



Ascension  
Brighton

Center for Recovery

# **Addiction Physiology:**

# **Basic Physiology and Clinical Implications**

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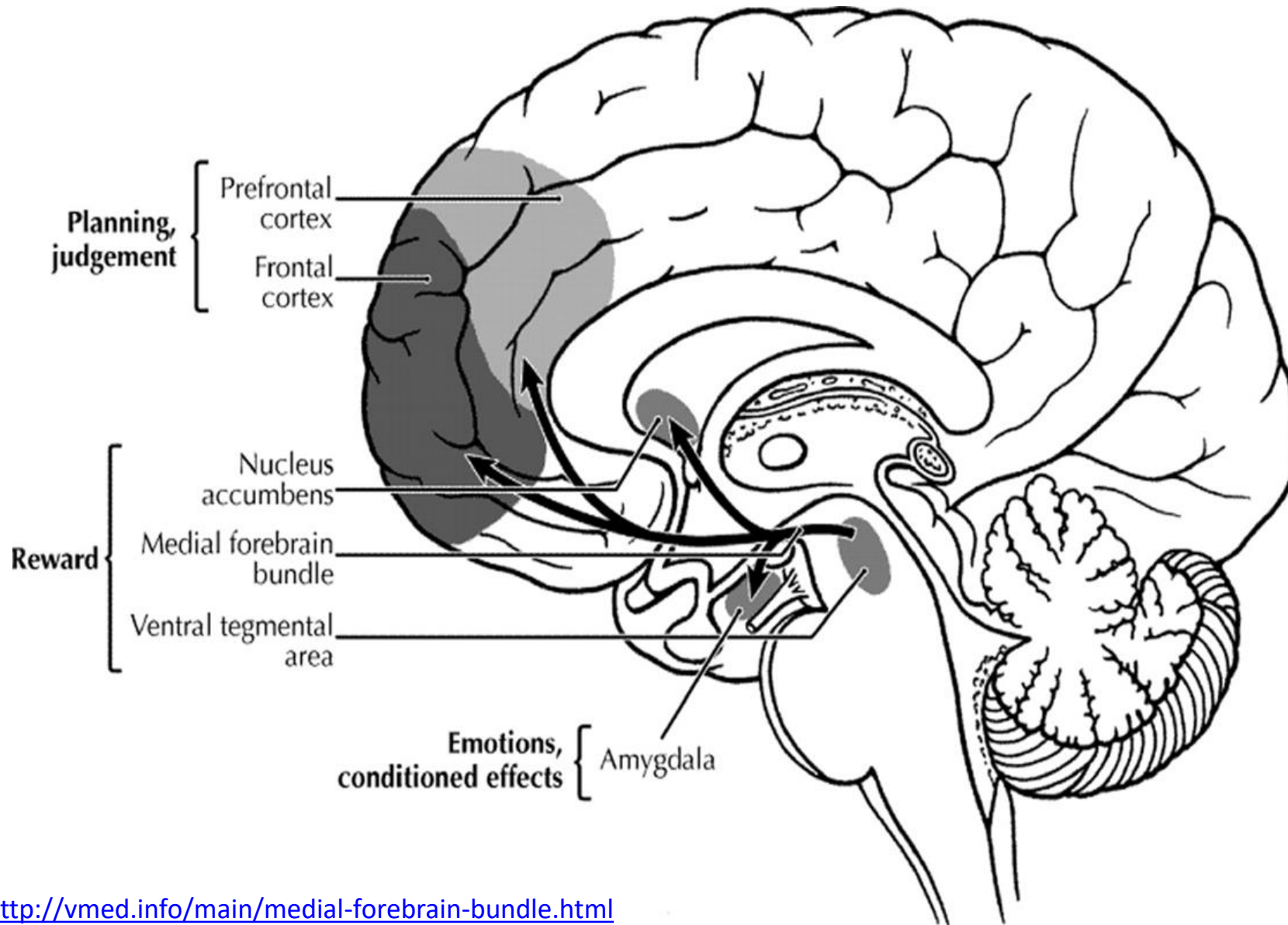
# Disclosures

- Chief Medical Officer
  - Ascension Brighton Center for Recovery
- American Board of Addiction Medicine Foundation
  - Lifetime Learning and Self-Assessment Committee Member
- I do not have any relevant financial relationships with any commercial interests or any other conflicts of interest to disclose

# Key Objectives

- Understanding how addiction as a disease modulates the brain
- Understanding what chronic opioid therapy does to change the physiology of the body
- Understanding the concept of how multiple drug types can interact to cause unintentional overdose

# Addiction Brain Region Effects



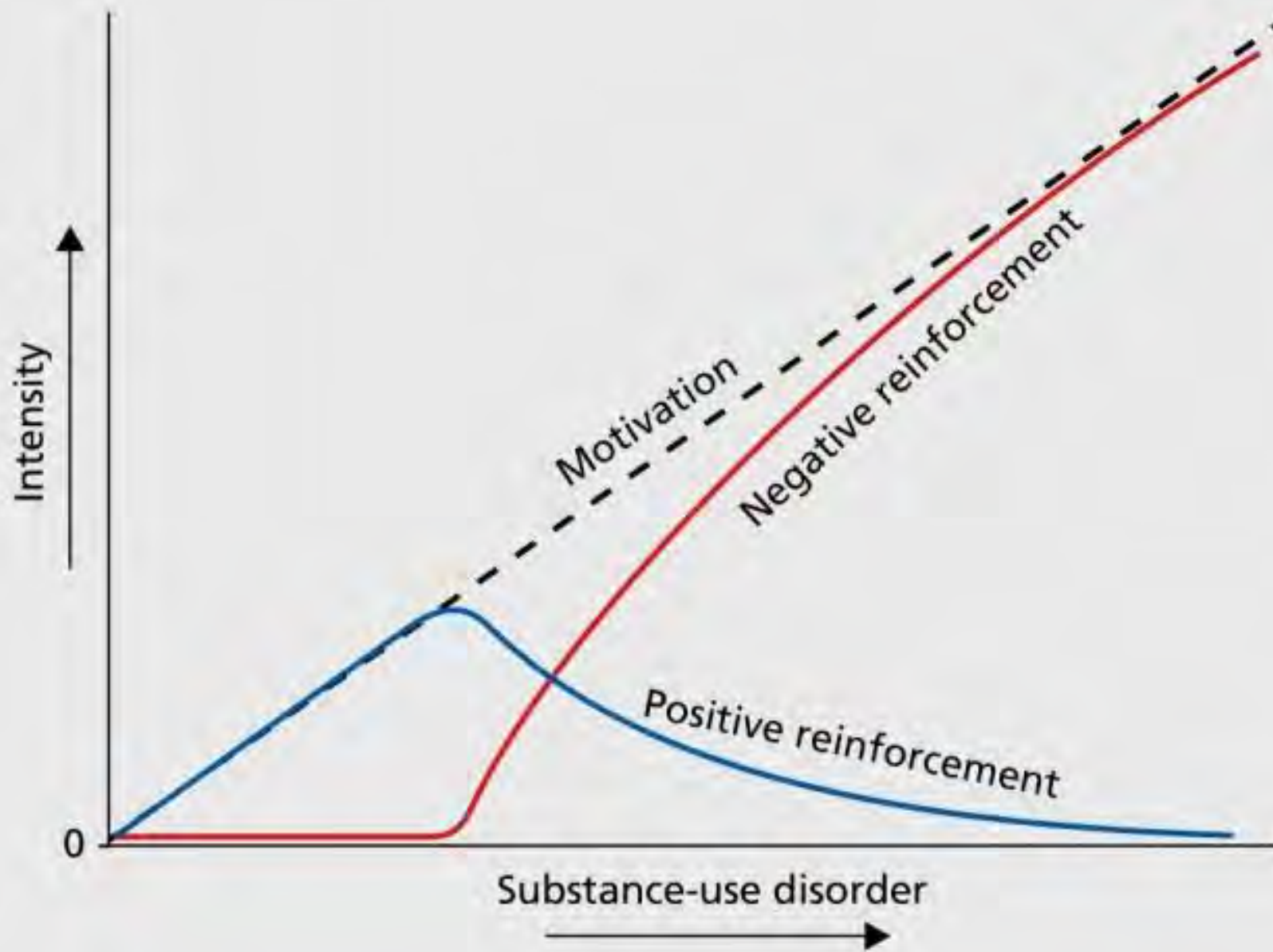
# Addiction Definition

- Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

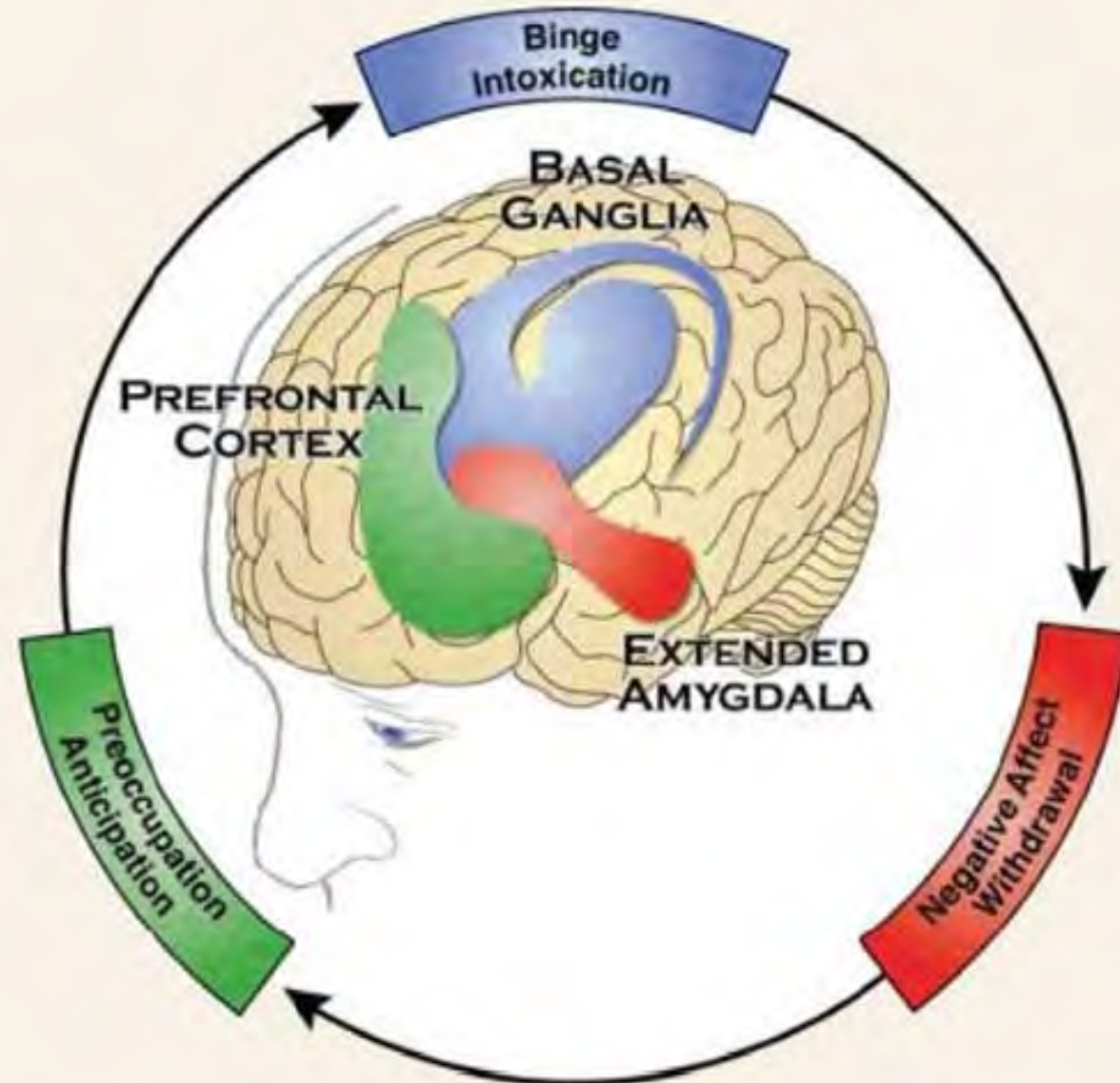
# Addiction Definition

- Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

# Disease Progression<sup>1</sup>



# The Addiction Cycle



<https://www.drugabuse.gov/news-events/news-releases/2018/04/understanding-neuroscience-addiction-what-it-means-prevention-treatment>



# Binge/Intoxication Stage<sup>1</sup>



- Main Issue
  - Incentive Salience
- Brain Region
  - Basal Ganglia
- Base Modulators
  - Dopamine
  - Opioid Peptides

# Withdrawal / Negative Affect Stage<sup>1</sup>



- Main Issue
  - Reward Deficit and Stress Surfeit
- Brain Region
  - Extended Amygdala
- Base Modulators
  - Norepinephrine
  - CRF
  - Dynorphins

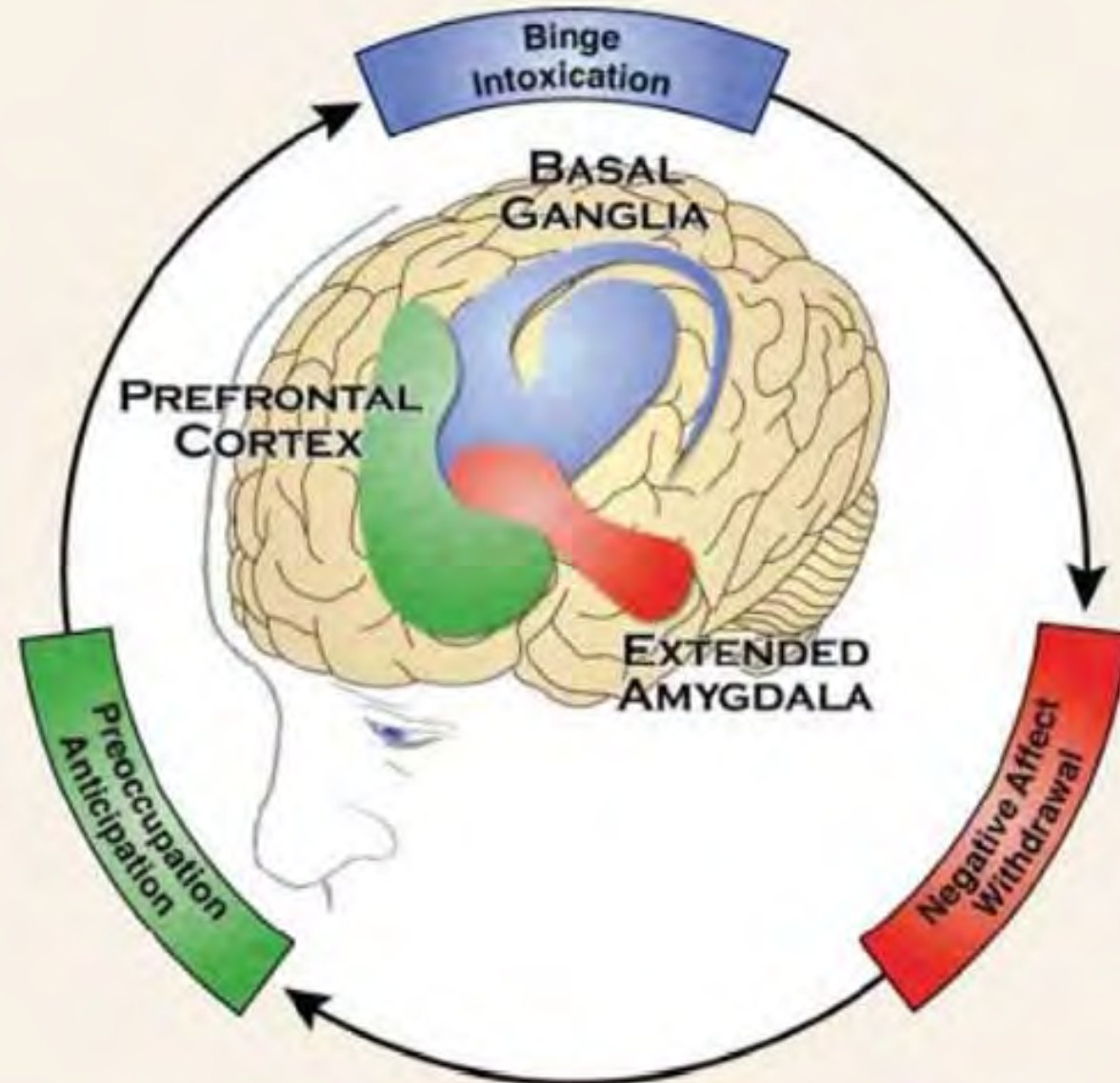
# Preoccupation / Anticipation Stage<sup>1</sup>

- Main Issue
  - Executive Function
- Brain Region
  - Prefrontal Cortex
- Base Modulators
  - Glutamate
  - GABA

<https://www.pb institute.com/blog/phenomenon-craving/>



# The Addiction Cycle



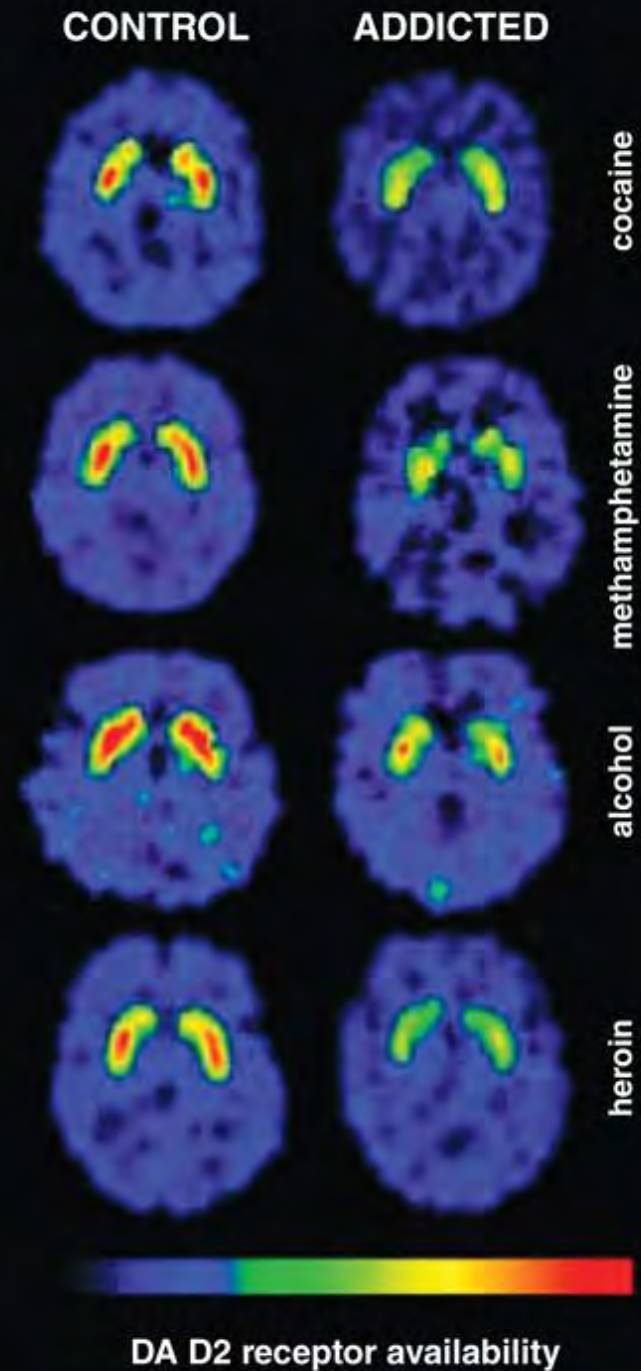
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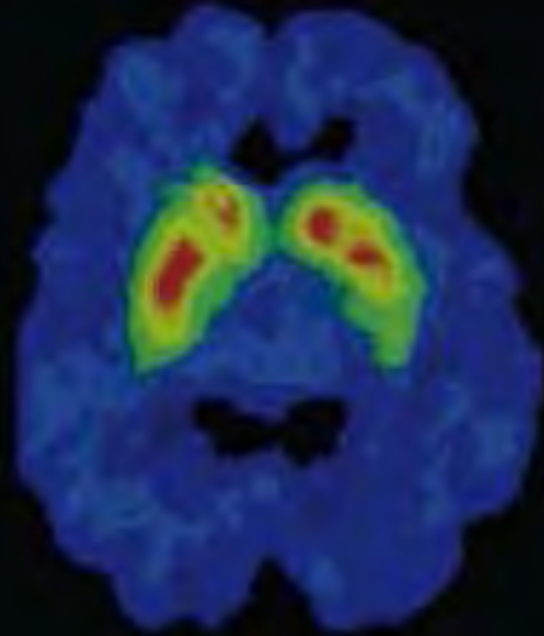
# Chronic Brain Alterations



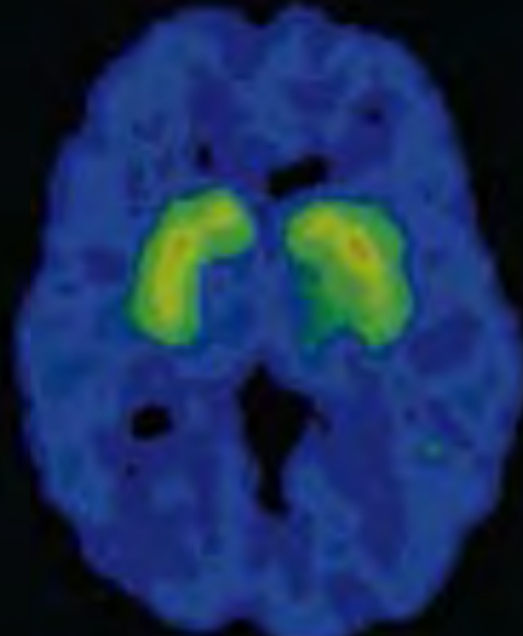
<http://www.sclance.com/images/solitary/view-page-2.htm>



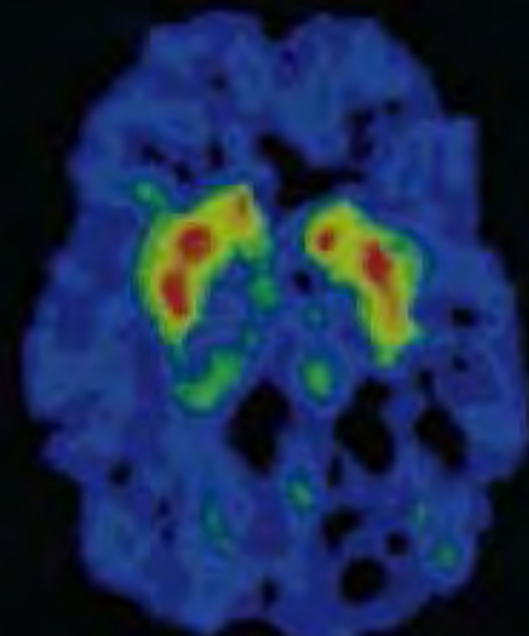
# Brain Recovery / Prolonged Abstinence



**Healthy Person**



**METH Abuser  
1 month abstinence**



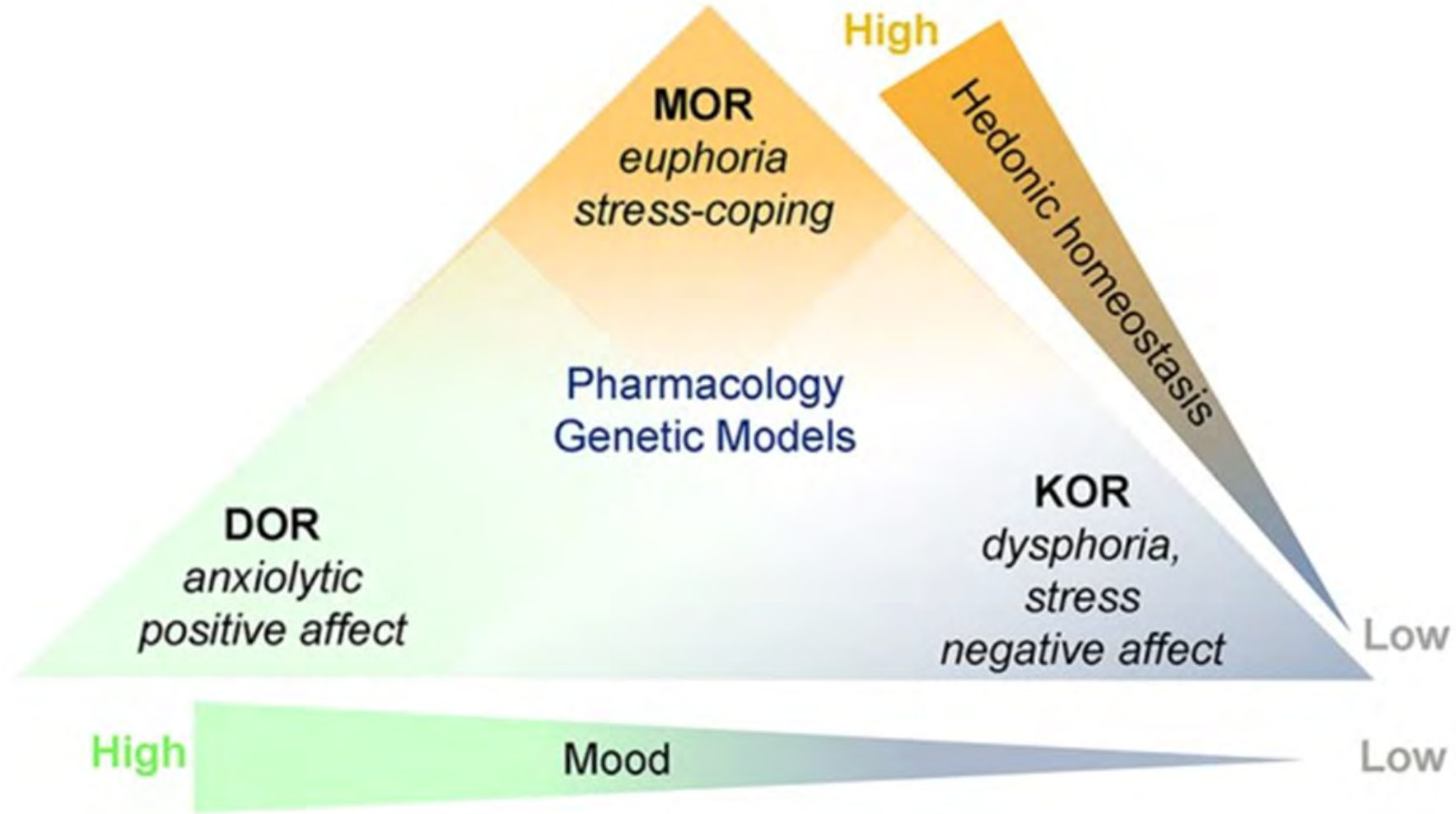
**METH Abuser  
14 months abstinence**

The brain with abstinence and time will heal . . .

# Addiction Physiology Section Review

- Addiction is a chronic disease that effects multiple parts of the brain
- There is a cycle that includes 3 stages:
  - Binge/Intoxication
  - Negative Affect/Withdrawal
  - Preoccupation/Anticipation
- The brain is plastic and has the capacity to heal with abstinence

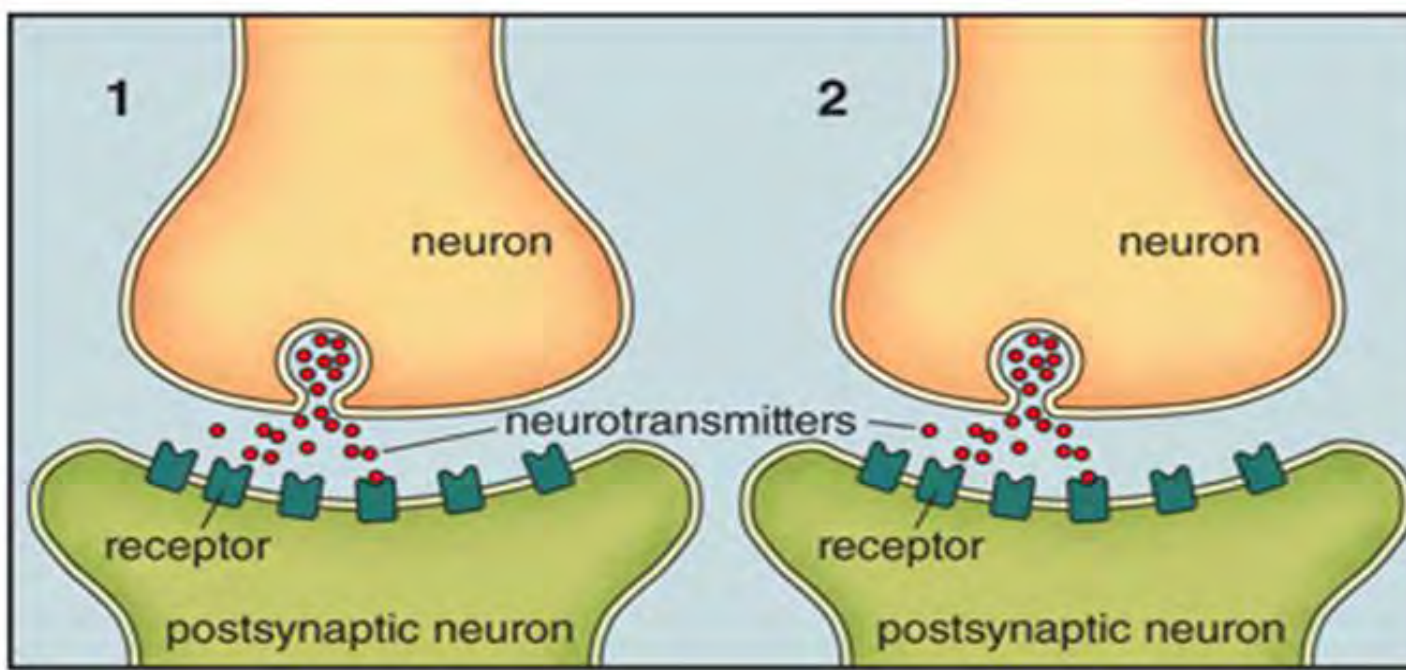
# Opioid Receptor Physiology<sup>2</sup>



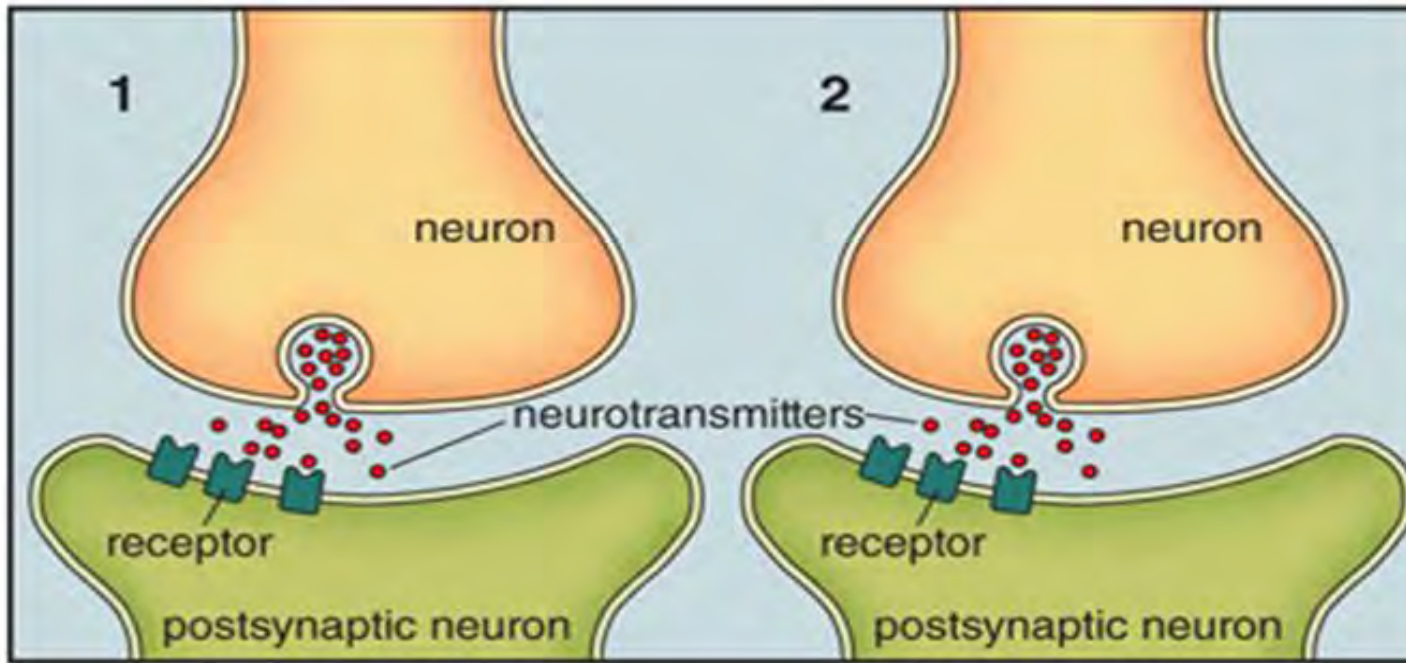


# What Do Opioids Do?

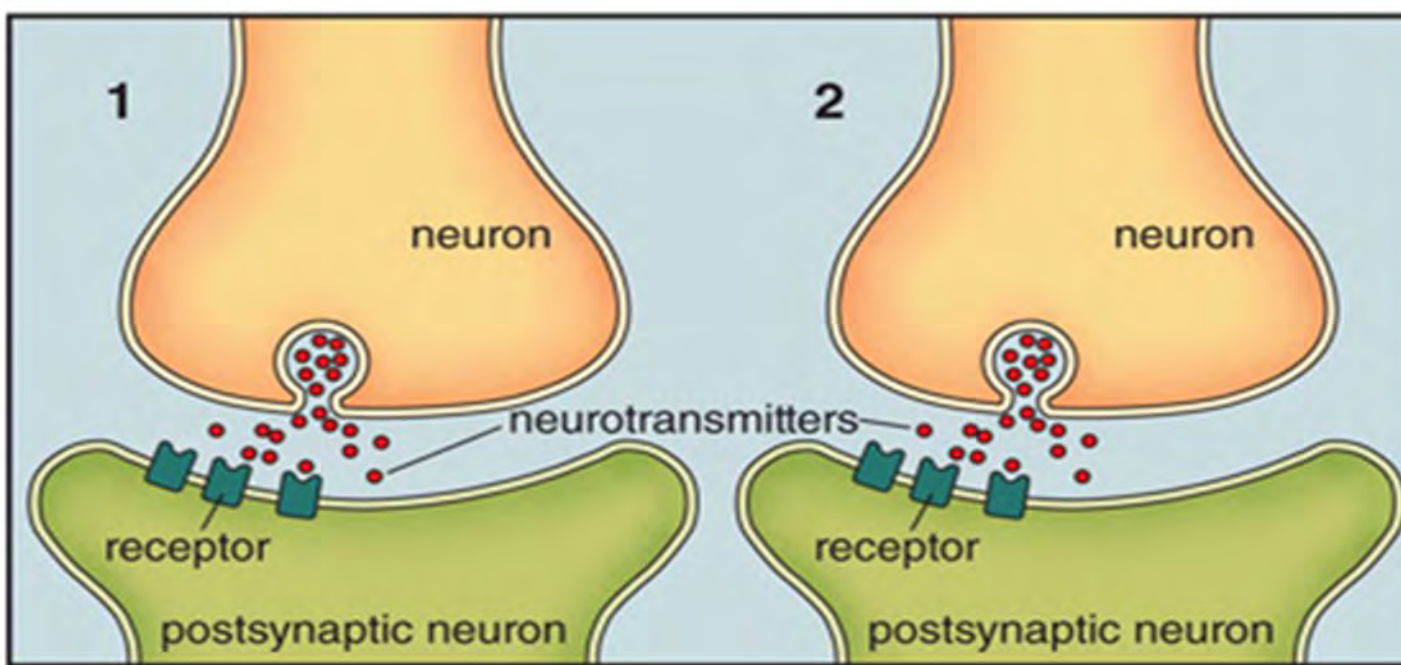
- Neurological Alterations
  - Mu receptors – downregulation and desensitization<sup>2</sup>
    - Tolerance
    - As doses increase, mu receptor density decreases
  - Nucleus accumbens – dopamine modulation<sup>3</sup>
    - Euphoric effects and craving
    - Dopamine alters regions for decision making



**NORMAL**  
Two normally functioning neurons (1 and 2). Binding potential of 100 percent with 12 receptors

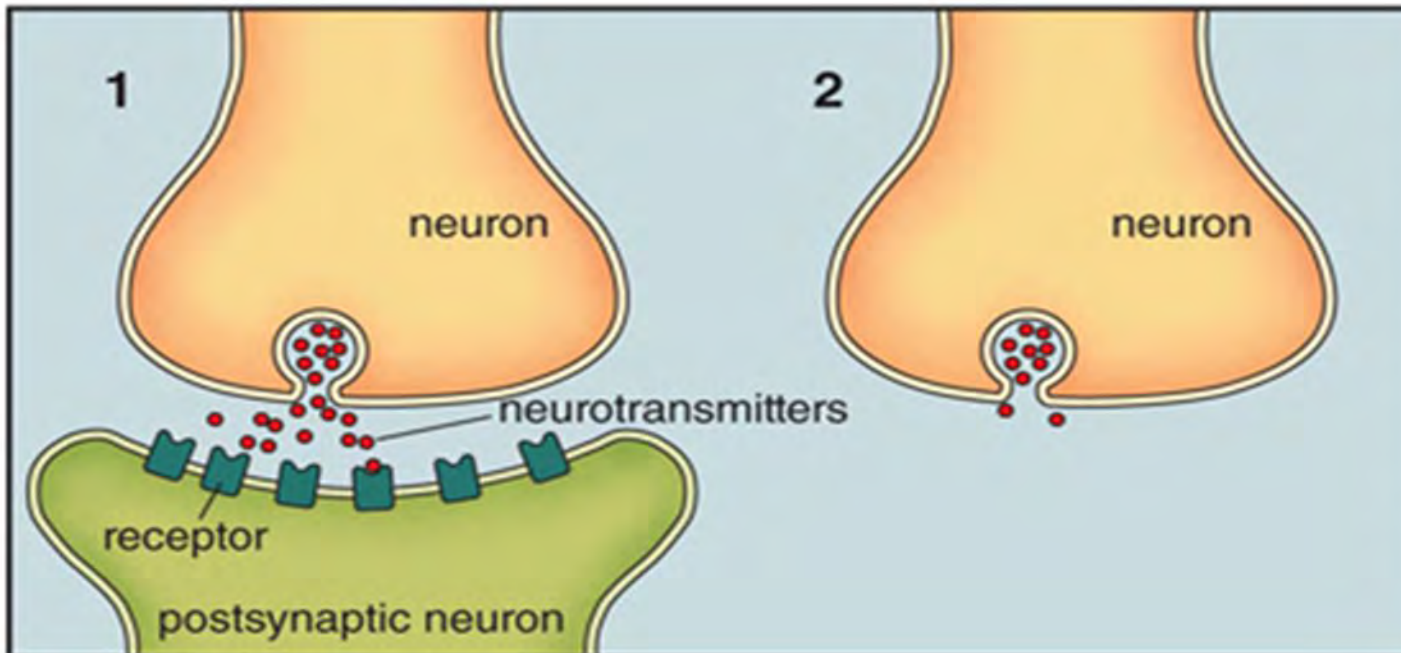


**TOLERANCE**  
There is a reduction of receptors for both neuron 1 and 2. This is an example of receptor down-regulation of 50 percent with 6 receptors.



## TOLERANCE

There is a reduction of receptors for both neuron 1 and 2. This is an example of receptor down-regulation of 50 percent with 6 receptors.



## NEUROTOXICITY

Neuron 1 remains unchanged, and postsynaptic neuron 2 is dead. Binding potential is 50 percent with 6 receptors.



# What Do Opioids Do?

- Neurological Alterations
  - Locus coeruleus – norepinephrine modulation<sup>3</sup>
    - Physiological withdrawal symptoms
    - May contribute to anxiety and insomnia in dependence
  - Spinothalamic Tracts – emotional dysregulation<sup>4</sup>

# What Do Opioids Do?

- Endocrine effects
  - Opioid Induced Androgen Deficiency (OPIAD)<sup>5</sup>
    - Reduction of testosterone via the HPG pathway; the HPA is also altered
    - Irregular menses, hypogonadism, reduced sexual function, osteopenia/osteoporosis, etc.
  - Associated with Lower Vitamin D Levels<sup>6</sup>
    - May increase inflammation and pain levels
    - May increase mood disorders

# What Do Opioids Do?

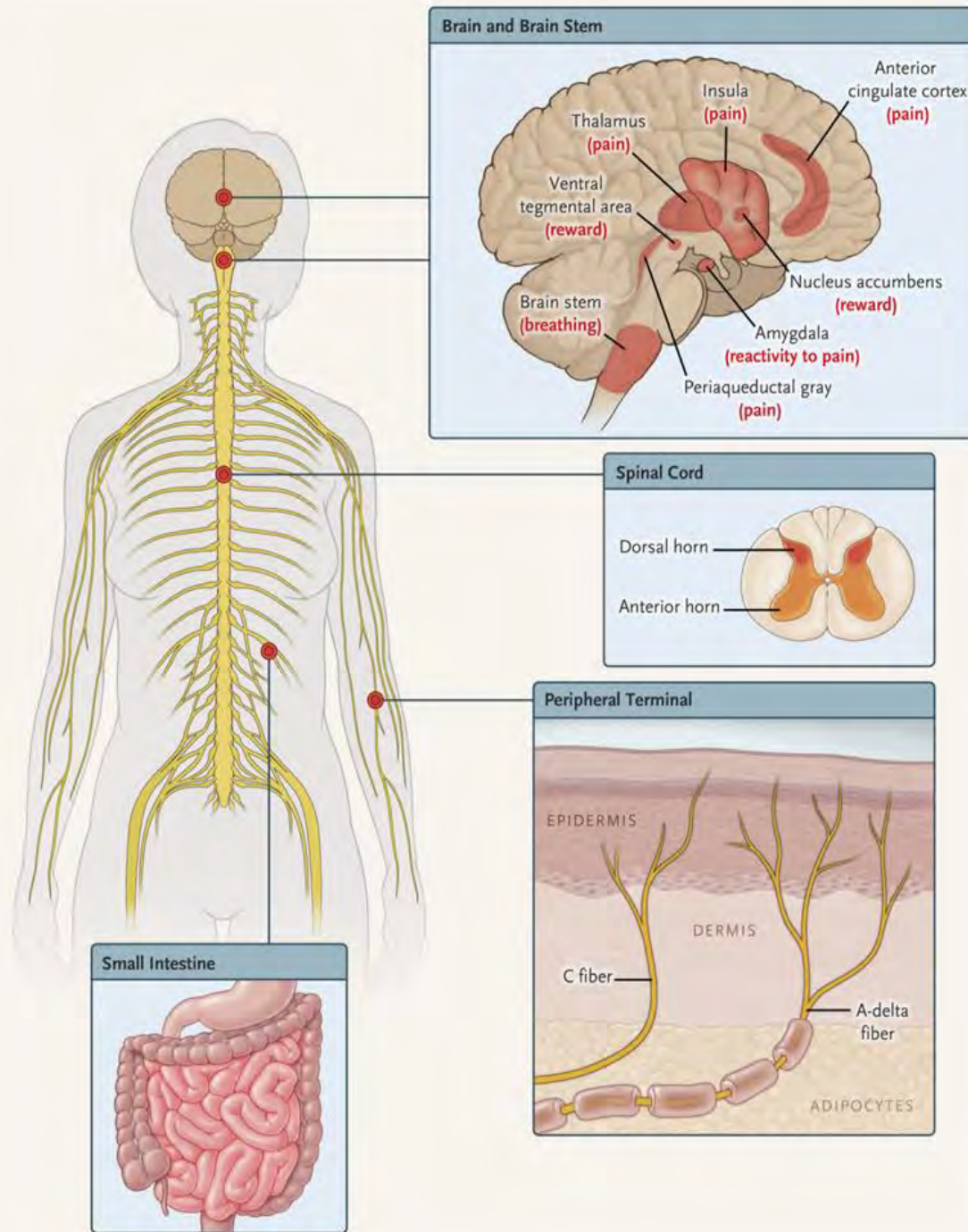
- Gastrointestinal Effects
  - Opioid-Induced Constipation
  - Opioid-Induced Microbiota Effects<sup>7</sup>
- Pain Modulating Effects<sup>8</sup>
  - Opioid Hyperalgesia
    - Most likely related to the NMDA receptor system and the effects of glutamate
    - Spinal dynorphins may also be implicated

# Mu Opioid Receptors



<http://mcveighmcblog.blogspot.com/2012/04/rx-drug-abuse.html>

Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies. N Engl J Med. 2016 Mar 31;374(13):1253-63. doi: 10.1056/NEJMra1507771. Review. PubMed PMID: 27028915.



# Chronic Opioid Effects

- Overstimulation
  - Insomnia and anxiety symptoms
- Emotional dysregulation
  - Emotional lability
  - Catastrophizing
- Hormonal dysregulation
  - Hot flashes, sweats, emotional dysregulation
  - Osteopenia/osteoporosis, low vitamin D status
- Pain dysregulation and hyperalgesia



# Opioid Physiology Section Review

- Opioids as a class effect multiple body systems including:
  - Brain physiology
  - Hormone physiology
  - Gastrointestinal/biome physiology
  - Pain physiology
- Opioids would be better thought of as a multi-target drug with profound long-term consequences with chronic use

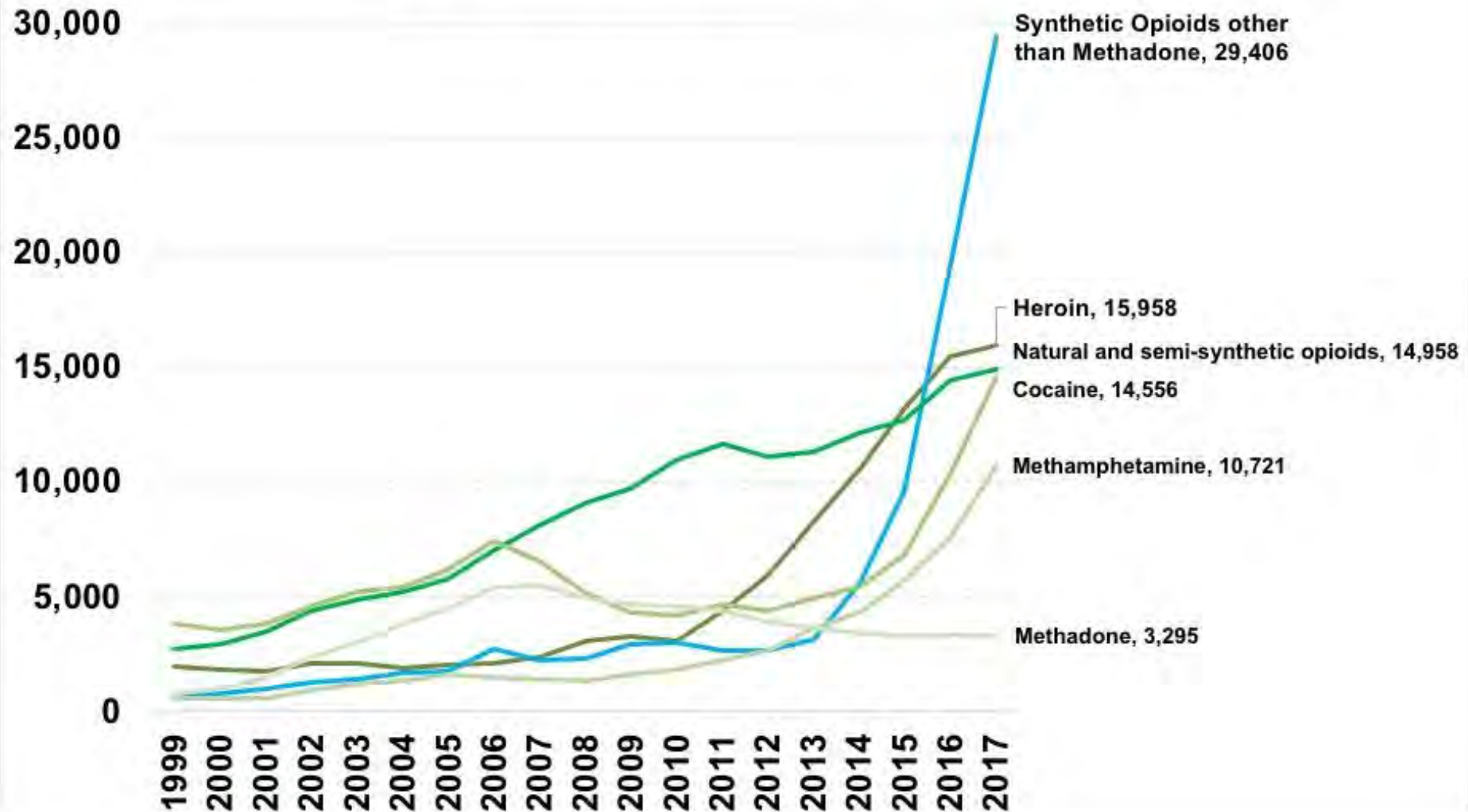
# Clinical Ramifications



<https://sacredcowonaspit.net/medical-thinking/>

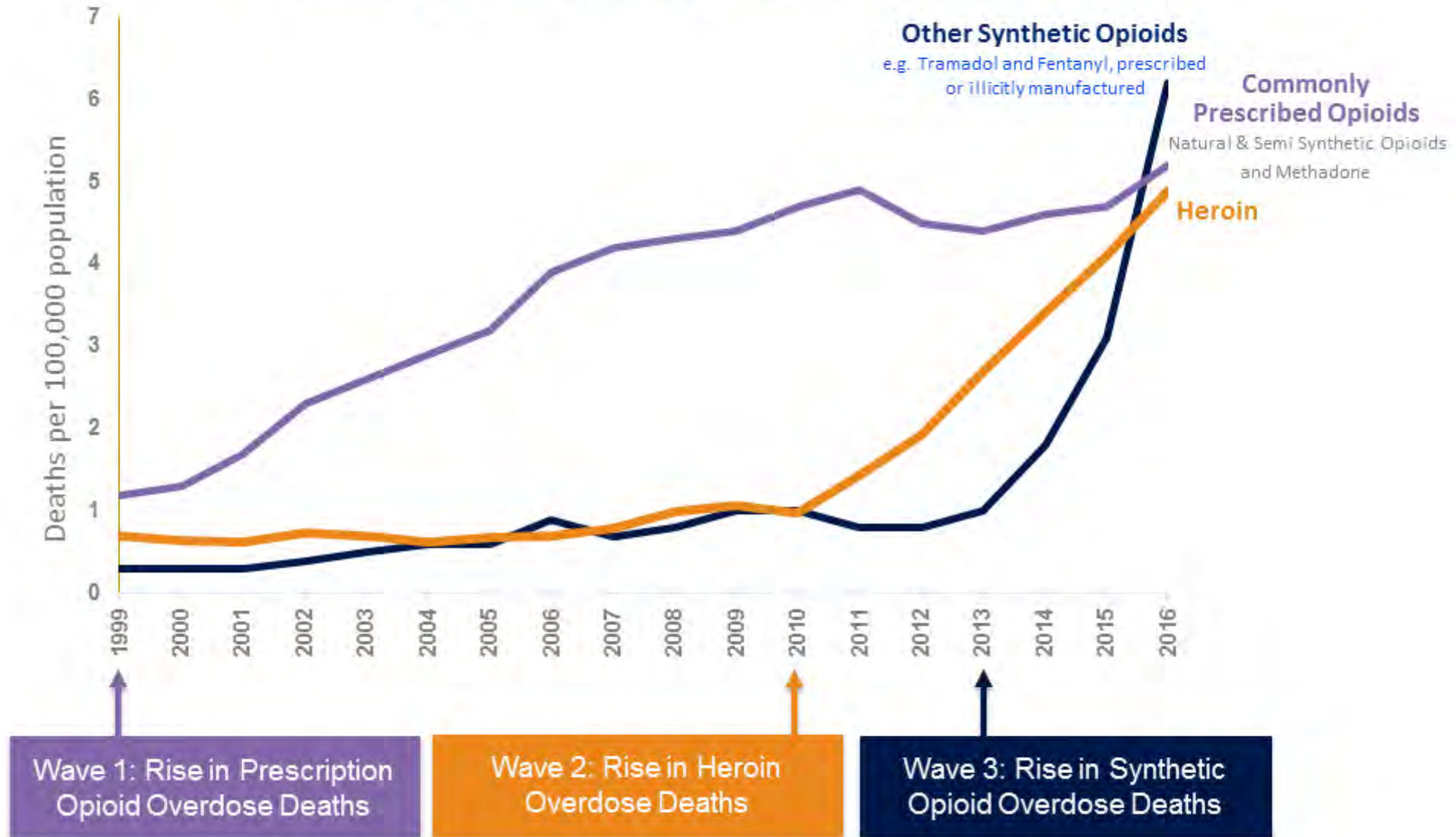
# Opioid Epidemic

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

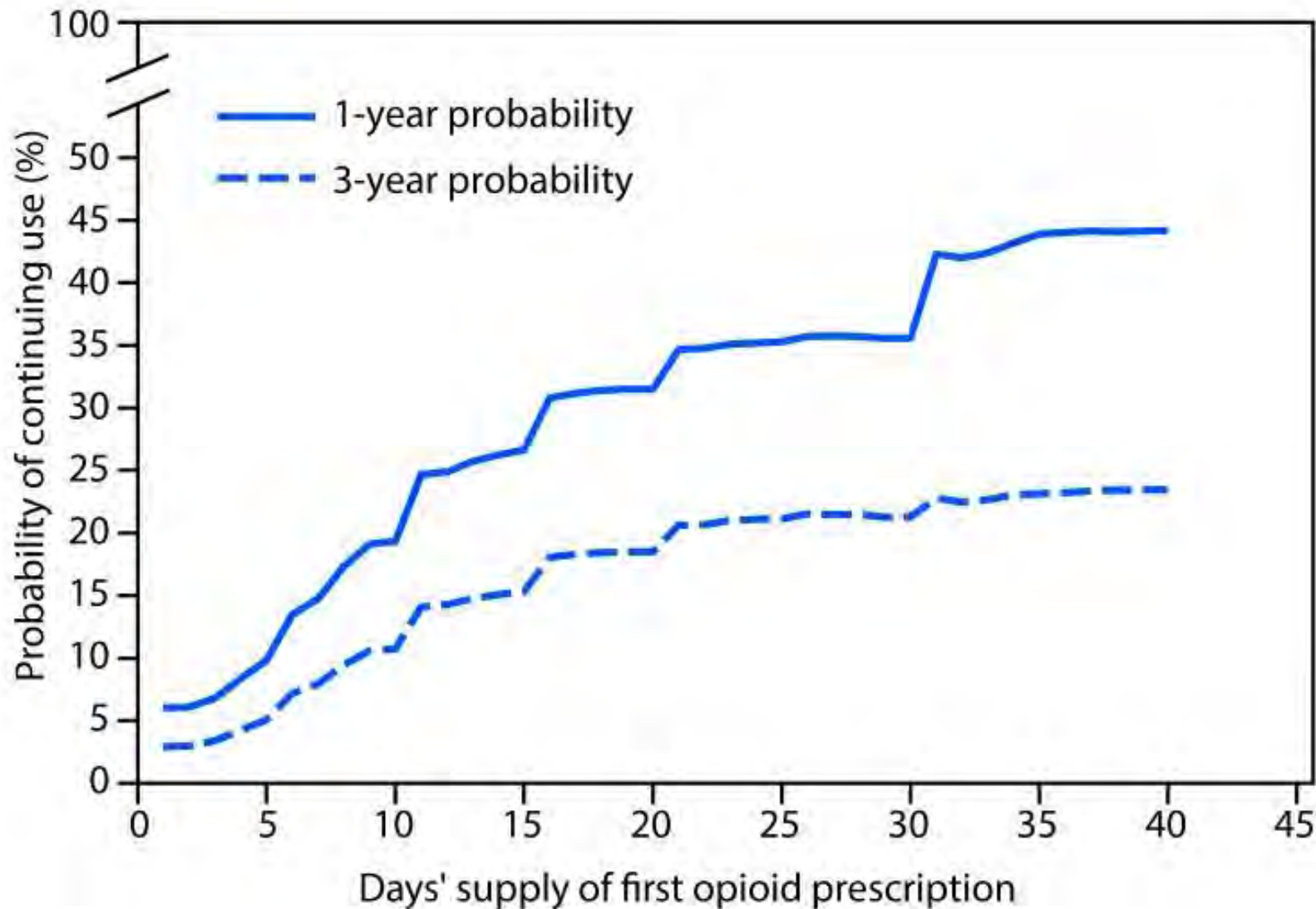


# Opioid Epidemic

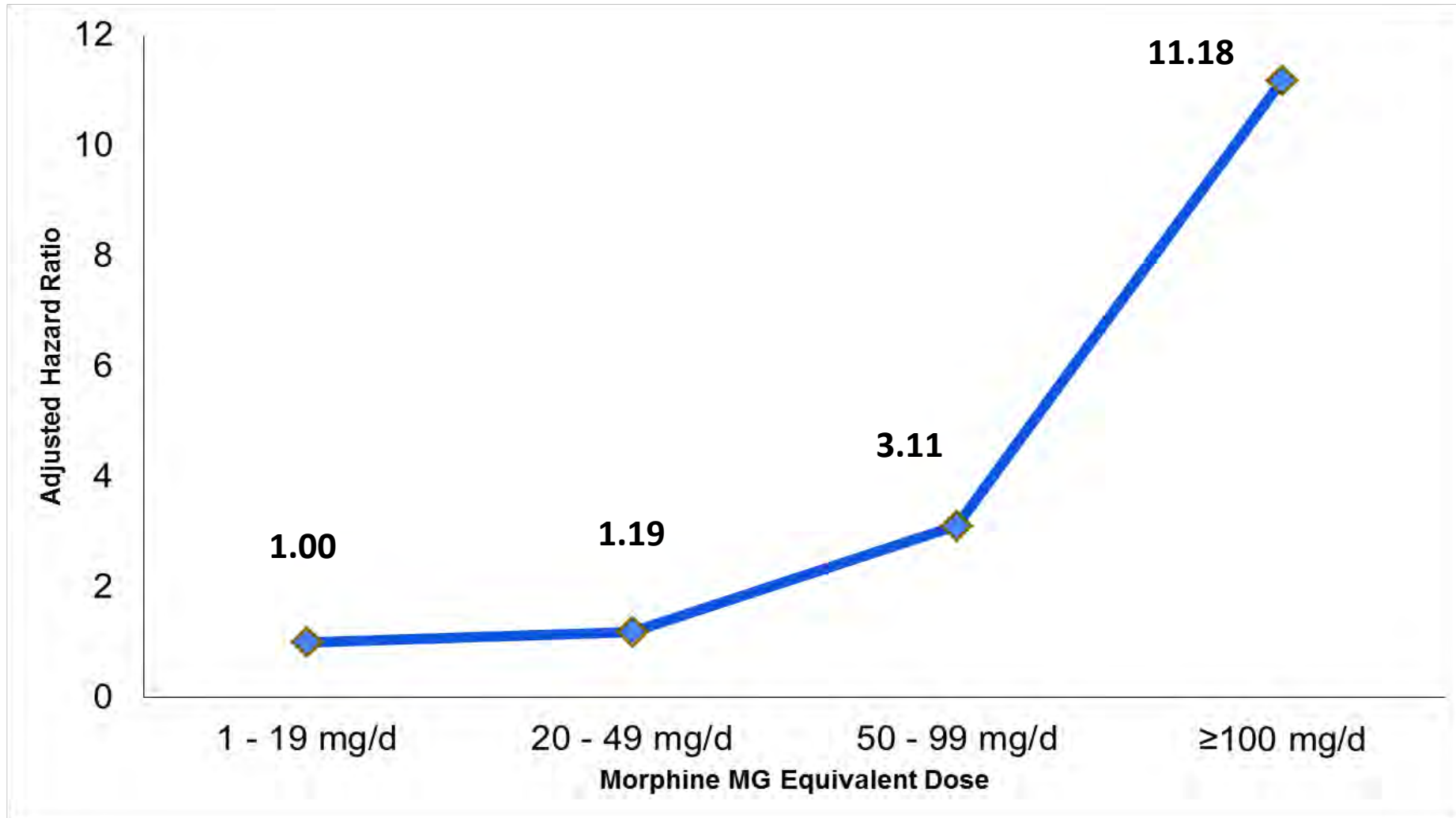
## 3 Waves of the Rise in Opioid Overdose Deaths



# How Long is Too Long?



# Opioid Dose & Overdose



# Remember Physiology?

- Overstimulation
  - Insomnia and anxiety symptoms
- Emotional dysregulation
  - Emotional lability
  - Catastrophizing
- Hormonal dysregulation
  - Hot flashes, sweats, emotional dysregulation
  - Osteopenia/osteoporosis, low vitamin D status
- Pain dysregulation and hyperalgesia
- If these are present, it may be related to the dose and ongoing use of the opioid medication itself!



# Smoking Status<sup>9</sup>

- Daily Smoker (30 days per month)
  - 5 times greater risk for opioid abuse / opioid dependence compared to non-smokers
  - 3 times greater risk for opioid misuse compared to non-smokers
- Intermittent smoker (4-27 days per month)
  - 3 times greater risk for opioid abuse / opioid dependence compared to non-smokers
  - 3 times greater risk for opioid misuse compared to non-smokers

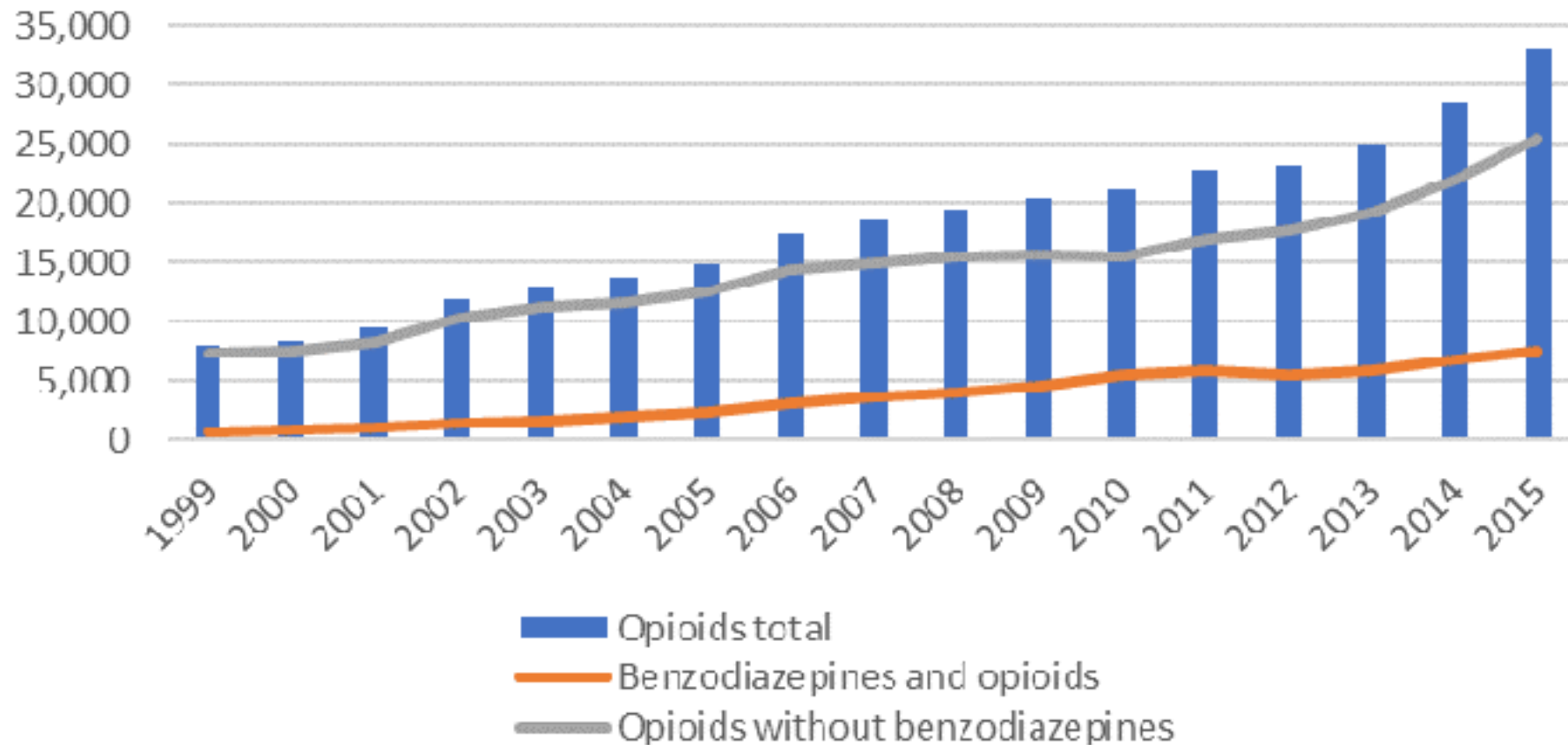


# Risk of Sedatives

- Using sedative medication with opioid medication is clearly dangerous
- Use of benzodiazepines increases the adjusted hazard ratio of opioid overdose death by 6.4 times<sup>10</sup>
- Use of benzodiazepines and skeletal muscle relaxers increases the adjusted hazard ratio of opioid overdose death by 12.6 times<sup>10</sup>
- Do not ignore the MAPS overdose risk score

# Opioids and Sedatives

## Opioid Overdose Deaths Involving Benzodiazepines

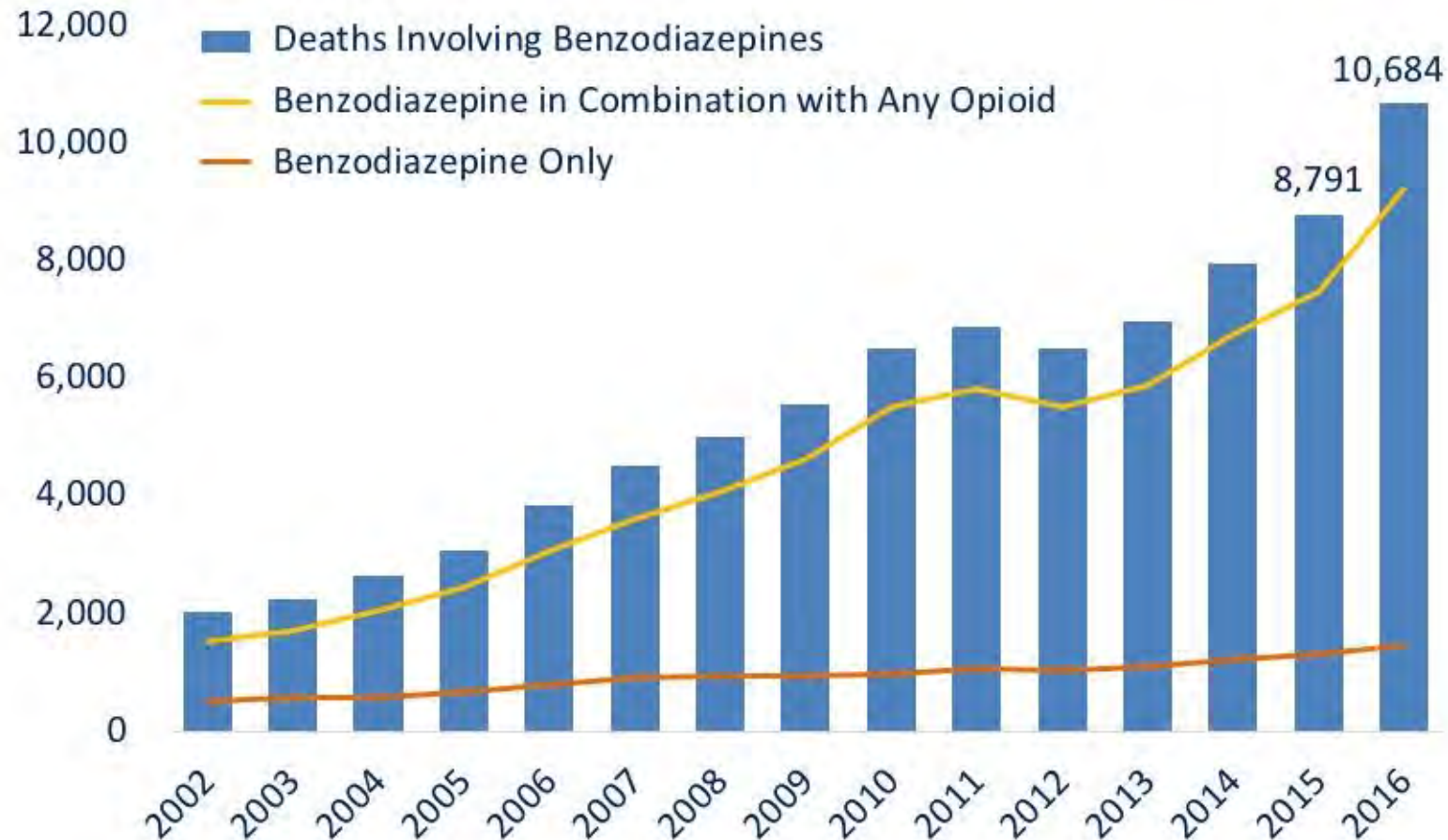


Source: Centers for Disease Control and Prevention (CDC). Multiple Cause of Death, 1999-2015.

# Opioids and Sedatives

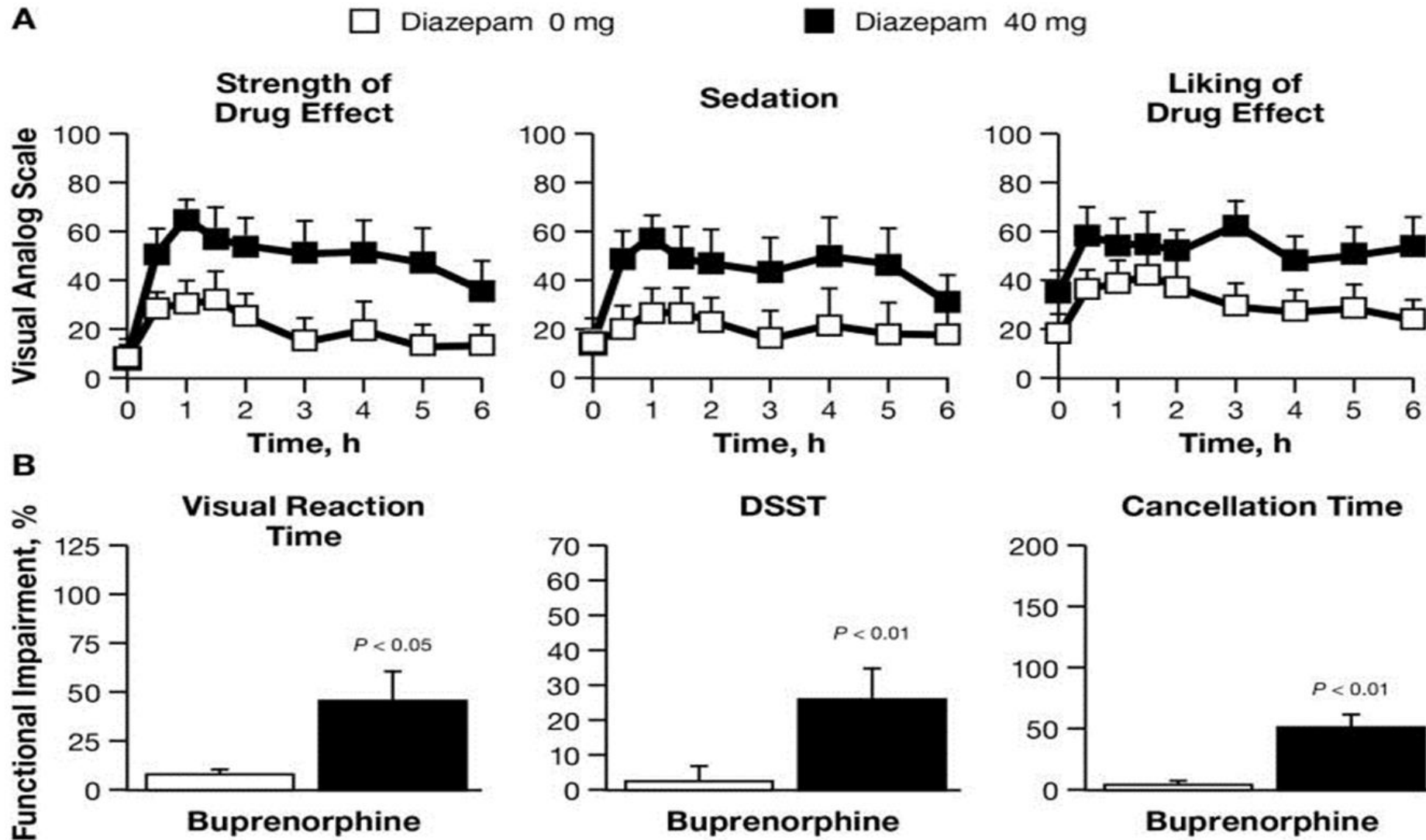


## Opioid Involvement in Benzodiazepine Overdose



Source: National Center for Health Statistics, CDC Wonder

# Buprenorphine with Benzos



Gudin JA, Mogali S, Jones JD, Comer SD. Risks, Management, and Monitoring of Combination Opioid, Benzodiazepines, and/or Alcohol Use. *Postgraduate medicine*. 2013;125(4):115-130. doi:10.3810/pgm.2013.07.2684.

# Remember Physiology!

- Overstimulation
  - Upregulated dopamine and norepinephrine
  - Causes insomnia and anxiety
- If these are present, it may be related to the dose and ongoing use of the opioid medication itself!
- These symptoms should prompt the clinician to decrease the dose of the opioid through tapering
- Do not use benzodiazepine, z-class sedatives or pregabalin/gabapentin for management of these symptoms or overdose risks rise rapidly

# Cognition with OST

- An Australian Cognition Study (2012) studied the differences between maintenance patients (methadone and buprenorphine), abstinent opioid use disorder patients in a therapeutic community, and non-opioid users from the community (controls) in 5 main domains of cognitive function
- N = 225 (large for a neurocognitive study)
- Single testing point of 120 minutes with batteries of testing

# Cognition with OST

- Maintenance patients (methadone and buprenorphine) scored lower than abstinent patients and controls in the following domains:
  - Executive function
  - Information processing
  - Immediate and delayed logical memory (controls only)
  - Immediate recall

# Cognition with OST

- Overall, the maintenance patients were worse than controls in 6/13 tests and worse than abstinence patients in 5/13 tests
- This has implications for what therapeutic interventions will work
- Also has implications for drop out rates and non-adherence



# Clinical Section Review

- Opioids as a class, create many symptoms that need treatment (anxiety, insomnia, etc.)
- Reducing opioids should be first goal if there are unacceptable side effects of therapy
- Sedatives are particularly dangerous to use in combination with opioids
- Chronic use of any opioid has long-term opioid related physiological consequences

# Conclusions

- Addiction physiology changes follow a 3 cycle pattern which repeats itself with increasing severity
- Chronic opioid therapy has profound impacts on multiple body systems over time
- Combining opioids with sedatives is very dangerous
- The addicted brain heals with abstinence through extended time

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# Questions?

