

## Opioid Epidemic: Myths versus Facts

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Adjunct Associate Professor Albany College of Pharmacy & Health Sciences, Albany NY  
Western New England University College of Pharmacy, Springfield MA

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## Disclosures – Jeffrey Fudin, PharmD, FCCP, FASHP, FFSMB

Affiliation	Role
Abbott Laboratories	Speaker
AcelRx Pharmaceuticals	Advisory Board
Acutis Diagnostics, Inc	Speaker
Astra Zeneca	Speakers Bureau
BioDelivery Sciences International	Advisory Board, Consultant
Daiichi Sankyo	Advisory Board, Speakers Bureau
Firstox Laboratories	Consultant
GlaxoSmithKline (GSK)	Advisory Board, Collaborative Presentations
Human Half-Cell, Inc	Advisory Board
Quest Diagnostics	Advisory Board
Scilex Pharmaceuticals	Advisory Board, Collaborative Publications
Salix Pharmaceuticals	Advisory Board, Speakers Bureau, Publications

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## More specifically...

- › Where were we?
- › Where are we now?
- › How we got here (dispelling the myths)?
- › Clarification of alternative facts

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## Objectives

1. Interpret current opioid usage and outcomes data
2. Summarize the neurobiology of addiction
3. Evaluate facts and myths associated with opioid usage and mortality
4. Recognize at least 3 medical disorders of “epidemic proportion” other than opioid abuse that may involve addictive personality
5. Summarize prescriber and pharmacist strategies to address the opioid epidemic and mitigate opioid risk

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## Pretest Question #1

Which of the following are necessary for addictive behavior?

- A. Euphoria, opioids, and benzodiazepines
- B. Exposure to drug, vulnerable person, vulnerable time
- C. Exposure to drugs and alcohol
- D. Opioids taken for longer than 3-months

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## Pretest Question #2

Select the correct sequence of highest to least baseline addiction vulnerability

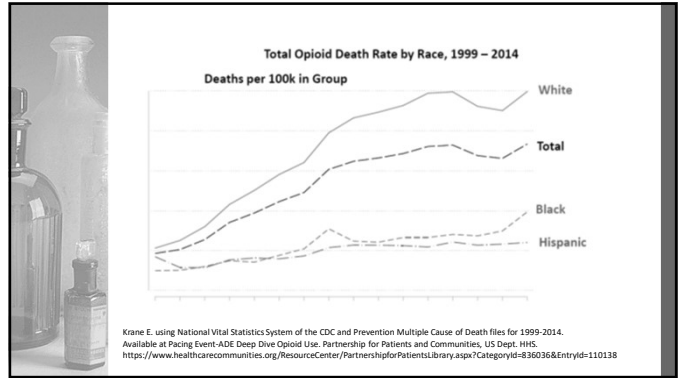
- A. Alcohol, opioids, nicotine
- B. Opioids, alcohol, nicotine
- C. Nicotine, alcohol, opioids
- D. They all have equal vulnerability

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**Pretest #3**

- A. Which of the following is true?
- B. There are approximately 64,000 deaths per year due to prescription opioids.
- C. Prescription fentanyl has a high prevalence of US deaths and continues to rise.
- D. CDC, HHS, managed care, several community pharmacy chains, and state regulatory agencies have largely reached consensus on morphine equivalent daily doses.
- E. None of the above

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**CDC Newsroom**

U.S. drug overdose deaths continue to rise; increase fueled by synthetic opioids

**Press Release**  
Embargoed Until: Thursday, March 29, 2018, 1:00 p.m. ET  
Contact: Media Relations  
(404) 639-3286

**U.S. drug overdose deaths continue to rise; increase fueled by synthetic opioids**

An in-depth analysis of 2016 U.S. drug overdose data shows that America's overdose epidemic is spreading geographically and increasing across demographic groups. The report, from researchers at the Centers for Disease Control and Prevention (CDC), appears in today's issue of *MMWR*.

**Drug overdoses killed 64,000 Americans in 2016; nearly two-thirds of those deaths (64%) involved a prescription or illicit opioid.** Over time, deaths increased in all states. CDC also examined by race and ethnicity, people ages 15 and older, all races and ethnicities, and across all levels of urbanization.

CDC's new analysis confirms that recent increases in drug overdose deaths are driven by continued sharp increases in deaths involving synthetic opioids other than methadone, such as illicitly manufactured fentanyl (IMF).

"No area of the United States is exempt from this epidemic—we all know a friend, family member, or loved one devastated by opioids," said CDC Principal Deputy Director Anne Schuchat, M.D. "All levels of the federal government are working together to reduce the availability of illicit drug, prevent deaths from overdoses, treat people with substance use disorders, and prevent people from starting using drugs in the first place."

**This is ALL drugs, not just opioids**  
<https://www.cdc.gov/media/releases/2018/p0329-drug-overdose-deaths.html>

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**Alternative Facts - 1**

## Deaths from Opioid Overdoses Now Higher Than Car Accident Fatalities

CDC estimates more than 42,000 people overdosed on opioids in 2016. Fentanyl-related drugs are one of the major reasons.

<https://www.healthline.com/health-news/deaths-from-opioid-overdoses-higher-than-car-accident-fatalities#modal-close>

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**The Opioid Epidemic: A Crisis Years in the Making**  
By Max Kinn  
Nov 16, 2017

**Alternative Facts - 2**

<https://www.nytimes.com/2017/10/26/us/opioid-crisis-public-health-emergency.html>

The current opioid epidemic is the deadliest drug crisis in American history. Overdoses, fueled by opioids, are the leading cause of death for Americans under 50 years old — killing roughly 64,000 people last year, more than guns or car accidents, and doing so at a pace faster than the H.I.V. epidemic did at its peak.

President Trump declared the opioid crisis a "public health emergency" on Thursday, though he did not release additional funding to address it. Had he declared it a "national emergency," as he promised to do in August, it would have led to the quick allocation of federal funds.

Notice title says "opioids" but 64,000 is all drugs including antidepressants, anticonvulsants, NSAIDs, and others

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**All that Glitters is Not Gold**  
Shakespeare W, Kaplan ML. *The Merchant of Venice*. In: *The Merchant of Venice*. 2002 (pp. 25-120). Palgrave Macmillan, New York.

**Drug Overdose Death Data**


**Opioids—prescription and illicit—are the main driver of drug overdose deaths.** Opioids were involved in 42,249 deaths in 2016, and opioid overdose deaths were five times higher in 2016 than 1999.

In 2016, the five states with the highest rates of death due to drug overdose were West Virginia (52.0 per 100,000), Ohio (39.1 per 100,000), New Hampshire (39.0 per 100,000), Pennsylvania (37.9 per 100,000) and Kentucky (33.5 per 100,000).

Significant increases in drug overdose death rates from 2015 to 2016 were seen in the Northeast, Midwest and South Census Regions. States with statistically significant increases in drug overdose death rates included Connecticut, Delaware, Florida, Illinois, Indiana, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Vermont, Virginia, West Virginia, and Wisconsin.\*

<https://www.cdc.gov/drugoverdose/data/index.html>

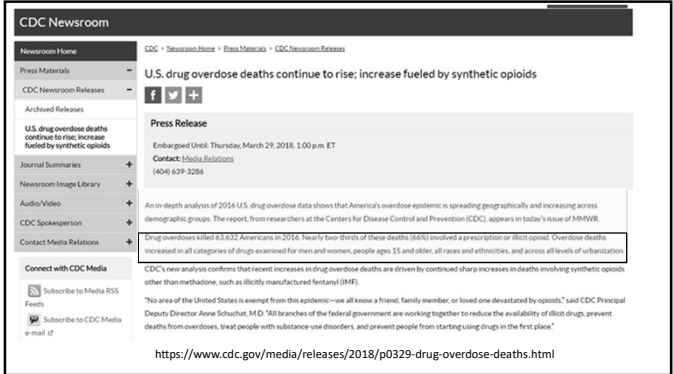
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**Glitter that ISN'T Gold**

Opioids - prescription and illicit - are the main driver of drug overdose deaths. Opioids were involved in 42,249 deaths in 2016, and opioid overdose deaths were five times higher in 2016 than 1999. (17-years later)

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Drug overdoses killed 63,632 Americans in 2016. Nearly two-thirds of these deaths (66%) involved a prescription or illicit opioid. Overdose deaths increased in all categories of drugs examined for men and women, people ages 15 and older, all races and ethnicities, and across all levels of urbanization.

CDC's new analysis confirms that recent increases in drug overdose deaths are driven by continued sharp increases in deaths involving synthetic opioids other than methadone, such as illicitly manufactured fentanyl (IMF).

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<https://www.cdc.gov/media/releases/2018/p0329-drug-overdose-deaths.html>

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**What exactly does "involve" mean?**

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**The Opioid Epidemic: A Crisis Years in the Making** Alternative Facts - 2

By Maya Schindler

The current opioid epidemic is the deadliest drug crisis in American history. Overdoses, fueled by opioids, are the leading cause of death for Americans under 50 years old — killing roughly 64,000 people last year, more than guns or car accidents, and doing so at a pace faster than the H.I.V. epidemic did at its peak.

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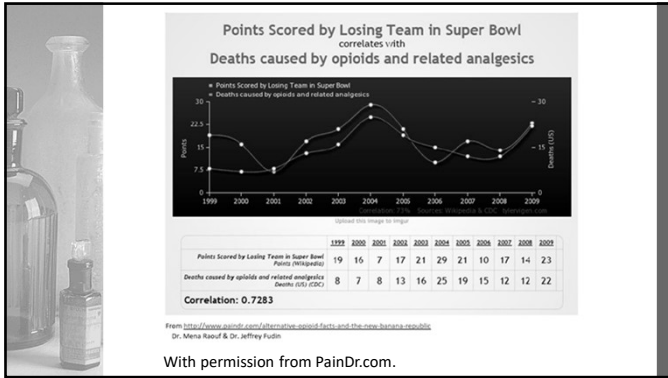
Remembering the body of a woman who died of an overdose in August. <https://www.nytimes.com/2017/10/26/us/opioid-crisis-public-health-emergency.html>

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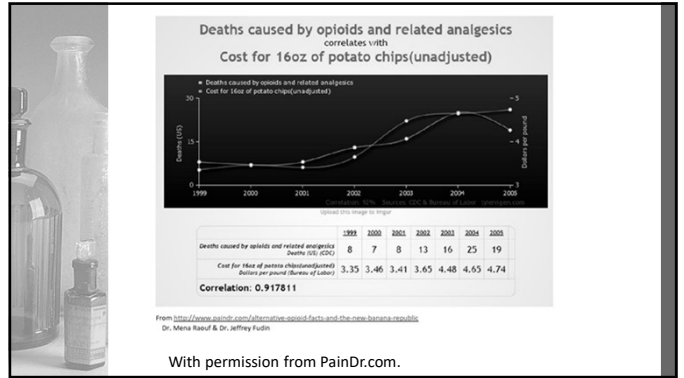
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**Overdoses fueled by opioids, are the leading cause of death for Americans under 50 years old - killing roughly 64,000 people last year; more than guns or car accidents, and doing so at a pace faster than the H.I.V epidemic did at its peak.**

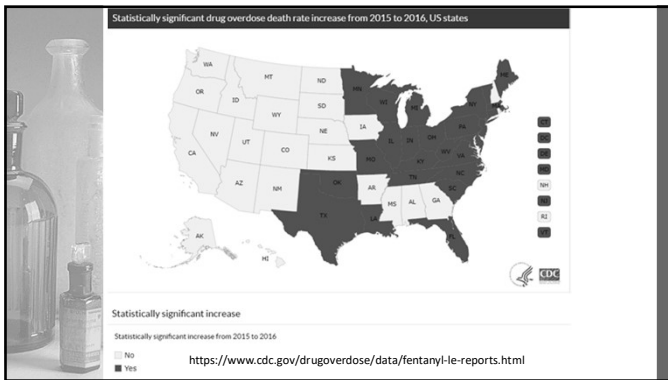
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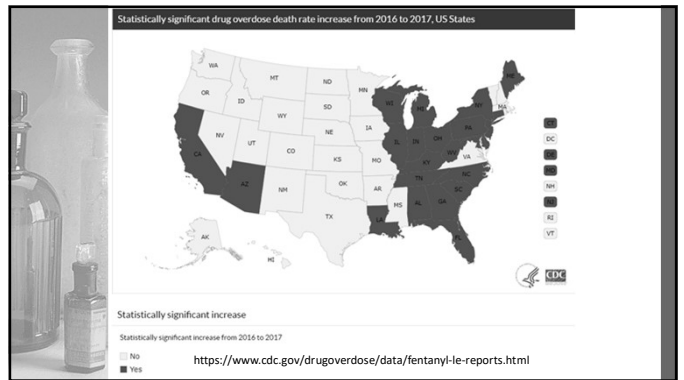
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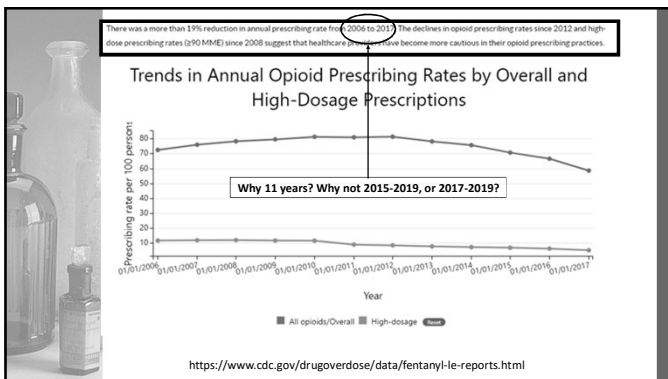
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




**Percentage of counties with changes in opioid prescribing United States, 2010–2015**

Opioid prescribing measures	Decrease (%)	Stable (%)	Increase (%)
MEDD per capita	49.6	27.8	22.6
Overall prescribing rate	46.5	33.8	19.6
High-dose prescribing rate	86.5	6.7	6.9
Average daily MME per prescription	72.1	25.7	2.2

Guy GP, et al. MMWR Morb Mortal Wkly Rep. 2017;66:697–704.

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### Chemical Classes of Opioids

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLPROPANES	PHENYLPROPYL AMINES
 MORPHINE Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl morphine) Hydrocodone* Hydromorphone* Levorphanol* Methadone** Morphine (Opium, conc) Naloxone* Nalbexone* Nalmefene** Oxycodone** Oxycodone**	 PENTAZOCINE Pentazocine	 FENTANYL Alfentanil Fentanyl Remifentanyl Sufentanil Sufentanil Diphenoxylate* Loperamide* <b>Illicit Fentanyl</b> Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanyl Otilone*	 METHADONE Methadone Propoxyphene	 TRAMADOL Tapentadol Tramadol
CROSS-SENSITIVITY RISK				
PROBABLE		POSSIBLE	LOW RISK	LOW RISK
*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group **N-position is substituted with a ketone group and tolerability is similar to hydrocodone				
http://painr.com/resources/quick-references/ (With permission, Fudin J. 2018)				

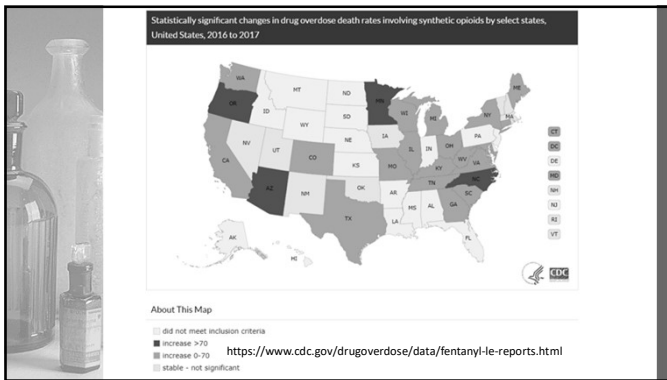
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### Schedule I Imported Fentanyl Derivatives

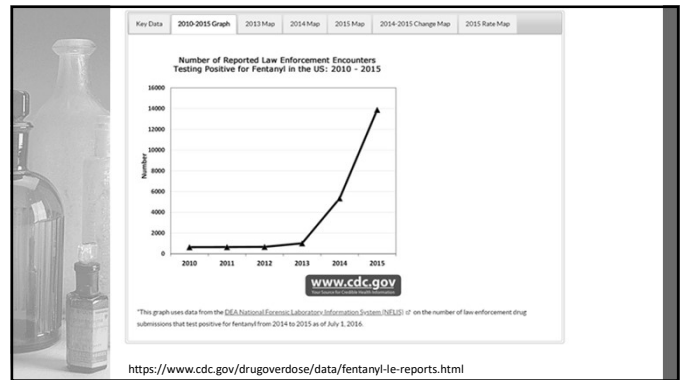
- Methoxyacetyl fentanyl
- 3-methylfentanyl, 3-methylthiofentanyl, China White
- > Alpha-methylfentanyl, alpha-methylthiofentanyl
- > Beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, beta-hydroxythiofentanyl
- Para-fluoroisobutyl fentanyl
- Acetyl fentanyl
- Acetyl-alpha-methylfentanyl
- Acryloylfentanyl
- Butyl fentanyl
- Cyclopentyl fentanyl
- Cyclopropyl fentanyl
- Furanyl fentanyl
- Isobutyl fentanyl
- Tetrahydrofuran fentanyl
- Ortho-fluorofentanyl or 2-fluorofentanyl
- Ocfentanil
- Para-chloroisobutyl fentanyl
- Para-fluorobutyl fentanyl
- Para-fluorofentanyl
- Para-methoxybutyl fentanyl
- Thiofentanyl
- Valeryl fentanyl

<https://www.ncbi.nlm.nih.gov/pccompound/?term=fentanyl>

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### Fentanyl Analogues in NH in 2017

- 4ANPP
- U-47700
- Furanyl fentanyl
- Acetyl fentanyl
- Fluoro-fentanyl
- Carfentanil
- Para-fluorobutyl fentanyl/FIBF

**Fentanyl analogues are drugs whose chemical structure is similar to fentanyl. They can be more or less potent than fentanyl.**

<https://www.doh.nh.gov/medical-examiner/documents/drug-data-update.pdf>

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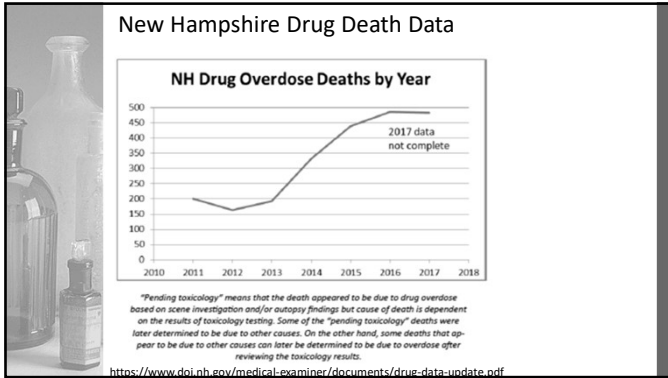
### Illicit Fentanyl Analogues in New Hampshire 2018 Drug Death Data as of 3/18/2019

OPIATES/OPIOIDS	# OF DEATHS
Fentanyl (no other drugs)	192
Fentanyl and Other Drugs (excluding heroin)	171
Heroin (no other drugs)	1
Heroin and Other Drugs (excluding fentanyl)	0
Heroin and Fentanyl	3
Other Opiates/Opioids	29
Unknown Opioids	1
<b>Total Deaths Caused By Opiates/Opioids</b>	<b>397</b>
Other drugs	47
Unknown Drugs	2
<b>Total Drug Deaths</b>	<b>446</b>

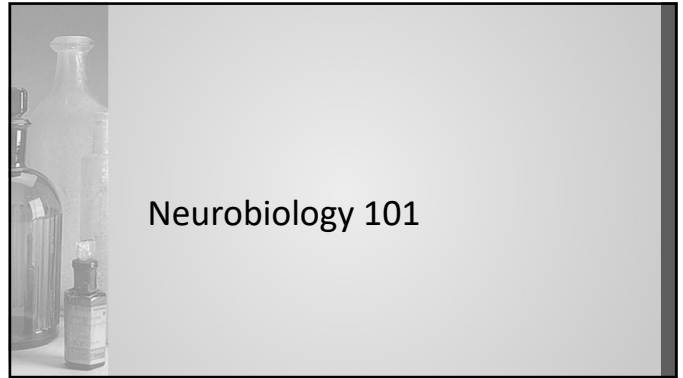
We know that AT LEAST 363/446 = 81.4% involve an identified fentanyl derivative

<https://www.doh.nh.gov/medical-examiner/documents/drug-data-update.pdf>

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### Addiction (ASAM-short)

- > A primary, chronic disease involving brain dysfunction which encompassing reward, motivation, memory and related circuitry.
  - Includes biological, psychological, social and spiritual manifestations.
  - Compulsive reward seeking
    - > relief by substance use and other behaviors
    - > Examples?

<https://www.asam.org/quality-practice/definition-of-addiction>

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### Addiction (continued)

- > Inability to abstain
- > Impairment in behavioral control and craving
- > Diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response.

<https://www.asam.org/quality-practice/definition-of-addiction>

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### Base Rates of Addiction/Abuse: Vulnerabilities in the Population

- > 8.7% Illicit Drugs
- > 12.5% Alcohol
- > 26.5% Nicotine

SAMHSA 2011 National Survey on Drug use and Health  
 Hasin DS, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States. *Arch Gen Psychiatry.* 2007; 64(7): 830-842.

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### Mesolimbic Reward System

VTA: ventral tegmental area  
 NAc: nucleus accumbens  
 PFC: prefrontal cortex  
 LC: locus ceruleus

### Stages of Addiction Cycle

- a. Binge and Intoxication
- b. Withdrawal and Negative Affect
- c. Preoccupation and Anticipation


1. Kosten, T. R., & George, T. P. (2002). The neurobiology of opioid dependence: implications for treatment. *Science & Practice Perspectives*, 1(1), 13.
2. Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, 374(4), 363-371.

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Stage of Addiction	Neuroadaptive Changes		
Binge and Intoxication	Euphoria	Feeling Happy	Escaping depression, anxiety, or agitation
Withdrawal and negative Affect	Reduced Energy	Reduced Pleasure	Feeling dysphoric
Preoccupation and anticipation	Anticipation	Craving	Obsessing /Planning for Drug

Volkow N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, 374(4), 363-371.

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## Neurobiological Explanation for Dependence and Withdrawal

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**A. Baseline: Normal production of NA**



### What's the impact of diminished noradrenalin?


**B. Acute opioid inhibition of converting enzymes: Abnormally low production of NA**



Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, 374(4), 363-371.

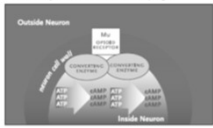
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**C. Chronic opioid inhibition leads to increased converting enzyme activity: Normal NA level**



### Can we explain the physiological symptomatology?

**D. Discontinuing opioid leads to increased cyclic AMP due to loss of inhibition: NA excessively high**



Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, 374(4), 363-371.

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### Addiction Comes in All Varieties



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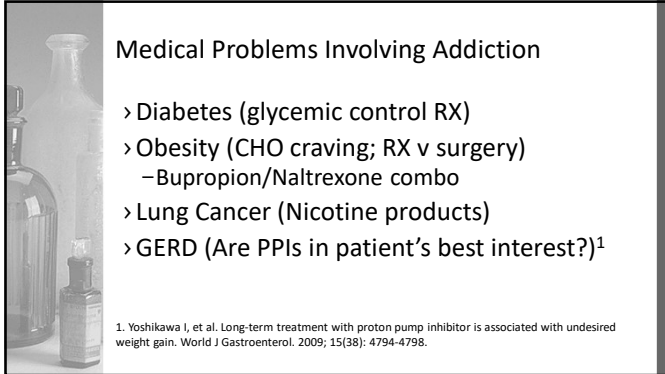
### Addiction is not Simply a Disease of Exposure

Exposure is necessary but not sufficient

- ✓ Exposure to drug
- ✓ Vulnerable person
- ✓ Vulnerable time

Savage SR, Kirsh KL, Passik SD. Challenges in using opioids to treat pain in persons with substance use disorders. *Addiction science & clinical practice*. 2008 Jun;4(2):4.

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### Medical Problems Involving Addiction


- › Diabetes (glycemic control RX)
- › Obesity (CHO craving; RX v surgery)
  - Bupropion/Naltrexone combo
- › Lung Cancer (Nicotine products)
- › GERD (Are PPIs in patient's best interest?)<sup>1</sup>

1. Yoshikawa I, et al. Long-term treatment with proton pump inhibitor is associated with undesired weight gain. World J Gastroenterol. 2009; 15(38): 4794-4798.

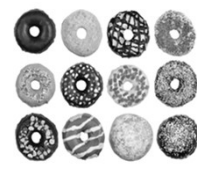
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### Does formulation selection matter?



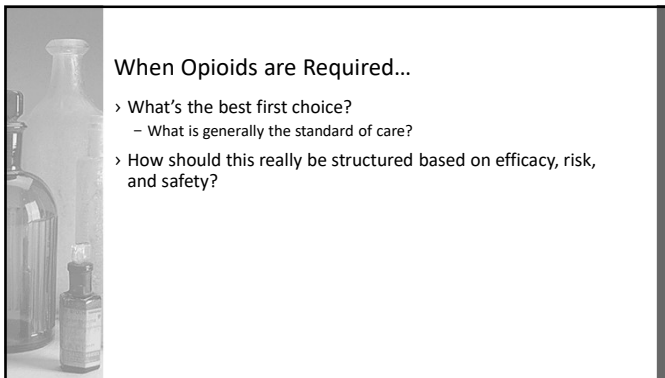
Fentanyl Patch



Fentanyl TIRF

Included with permission from Dr. Steven Passik with revisions

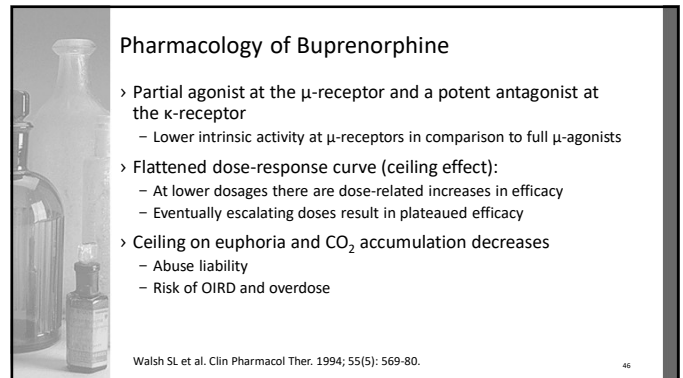
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### When Opioids are Required...

- › What's the best first choice?
  - What is generally the standard of care?
- › How should this really be structured based on efficacy, risk, and safety?

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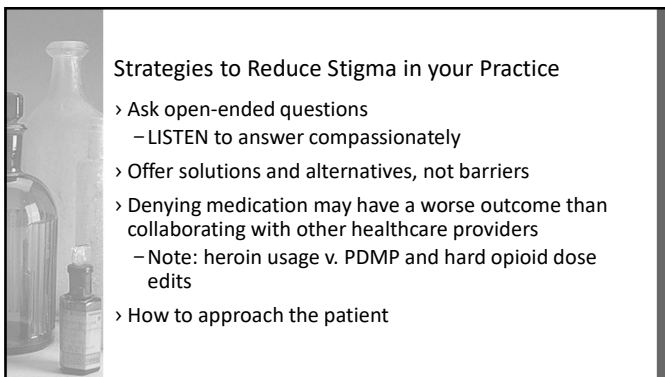


### Pharmacology of Buprenorphine

- › Partial agonist at the  $\mu$ -receptor and a potent antagonist at the  $\kappa$ -receptor
  - Lower intrinsic activity at  $\mu$ -receptors in comparison to full  $\mu$ -agonists
- › Flattened dose-response curve (ceiling effect):
  - At lower dosages there are dose-related increases in efficacy
  - Eventually escalating doses result in plateaued efficacy
- › Ceiling on euphoria and CO<sub>2</sub> accumulation decreases
  - Abuse liability
  - Risk of OIRD and overdose

Walsh SL et al. Clin Pharmacol Ther. 1994; 55(5): 569-80.

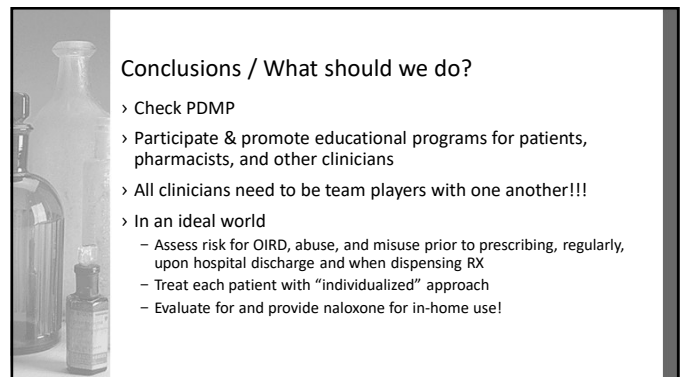
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### Strategies to Reduce Stigma in your Practice

- › Ask open-ended questions
  - LISTEN to answer compassionately
- › Offer solutions and alternatives, not barriers
- › Denying medication may have a worse outcome than collaborating with other healthcare providers
  - Note: heroin usage v. PDMP and hard opioid dose edits
- › How to approach the patient

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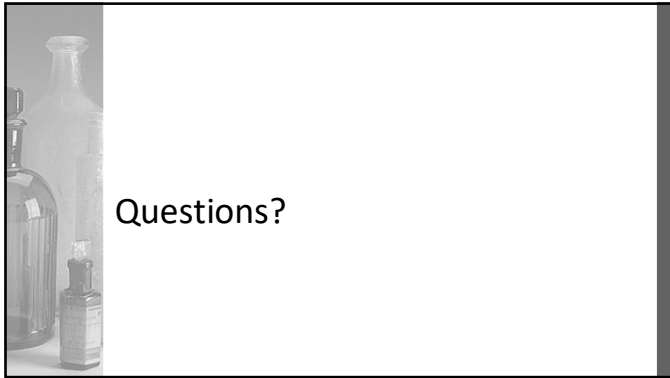


### Conclusions / What should we do?

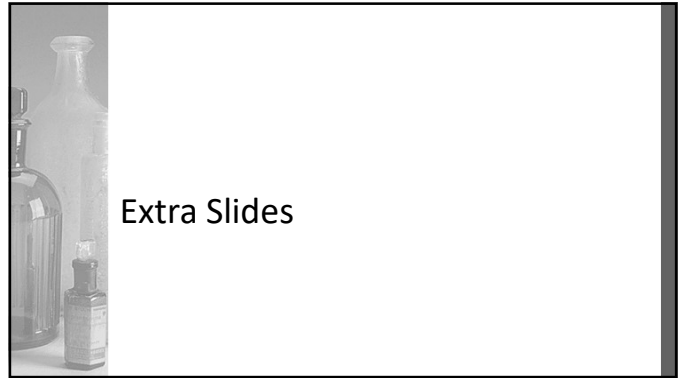
- › Check PDMP
- › Participate & promote educational programs for patients, pharmacists, and other clinicians
- › All clinicians need to be team players with one another!!!
- › In an ideal world
  - Assess risk for OIRD, abuse, and misuse prior to prescribing, regularly, upon hospital discharge and when dispensing RX
  - Treat each patient with "individualized" approach
  - Evaluate for and provide naloxone for in-home use!

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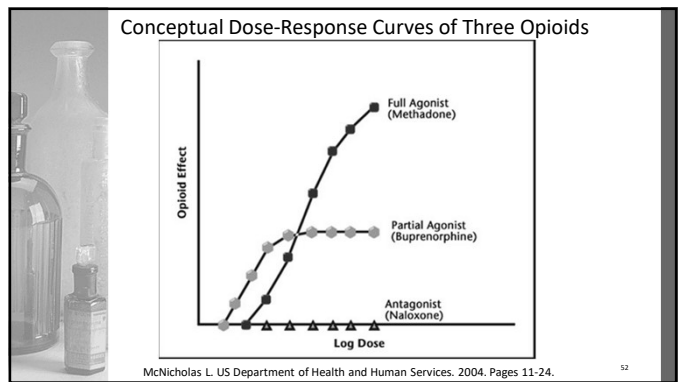
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### Opioid Pharmacology Schematic

**Important Qualities**

1. Affinity (pull towards receptor)
2. Binding Strength (k<sub>i</sub>, "rubber v metal")
3. Receptor Dissociation
  - Consider methadone
4. Potency (chemical configuration)

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### Mu Receptor Binding Affinity of Buprenorphine

Opioids	Range of K <sub>i</sub> Value
Buprenorphine	0.21- 1.5
Naltrexone	0.4-0.6 (antagonist effects)*
Fentanyl	0.7-1.9
Methadone	0.72-5.6
Naloxone	1.0-3.0 (antagonist effects)*
Morphine	1.02-4
Pentazocine	3.9-6.9
Codeine	65-135

\*Wang D, Sun X, Sadee W. Different effects of opioid antagonists on  $\mu$ -,  $\delta$ -, and  $\kappa$ -opioid receptors with and without agonist pretreatment. *Journal of Pharmacology and Experimental Therapeutics*. 2007 May 1;321(2):544-50.  
Fudin J, Chu R, Ciari A, Raouf M. Opioid Agonists, Partial Agonists, Antagonists: Oh My! *Pharmacy Times*. January 6, 2016. Available at <http://www.pharmacytimes.com/contributor/jeffrey-fudin/2016/01/opioid-agonists-partial-agonists-antagonists-oh-my>


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### Available Doses of Buprenorphine/Naloxone Combination Products

Suboxone SL Tablet	Suboxone SL Film	Zubolv SL Tablet	Bunavail Buccal Film
2 / 0.5 mg	2 / 0.5 mg	1.4 / 0.36 mg	-----
4 / 1 mg	4 / 1 mg	-----	2.1 / 0.3 mg
8 / 2 mg	8 / 2 mg	5.7 / 1.4 mg	4.2 / 0.7 mg
12 / 3 mg	8 / 2 mg + TWO 2 / 0.5mg films	-----	6.3 / 1 mg

Fudin J, Cleary J, Gottwald J. A Brief Review of Buprenorphine Products. *Pharmacy Times*. March 22, 2016. Available at <http://www.pharmacytimes.com/contributor/jeffrey-fudin/2016/03/a-brief-review-of-buprenorphine-products>

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### Buprenorphine Product Bioavailability

PRODUCT	Available Strengths	PERCENT BIOAVAILABILITY
<b>Buprenorphine – buccal film (Belbuca)</b>	75, 150, 300, 450, 600, 750, 900mcg	45-65 %
<b>Buprenorphine – TD patch (Butrans)</b>	5, 7.5, 10, 15, 20 mcg/hr	15 %
<b>Subutex (SL)</b>	See previous slide	29 +/- 10 %
<b>Suboxone/Bunavail/Zubsolv</b>		
<b>Buprenex (injectable)</b>	0.3mcg/mL	100%

Revised from:  
Bettiger JJ, Fudin J, Argoff C. Buprenorphine and Surgery: What's the Protocol? In Kean N, 2nd ed., Opioid Prescribing and Monitoring—How to Combat Opioid Abuse and Misuse Responsibly, Chap. 6, Pg. 73-78. Pub. Vertical Health, LLC, September 2017.

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