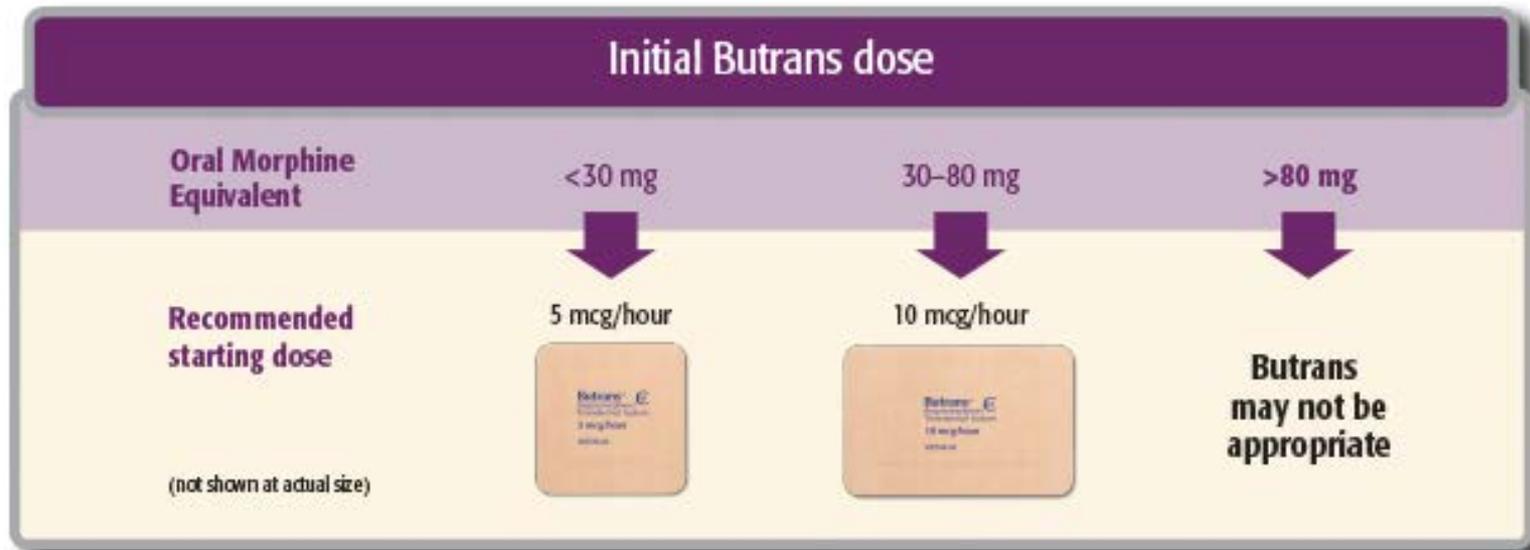
- Mu- opioid receptor agonist
- Norepinephrine reuptake inhibitor
- 50, 75, 100 mg tablets NMT 600/day
- 100,150,200 mg SR
- Oral bioavailability 32%, T  $\frac{1}{2}$  4 hours
- 97% hepatic metabolism Renal elimination
- Analgesia comparable to:
  - Oxycodone, Morphine



# Buprenorphine Butrans



- Once weekly Schedule III
- Low to Moderate potency
- 5,10,15,20 mcg/hour



~ Belbuca, Probuphine, and Buprenex are other buprenorphine brands

# Are they really “Abuse Deterrent”

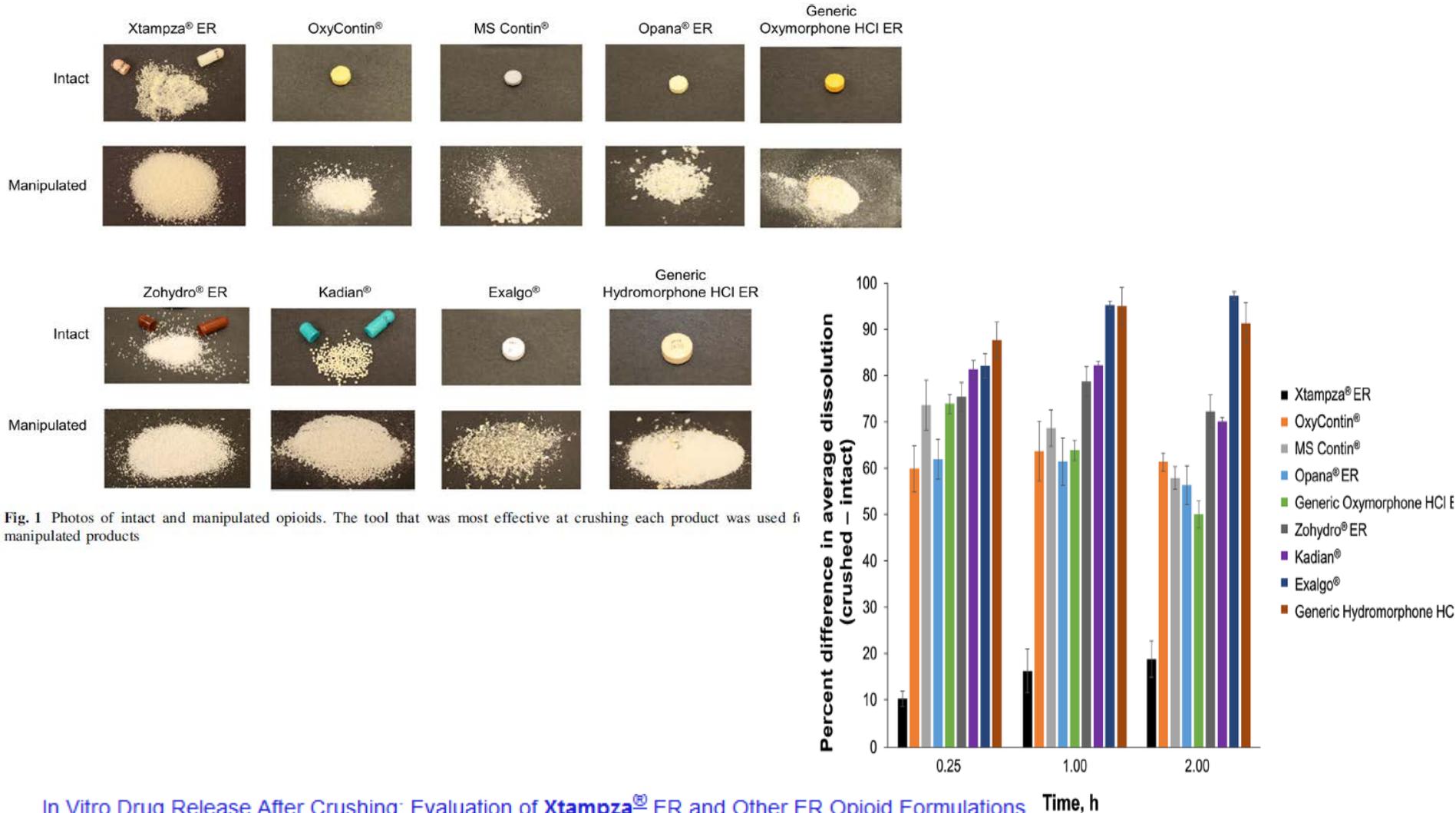


Fig. 1 Photos of intact and manipulated opioids. The tool that was most effective at crushing each product was used for manipulated products

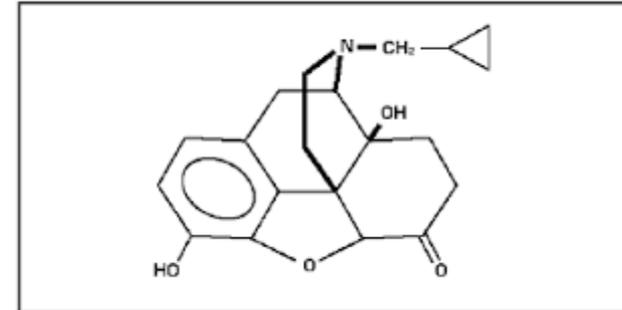
[In Vitro Drug Release After Crushing: Evaluation of Xtampza<sup>®</sup> ER and Other ER Opioid Formulations](#) Time, h

Stephen P. Mayock, Said Saim, Alison B. Fleming

Clin Drug Investig. 2017; 37(12): 1117–1124. Published online 2017 Sep 22. doi: 10.1007/s40261-017-0561-9

# Long Acting Agonist Antagonist

- Naltrexone: Antagonists
  - Indicated for Alcohol Abstinence
  - Indicated for Opioid Abstinence
  - Orally: Daily
    - Revia, Generics 50 mg
    - Depo Injection: Vivitrol
- Buprenorphine: Agonists/Antagonist
  - Implants: Probuphine
    - 4 Implants Q 6 Months
  - Depo Injection: Sublocade
    - Induction, 300,300,100 Q month



**Vivitrol**<sup>®</sup>  
(naltrexone for extended-release  
injectable suspension)

**Probuphine**<sup>®</sup>  
(buprenorphine) implant 

ONCE-MONTHLY  
**Sublocade**<sup>™</sup>  
(buprenorphine extended-release)  
injection for subcutaneous use   
100mg-300mg