

# Opioid Prescribing

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Knowledge that will change your world



**NEW DISCLOSURE RULES TAKE EFFECT  
ON DOCTORS' TIES TO DRUG COMPANIES**

DO YOU HAVE  
ANY QUESTIONS  
ABOUT YOUR  
MEDICATION?



# Disclosures

**Dr. Bailey has no  
relevant financial  
conflicts of interest or  
disclosures.**

**Off Label use of  
medications will be  
clearly identified as  
such.**

# Objectives

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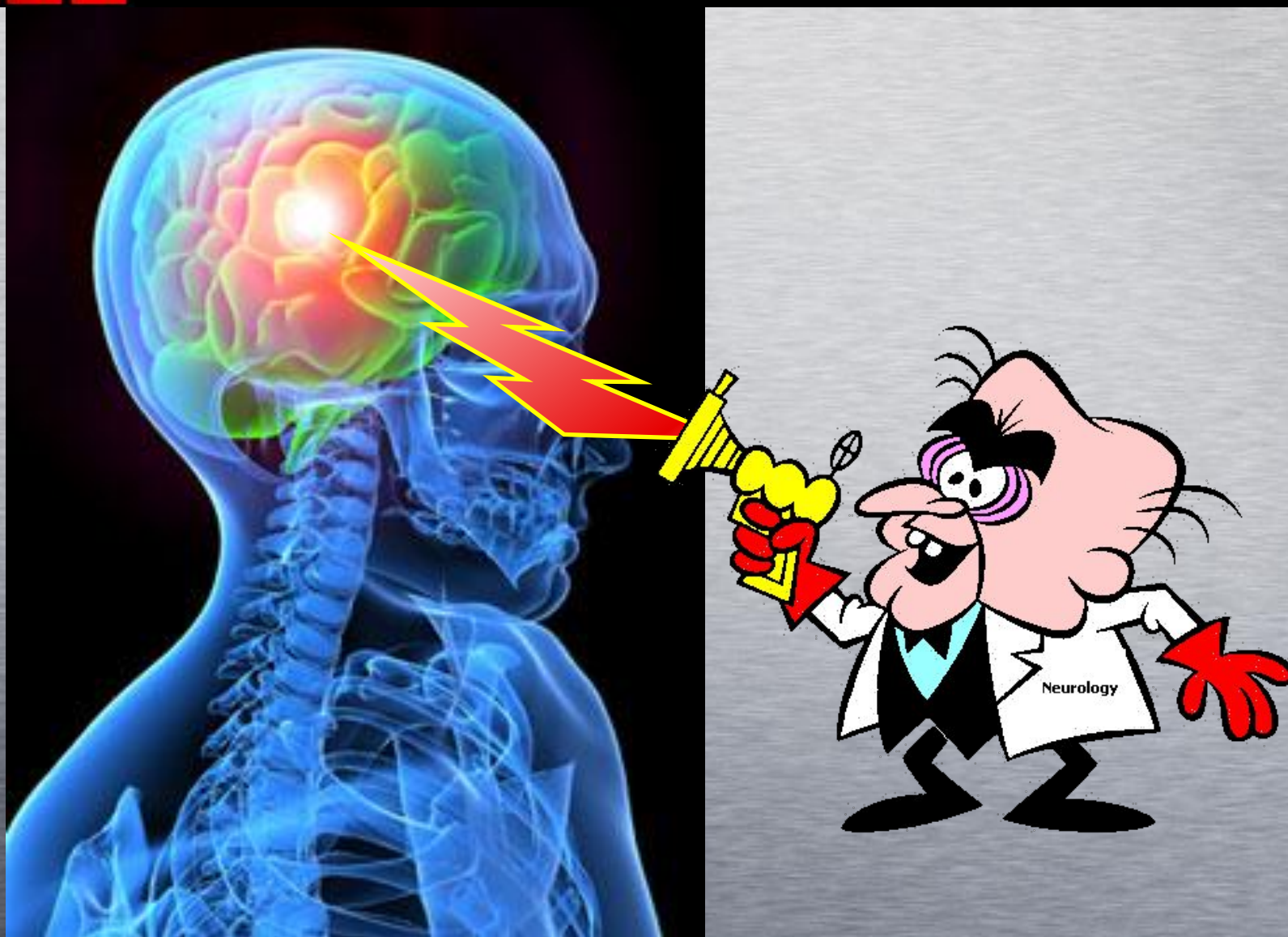
- **Identify and better understand opioid taxonomy and nomenclature**
- **Know where and how opioids work**
- **Expand understanding of opioid kinetics and dynamics**
- **Know basic opioid dose conversion factors**
- **Better understand the uses and limitations of urine drug screening**

# Overview

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- **Opioid Basics**
- **Opioid Effectiveness**
  - Acute
  - Chronic
- **When is the use of opioids appropriate?**
- **Evolving trends in pain management**
- **Prognostications**

# Opioid Basics



# Opioid Taxonomy

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- **Opioids**

- **Synthetic**

- Fentanyl
    - Methadone
    - Tapentadol
    - Meperidine

- **Semisynthetic**

- Hydrocodone
    - Oxycodone
    - Hydromorphone
    - Oxymorphone
    - Buprenorphine

- **Opiates**

- **Natural**

- Morphine
    - Codeine
    - Endogenous

# Opioid Nomenclature

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- **Narcotics** – an often misused term that has come to mean any illegal drug.
- By convention and common use, opioids are any drug that activates the body's opioid receptors
- Legal definition includes opioids as well as cocaine and its derivatives

# Opioid Receptors

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- Types
  - mu – subtypes 1-3
  - delta – analgesia, seizures at high doses
  - kappa – mu antagonist, dysphoria, ? addiction
  - epsilon – related to beta-endorphin
  - nociceptin – tolerance, but not analgesia
- Location
  - Brain
  - Spinal Cord
  - Digestive Tract
  - Peripheral

# Duration of Action

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- **Short-acting**

- Morphine
- Codeine
- Hydrocodone
- Oxycodone
- Fentanyl
- Oxymorphone
- Hydromorphone
- Tapentadol

- **Long-Acting**

- Methadone
- Levorphanol

- **ER-Formulations of short-acting drugs**

Advantage of one vs.  
the other?

# Pure Opioid Agonists

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## Weak

- Tramadol
- Codeine
- Propoxyphene
- Loperamide (Imodium)
  - Peripheral Only

The terms 'weak' and 'strong' are rarely used in present-day nomenclature.

## Strong

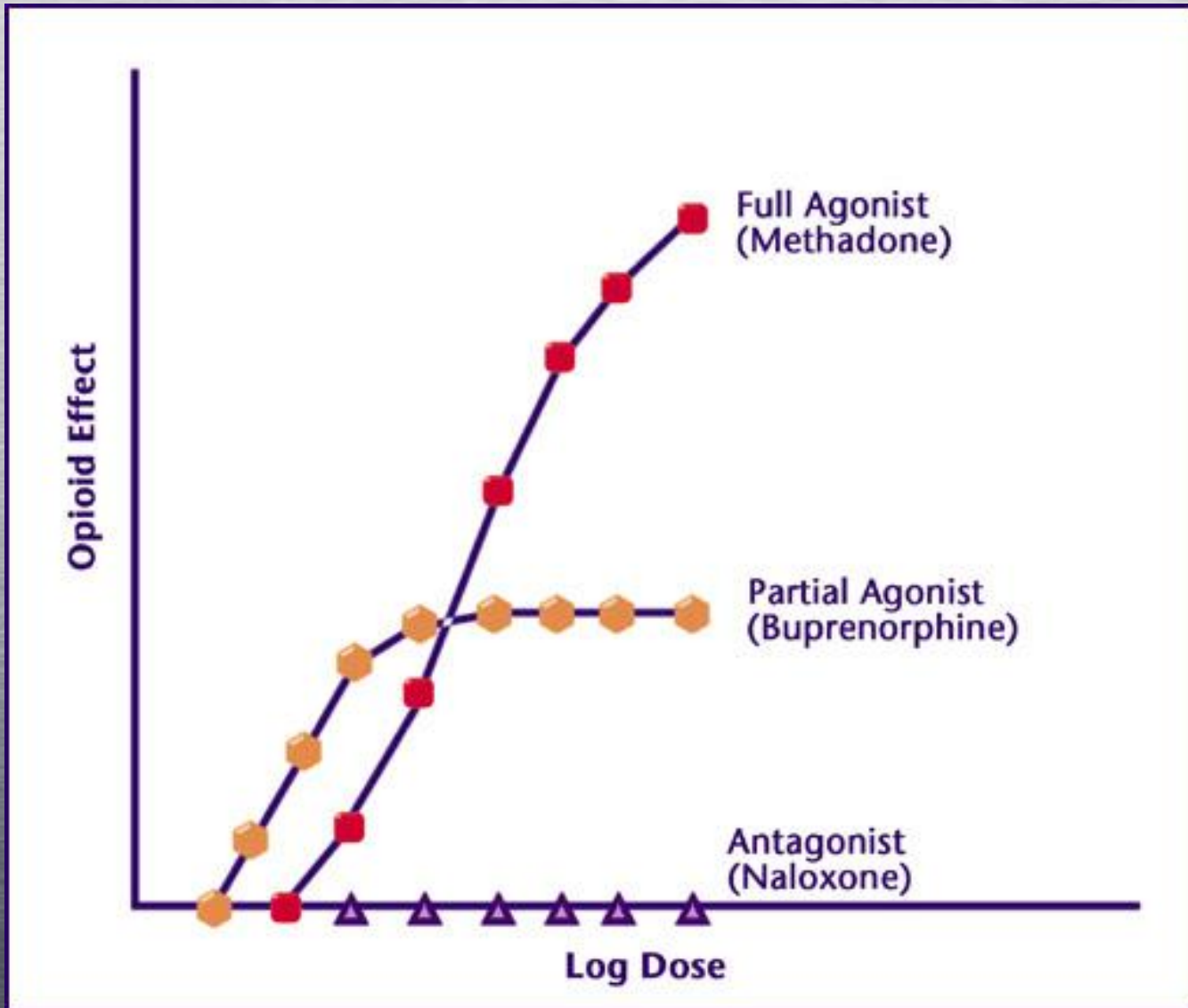
- Morphine
- Hydromorphone
- Hydrocodone
- Methadone
- Oxycodone
- Oxymorphone
- Meperidine
- Tapentadol
- Fentanyl

# Opioid Partial Agonists

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- **Butorphanol (Stadol)**
- **Nalbuphine (Nubain)**
- **Pentazocine (Talwin)**
- **Buprenorphine (Suboxone, Butrans)**

# Ceiling Effect



# Pure Opioid Antagonists

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- **Central Acting**
  - Naloxone (Narcan)
  - Naltrexone (Trexan)
- **Peripheral Only**
  - Methylnaltrexone (Relistor)
  - Naloxegol (Movantik)

# Multiple Receptors

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- **Tapentadol**
  - Opioid
  - Noradrenergic reuptake inhibitor
- **Methadone**
  - Opioid
  - NMDA receptor antagonist
- **Tramadol**
  - Opioid
  - May be anti-inflammatory
  - May be anti-depressant (serotonin release)

# Methadone

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- Half-life for pain vs. toxicity
- Complex conversion from other opioids
- Volume of Distribution
- Elimination
- Drug Interactions
- Cardiac Toxicity
- 40mg tabs for inpatient or addiction only
- Medical / legal considerations
- Methadone Maintenance Clinics

# Less Familiar Formulations

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- **Avinza (ER morphine)**
- **Butrans (transdermal buprenorphine)**
- **Exalgo (ER hydromorphone)**
- **Embeda (ER morphine + naltrexone)**
- **Kadian (ER morphine)**
- **Morphabond (ER morphine)**
- **Nucynta IR & ER (tapentadol)**
- **Opana IR & ER (oxymorphone)**
- **Short-acting Fentanyl Preparations**
- **Xartemis XR (ER oxycodone / ACP)**
- **Zohydro ER; Hysingla ER (ER hydrocodone)**

# Opioid Metabolism

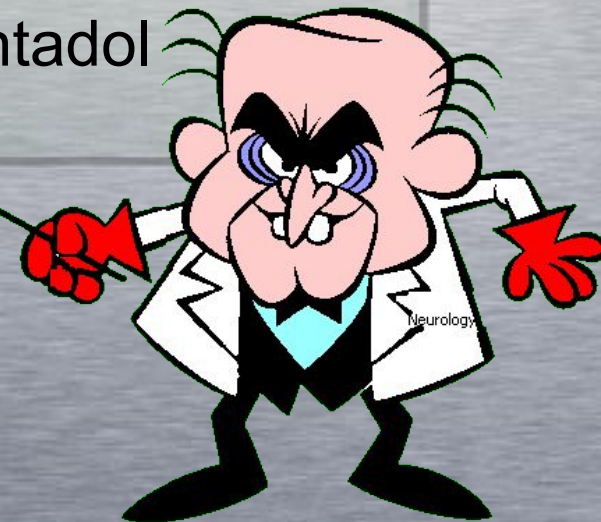
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- **Pro-Drugs**

- Hydrocodone
- Codeine
- Tramadol

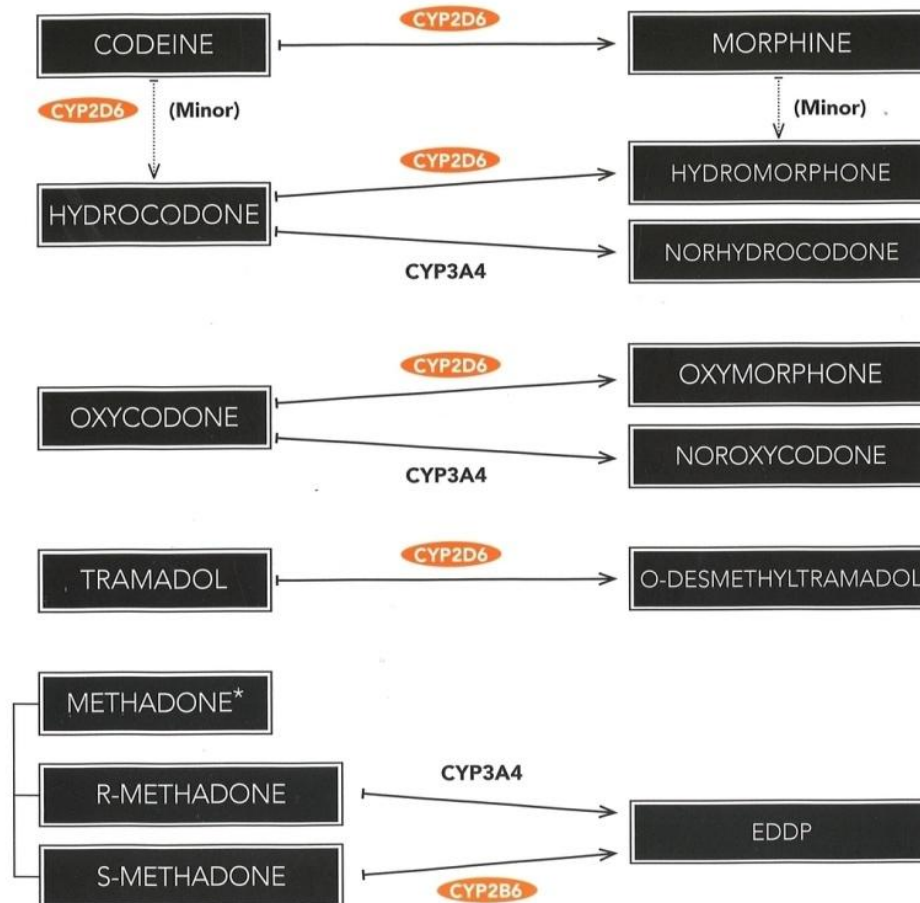
- **Natively Active**

- Morphine
- Hydromorphone
- Oxycodone
- Tapentadol



# Opioid Metabolism

## PRIMARY OPIOID METABOLIC PATHWAYS<sup>2,3</sup>



\*Lesser metabolic pathways for methadone also mediated by 2D6, 2C9, 2C19 to varying degrees

————→ Major metabolic pathway

- - - - -> Minor metabolic pathway

● = Tested by Millennium PGT

CYP = cytochrome P450

EDDP = 2-Ethylidene-1, 5-Dimethyl-3, 3-Diphenylpyrrolidine

PARENT DRUG	PRIMARY METABOLITES
CODEINE	Morphine, Hydrocodone (minor)
HYDROCODONE	Hydromorphone; Norhydrocodone
OXYCODONE	Oxymorphone; Noroxycodone
TRAMADOL	O-Desmethyltramadol
METHADONE (R- AND S-ISOMERS)	EDDP

(2) Adapted from Smith HS. Opioid Metabolism. *Mayo Clin Proc.* 2009; 84(7):613-624.

(3) Adapted from Trescot AM, et al. Opioid Pharmacology. *Pain Physician.* 2008;11(suppl):135S-153S.

# Detection Times of Common Drugs

Amphetamines	<ul style="list-style-type: none"><li>• 48 hours</li></ul>
Barbiturates	<ul style="list-style-type: none"><li>• Short-acting (eg, secobarbital), 24 hours</li><li>• Long-acting (eg, phenobarbital), 2–3 weeks</li></ul>
Benzodiazepines	<ul style="list-style-type: none"><li>• 3 days if therapeutic dose is ingested</li><li>• Up to 4–6 weeks after extended dosage (<math>\geq 1</math> year)</li></ul>
Cannabinoids	<ul style="list-style-type: none"><li>• Moderate smoker (4 times/week), 5 days</li><li>• Heavy smoker (daily), 10 days</li><li>• Retention time for chronic smokers may be 20–28 days</li></ul>
Cocaine	<ul style="list-style-type: none"><li>• 2–4 days, metabolized</li></ul>
Ethanol	<ul style="list-style-type: none"><li>• 2–4 hours</li></ul>
Methadone	<ul style="list-style-type: none"><li>• Approximately 30 days</li></ul>
Opiates	<ul style="list-style-type: none"><li>• 2 days</li></ul>
Phencyclidine	<ul style="list-style-type: none"><li>• Approximately 8 days</li><li>• Up to 30 days in chronic users (mean value = 14 days)</li></ul>
Propoxyphene	<ul style="list-style-type: none"><li>• 6–48 hours</li></ul>

SUBSTANCE FALSELY IDENTIFIED ON TEST	ACTUAL SUBSTANCE	TYPE OF STUDY	NOTES
Amphetamine and methamphetamine	Selegiline	Single case report <sup>1,2</sup>	L-stereoisomer only detected (D-stereoisomer present in illicit drugs)
Amphetamine and methamphetamine	Vicks Inhaler	Several case reports, controlled-exposure studies <sup>1,3</sup>	L-stereoisomer only detected; most positives noted with twice recommended dosage
Barbiturate	NSAIDs (ibuprofen, naproxen)	Controlled-exposure study of 60 subjects (510 specimens) <sup>4</sup>	0.4% false-positive rate
Benzodiazepine	Oxaprozin	Controlled-exposure study of 12 patients (36 specimens) <sup>5</sup>	100% false-positive rate, some cases lack controls
Cannabinoid	NSAIDs (ibuprofen, naproxen)	Controlled-exposure study of 60 subjects (510 specimens) <sup>4</sup>	0.4% false-positive rate
Opiate	Fluoroquinolone*	Controlled-exposure studies (8 subjects) and case series (9 subjects) <sup>6</sup>	Most levels detected were below new 1998 threshold (2000 ng/mL)
Opiate	Rifampin	3 case reports <sup>7</sup>	
Phencyclidine	Venlafaxine	1 case report <sup>8</sup>	Confirmed by GC-MS (7200 mg intentionally ingested)
Phencyclidine	Dextromethorphan	1 case report <sup>9</sup>	(500 mg ingested)
*Ofloxacin and levofloxacin most likely to cause false positive.			

# Opioid Effectiveness

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- **Acute pain**

- Opioids are among our most powerful analgesics and have been well demonstrated to be effective in acute pain.

- **Chronic pain**

- More problematic
- Side effects vs benefit



# When are opioids appropriate?

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- **Acute pain – this is probably their strongest indication**
- **Chronic pain – only when all else fails and at minimal doses**
- **Pain related to active cancer as well as end-of-life are excluded from most prescribing limitations.**

# Opioids

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- **“For chronic back pain, systematic reviews find scant evidence of efficacy.**
- **Randomized controlled trials have high dropout rates, brief duration (four months or less), and highly selected patients.**
- **Opioids seem to have short term analgesic efficacy for chronic back pain, but benefits for function are less clear.**
- **The magnitude of pain relief across chronic non-cancer pain conditions is about 30%.**
- **Given the brevity of randomized controlled trials, the long term effectiveness and safety of opioids are unknown.**
- **Loss of long term efficacy could result from drug tolerance and emergence of hyperalgesia.”**

- “There is substantial, albeit not definitive, scientific evidence of the effectiveness of opioids in treating pain and of high variability in opioid dose requirements and side effects.
- The estimated risk of death from opioid treatment involving doses above 100 MMED is ~0.25%/year.
- Multiple large studies refute the concept that short-term use of opioids to treat acute pain predisposes to development of opioid use disorder.
- The prevalence of opioid use disorder associated with prescription opioids is likely <3%.”

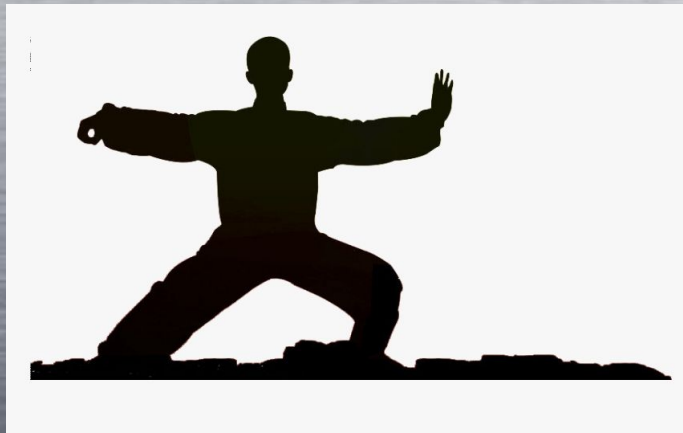
Nadeau SE, Wu JK and Lawhern RA (2021) Opioids and Chronic Pain: An Analytic Review of the Clinical Evidence. *Front. Pain Res.* 2:721357. doi: 10.3389/fpain.2021.721357

- Morbidity, mortality, and financial costs of inadequate treatment of the 18 million Americans with moderate to severe chronic pain are high.
- Because of the absence of comparative effectiveness studies, there are no scientific grounds for considering alternative non-pharmacologic treatments as an adequate substitute for opioid therapy but these treatments might serve to augment opioid therapy, thereby reducing dosage.

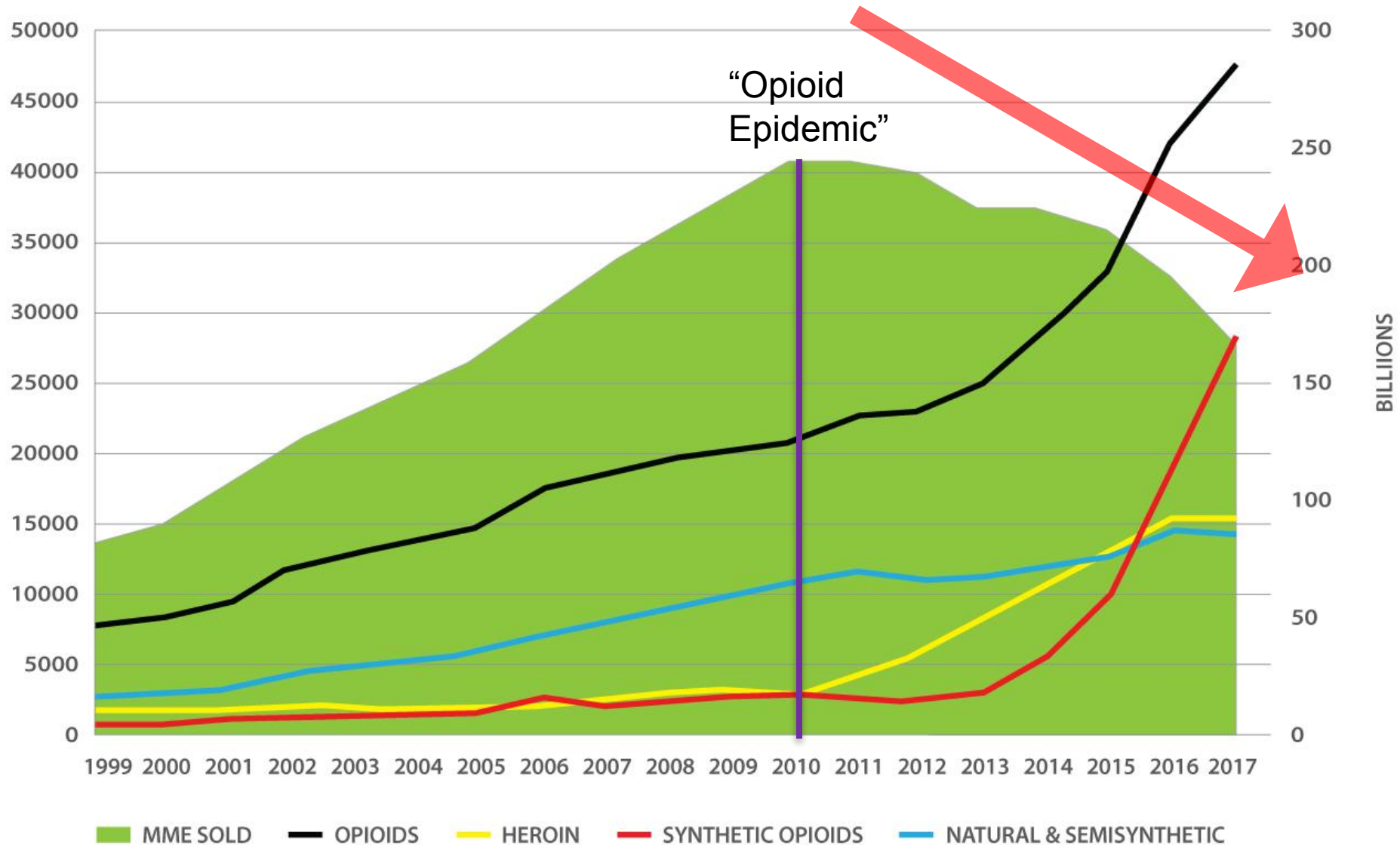
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# Pain Management Trends

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# Physician Response



# Benzos and Opioids

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- This is an extremely ‘hot-button’ item in the area of medical-legal scrutiny. It is a metric that is being calculated on all of us.
- If one of your patients is on chronic opioids \*please\* do not start benzos.
- If all other treatment modalities fail and the patient requires benzos, please put that in your note.
- Otherwise, it is likely the patients opioids will be tapered and discontinued.

# Prognostications

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- More and more opioids must be viewed as a **treatment of last resort** – to be used only when all else fails.
- **Non-opioid treatment** is going to have to assume a much more prominent role in chronic pain management – and our patients are going to have to buy into this.
- Both patients and physicians are going to have to get past the ‘**pill for every symptom**’ mentality
- Patients are going to have to become more active participants in their own health care
- Our present strategies for dealing with the opioid crisis **is not** reducing opioid-related overdose deaths

# Summary

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- **Chronic pain is a widespread, and expensive medical problem.**
- **Because of skyrocketing opioid overdose deaths, many new regulations are in place.**
- **There are a growing number of requirements and regulations; particularly when writing ER/LA opioids.**
- **Patient participation in their own health care is going to become more and more necessary in the current 'opioids are last resort' mentality.**
- **The role of non-pharmacologic treatment is going to have to increase.**

# Save the Pangolins!



TIM MASSON

# Contact Information

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