

**Saint Barnabas  
Medical Center**

**RWJBarnabas  
HEALTH**

# **THE OPIOID CRISIS IN THE UNITED STATES: PAST, PRESENT & FUTURE**

A Presentation for HealthTrust Members  
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# Speaker & Preceptor Disclosures

- The presenter and her preceptor have no conflicts of interest related to this presentation.
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# Learning Objectives for Pharmacists & Nurses

- Describe the neurobiology of addiction
- Review historical initiatives to combat opioid misuse and addiction
- Discuss current literature on new therapeutic modalities to combat opioid addiction and new legislation and advocacy efforts surrounding opioid prescribing and dispensing

# Learning Objectives for Pharmacy Technicians

- Review pertinent medications used to treat and mitigate opioid misuse and addiction
- Describe naloxone prescribing and dispensing practices
- Discuss new legislation regulating the prescribing and dispensing of opioid medications

# NEUROBIOLOGY OF ADDICTION

# Pain

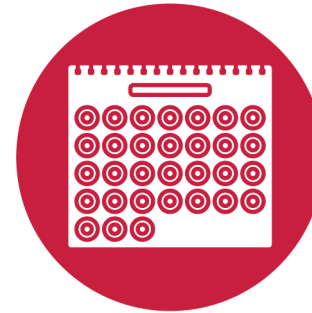
- An unpleasant sensory and emotional experience associated with actual or potential tissue damage
- Acute
  - ▣ Sudden, nociceptive
  - ▣ Resolves when cause is resolved
- Chronic
  - ▣ Pain that persists beyond normal healing time or three months
  - ▣ Untreated acute pain is a risk factor for developing chronic pain

# Prevalence of Pain

- 16.9% of men and 20.7% of women experience pain most days or every day over a three-month period
- 50 million Americans suffer from chronic pain; 50% have daily chronic pain

National Institutes of Health  
National Center for Complementary and Integrative Health

## Pain in the U.S.



**25.3 million**  
American adults  
suffer from daily pain



**23.4 million**  
American adults  
report a lot of pain

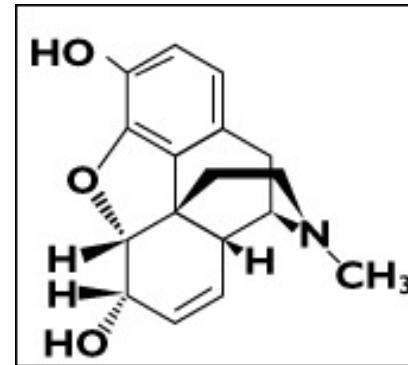
Nahin RL. Estimates of Pain Prevalence and Severity in Adults: United States, 2012, *Journal of Pain* (2015), doi: 10.1016/j.jpain.2015.05.002.



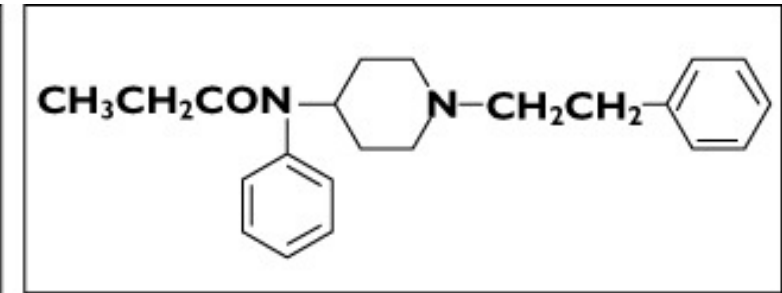
[nccih.nih.gov/health/pain](http://nccih.nih.gov/health/pain)

# Opioids

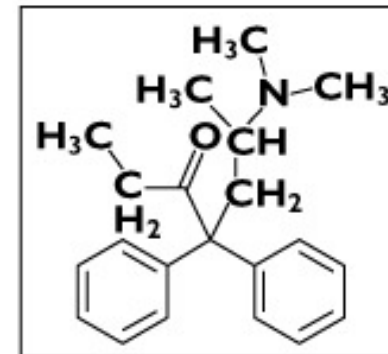
- Analgesic medications
  - ▣ Exert activity through the mu-opioid receptor on neurons
- Randomized clinical trials have shown no relevant clinical differences between opioids on a population level
  - ▣ Differences between agents lie in biochemical structures, onset of action, duration of activity and side effect profiles



**Morphine (the 4,5 epoxymorphinans)**



**Fentanyl (the phenylpiperidines)**

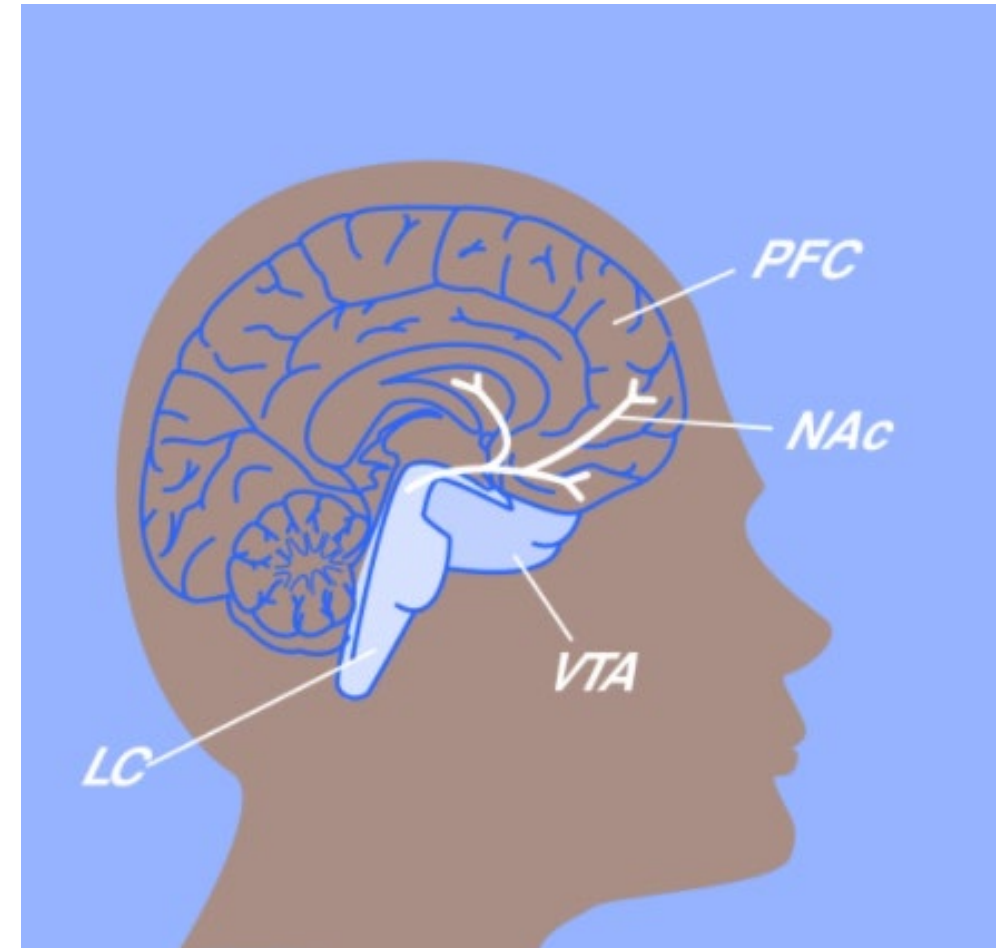


**Methadone (the diphenylheptylamines)**



# The Mesolimbic Reward Pathway

- Stimulation of the ventral tegmental area (VTA) leads to dopamine production and release in the nucleus accumbens (NAc)
  - ▣ Responsible for feelings of pleasure
- The locus cereleus (LC) releases norepinephrine to promote wakefulness, respiration, blood pressure and alertness

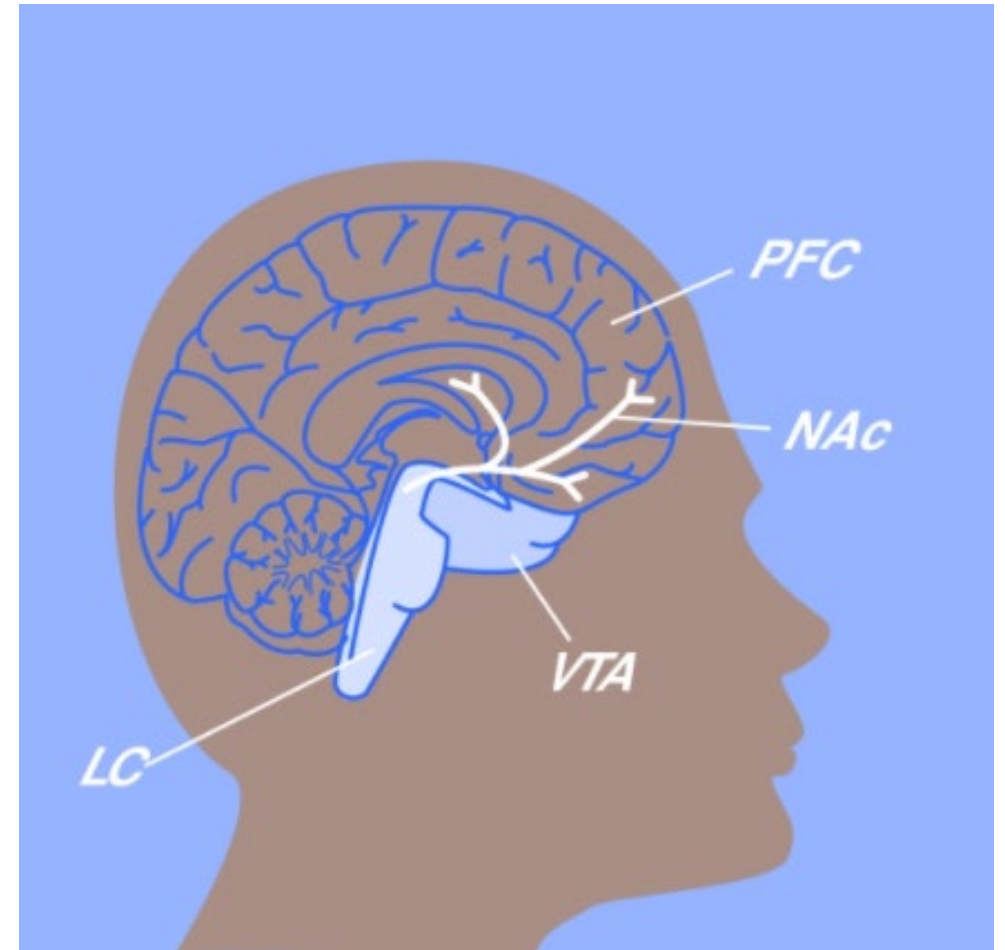


# Effects of Opioids on the Mesolimbic Reward Pathway

- Mu-opioid receptor stimulation in the VTA leads to dopamine production and release in the NAc
  - ▣ Responsible for feelings of pleasure
- Opioids decrease norepinephrine production in the LC
  - ▣ Leads to drowsiness, decreased respiration and low blood pressure
- Other areas of the brain associate these feelings with the environment under which it occurred
  - ▣ Conditioned associations lead to cravings

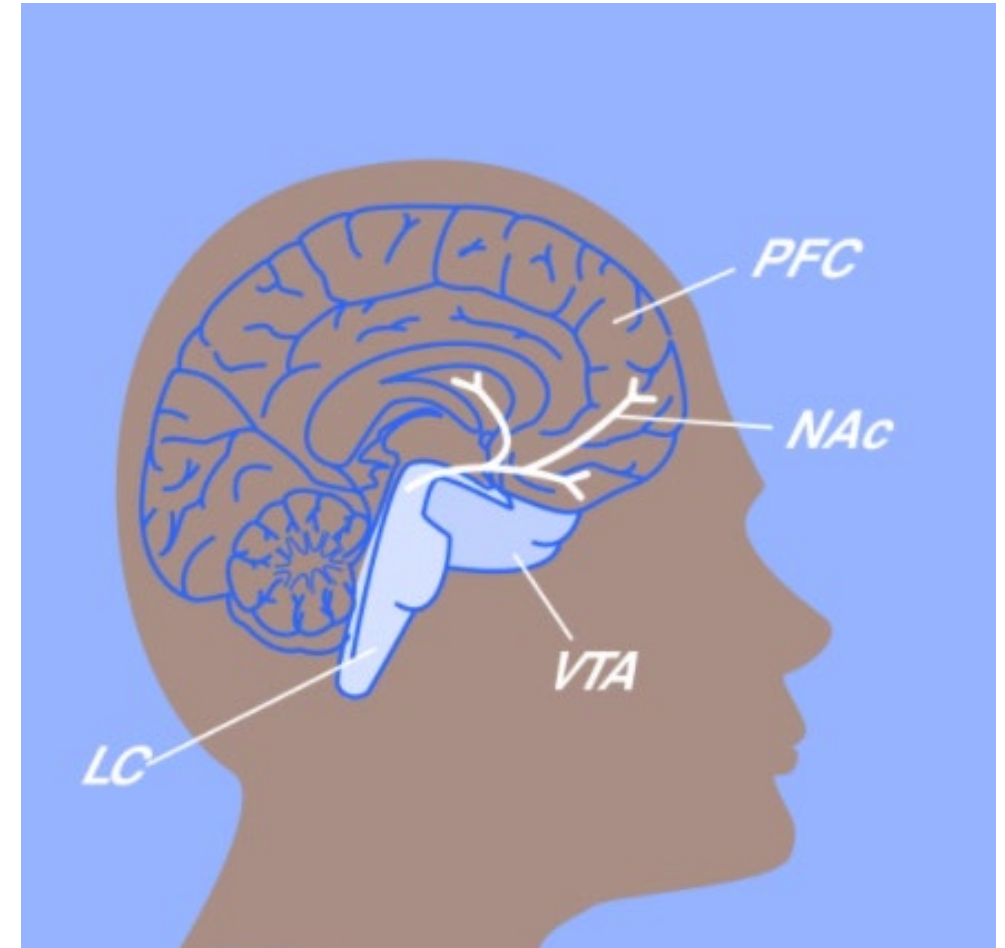
# Tolerance

- Repeated exposure to opioids results in opioid receptor hyporesponsiveness
- More opioid is required to produce the same amount of stimulation in the VTA



# Dependence

- Repeated use leads to heightened norepinephrine activity in the LC in the absence of opioids, leading to withdrawal symptoms
  - ▣ Anxiety
  - ▣ Nausea/diarrhea
  - ▣ Tremor
- Withdrawal symptoms only occur in patients who have developed tolerance



# Polling Question for Pharmacists/Nurses #1

Which of the following best describes the main hormones implicated in the neurobiology of addiction?

- a) Norepinephrine and dopamine
- b) Epinephrine and serotonin
- c) Norepinephrine and serotonin
- d) Epinephrine and dopamine

# Correct Response for Pharmacists/Nurses #1

Which of the following best describes the main hormones implicated in the neurobiology of addiction?

- a) **Norepinephrine and dopamine**
- b) Epinephrine and serotonin
- c) Norepinephrine and serotonin
- d) Epinephrine and dopamine

# Addiction

- Result of neurologic changes leading to the hallmark signs compulsive drug-seeking behavior
- Changed Set Point Model
  - ▣ Neurons in the mesolimbic reward pathway cannot release dopamine in the absence of opioids
  - ▣ Increased glutamate activity leads to drug seeking-behavior
    - Increased dopamine leading to cravings
    - Increased norepinephrine leading to withdrawal symptoms
- Cognitive Deficits Model
  - ▣ Signaling in the prefrontal cortex (PFC) is inhibited, leading to dysregulation of judgement, planning and executive functions

# DSM V Criteria for Opioid Use Disorder (OUD)

- Diagnosis is confirmed when at least two of the following are observed within a 12-month period:
  - Opioids are often taken in larger amounts or over a longer period than was intended.
  - There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
  - A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
  - Craving, or a strong desire or urge to use opioids.
  - Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
  - Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
  - Important social, occupational, or recreational activities are given up or reduced because of opioid use.
  - Recurrent opioid use in situations in which it is physically hazardous.
  - Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
  - Exhibits tolerance or withdrawal



# HISTORY & EPIDEMIOLOGY



# History of the Opioid Crisis

- 1980: The Jick Letter
- 1995: “Pain as the Fifth Vital Sign”
- 2005: HCAHPS Reimbursement
- 2017: Opioid crisis declared a national public health crisis by the U.S. government

## ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

*To the Editor:* Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients<sup>1</sup> who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,<sup>2</sup> Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

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Source: Porter et al. *N Engl J Med* 1980; 302:123

Source: Scher et al. *Pain Manag Nurs*. 2018 Apr; 19(2): 125–129.

# Epidemiology

- Drug overdose deaths have risen by 5.5% annually from 1999-2015
  - ▣ 90 Americans die from opioid overdoses every day
  - ▣ Increase is largely attributed to the rise in opioid-related deaths in non-Hispanic whites
- Opioid-involved overdoses
  - ▣ 60% of deaths in 2017 involved synthetic opioids such as fentanyl and sufentanil
  - ▣ Increased across all ethnic and age groups between 2015-2017
  - ▣ From 2011-2016, overdose rates among whites rose more than 260%
- The rate of increase in overdose deaths in black Americans has risen at a faster rate (43%) in the past five years compared to that of white Americans (22%)

Source: Rudd et al. *MMWR Morb Mortal Wkly Rep* 2016;65:1445-52.

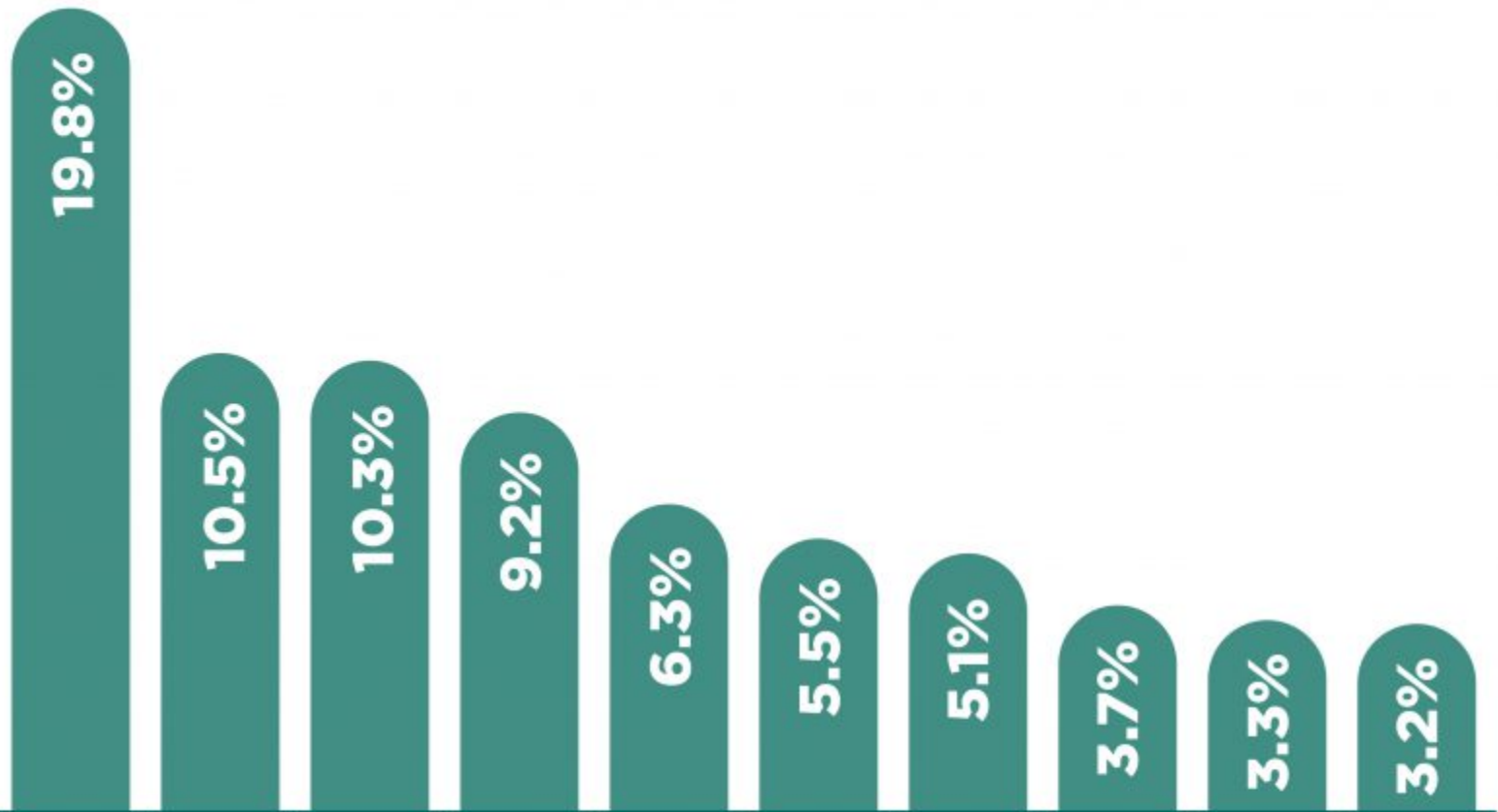
Source: Sheils et al. *Ann Intern Med.* 2018;168(6):453-455

# 2018 National Survey on Drug Use & Health

- 10.3 million people misused opioids in 2018
- Prescription pain reliever misuse is the second most common form of illicit drug use
  - ▣ 63.6% reported use was to decrease physical pain
  - ▣ 51.3% received pain reliever from friend or relative

# Most Overdose Deaths Involve One or More Illicit Drugs

The 10 most frequently occurring opioid and stimulant combinations accounted for 76.9% of overdose deaths.



Illicitly Manufactured Fentanyls*	●	●	●				●	●	●	
Heroin			●				●			●
Prescription Opioids				●					●	
Cocaine		●				●	●			
Methamphetamine					●			●		

Source: CDC's State Unintentional Drug Overdose Reporting System (SUDORS) 24 states and the District of Columbia reporting, January-June 2019

\*IMFs include fentanyl and fentanyl analogs

# National Institutes of Health HEAL Initiative

- Improve prevention and treatment of opioid misuse and addiction
  - ▣ Expand options for opioid addiction, overdose prevention and overdose reversal
  - ▣ Optimize existing treatment strategies for opioid addiction
- Enhance pain management
  - ▣ Safe, efficacious, nonaddictive interventions to manage chronic pain



# Polling Question for Pharmacists/Nurses #2

Which of the following is **NOT** a historical initiative that combats opioid misuse and addiction?

- A. National Institute of Health HEAL Initiative
- B. The Jick Letter
- C. Declaration of a national public health crisis in 2017
- D. None of the above

# Correct Response for Pharmacists/Nurses #2

Which of the following is **NOT** a historical initiative that combats opioid misuse and addiction?

- A. National Institute of Health HEAL Initiative
- B. **The Jick Letter**
- C. Declaration of a national public health crisis in 2017
- D. None of the above



# OPIOID OVERDOSE PREVENTION & REVERSAL

# Naloxone



- Competitive mu-opioid antagonist
- Uses
  - ▣ Acute overdose
  - ▣ Reversal of opioid-induced respiratory depression
- Products
  - ▣ Naloxone (IV, IM, SQ)
  - ▣ Narcan (Intranasal)
  - ▣ Evzio (Autoinjector)

Source: Narcan Nasal Spray (naloxone hydrochloride) [prescribing information]. Radnor, PA: Adapt Pharma Inc; August 2020.

Source: Naloxone hydrochloride injection [prescribing information]. Mendham, NJ: Somerset Therapeutics, LLC; December 2016.

# Naloxone Pharmacokinetics

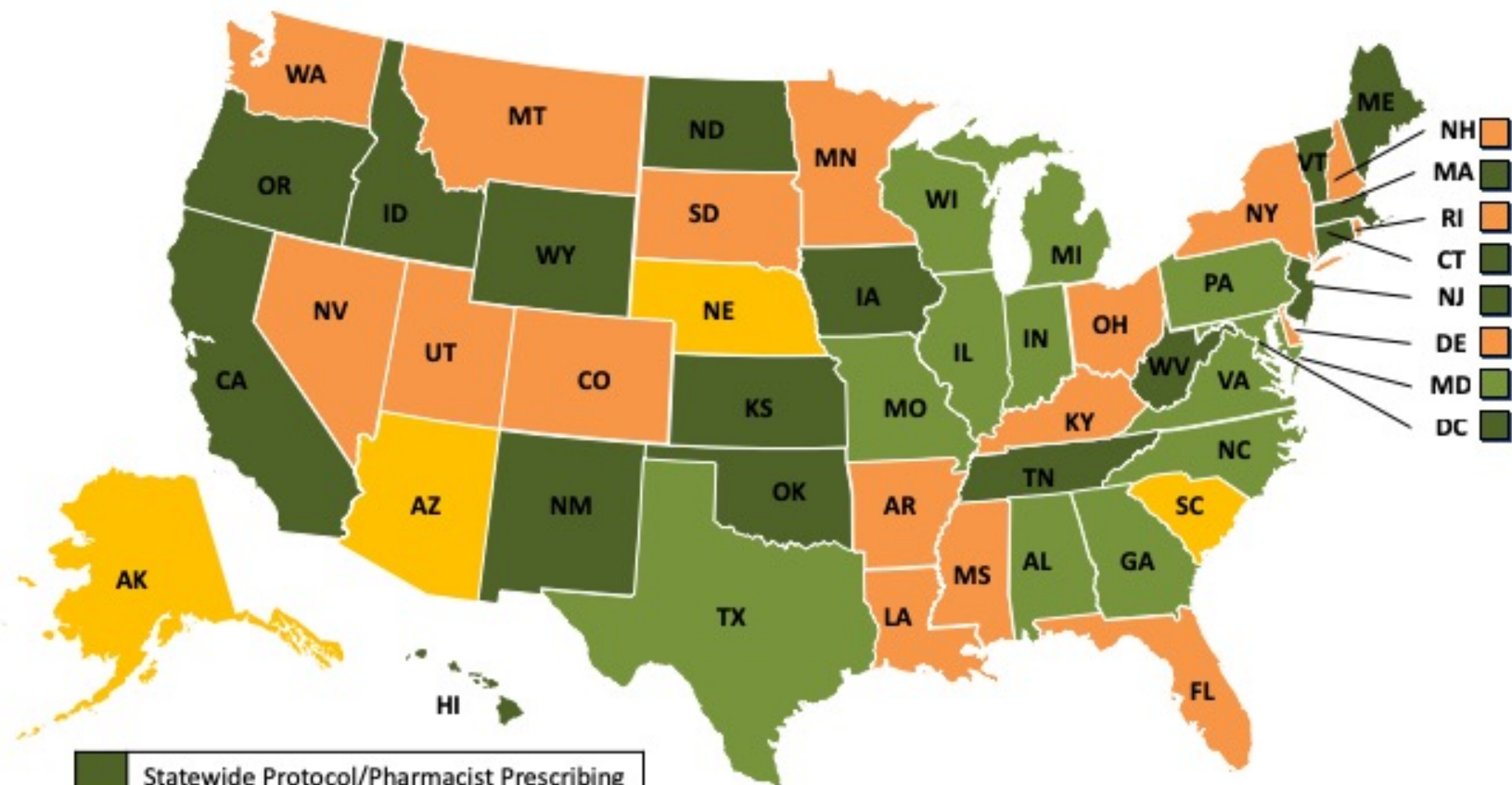
	<b>ET/IM/SQ/IV</b>	<b>Nebulized</b>	<b>Intranasal</b>
<b>Dose</b>	0.4-2 mg q 2-3 min: maximum 10 mg	2 mg	4 mg q 2-3 min
<b>Onset</b>	2-5 minutes	5 minutes	8-13 minutes
<b>Half Life</b>	30-90 minutes	30-90 minutes	120 minutes
<b>Duration</b>		30-120 minutes	

# Naloxone Access

- Naloxone prescriptions doubled from 2017-2018
  - ▣ One naloxone prescription is dispensed per 70 high-dose opioid prescriptions
- Rural counties have the lowest dispensing rates
  - ▣ Rural counties were almost 3 times more likely to be a low-dispensing county
  - ▣ Naloxone dispensing is 25 times greater in the highest-dispensing counties
- Half of naloxone prescriptions required a copay
  - ▣ 71% of Medicare prescriptions and 42% of commercial insurance prescriptions

# Naloxone Access in Community Pharmacies

Based on data collected by NASPA (updated January 2019)



Dark Green	Statewide Protocol/Pharmacist Prescribing
Medium Green	Statewide Standing Order
Yellow	Dispense without a prescription
Orange	Standing Order
Red	None



# Polling Question for Pharmacy Technicians #1

How many states allow dispensing of naloxone without a prescription?

- A. One
- B. Two
- C. Three
- D. Four

# Correct Response for Pharmacy Technicians #1

How many states allow dispensing of naloxone without a prescription?

- A. One
- B. Two
- C. Three
- D. **Four**

# Increasing Overdose Treatment & Prevention Modalities

- Increase community access to naloxone and decrease copay costs to patients
- Develop longer acting, more potent mu-opioid antagonists
- Other investigational options for opioid-induced respiratory depression
  - ▣ Serotonin 1A receptor agonists
  - ▣ Ampakines
  - ▣ Phrenic nerve stimulation
  - ▣ Wearable devices to detect overdose



# OPTIMIZATION OF OUD TREATMENT STRATEGIES

# Therapy for OUD

- Psychosocial support with opioid-assisted therapy (OAT) is the cornerstone of OUD treatment
  - Methadone: opioid agonist
    - Available at 1,500 federally certified treatment facilities in the US
  - Buprenorphine: partial opioid agonist
    - Can be prescribed by certified providers in an office setting
- Oral naltrexone is an opioid antagonist not commonly used for addiction treatment
  - Has shown no treatment benefit compared to placebo due to low rates of patient adherence

# OAT Barriers & Concerns

- Barriers to access
  - ▣ Long wait times to enter treatment facilities
  - ▣ Large travel distance to existing clinics
  - ▣ Lack of treatment facilities that offer OAT
  - ▣ Shortage of certified providers
  - ▣ Social stigmas and fear of legal repercussions
- Concerns of OAT therapy
  - ▣ Potential diversion
  - ▣ Patient compliance

# Solutions to OAT Access Barriers

- Expanded access to treatment centers and certified prescribers
- Long-acting OAT formulations
  - ▣ Monthly buprenorphine injection
  - ▣ 6-month buprenorphine (probuphine)
  - ▣ Weekly buprenorphine transdermal patch is FDA approved **only** for the treatment of chronic pain
- Naltrexone does not require special credentials to prescribe

# Long-Acting Naltrexone

- Opioid antagonist that may be administered as a long-acting injection every 4 weeks
- Historically patients must make a doctor's appointment every 4 weeks for injection purposes
- States have begun passing laws that allow pharmacists to administer long-acting naltrexone in community pharmacies
  - ▣ Ohio
  - ▣ Wisconsin



# Polling Question for Pharmacy Technicians #2

Which of the following is a pertinent medication used to treat and mitigate opioid misuse and addiction?

- A. Morphine
- B. Methadone
- C. Methylprednisolone
- D. Midodrine

# Correct Response for Pharmacy Technicians #2

Which of the following is a pertinent medication used to treat and mitigate opioid misuse and addiction?

- A. Morphine
- B. **Methadone**
- C. Methylprednisolone
- D. Midodrine

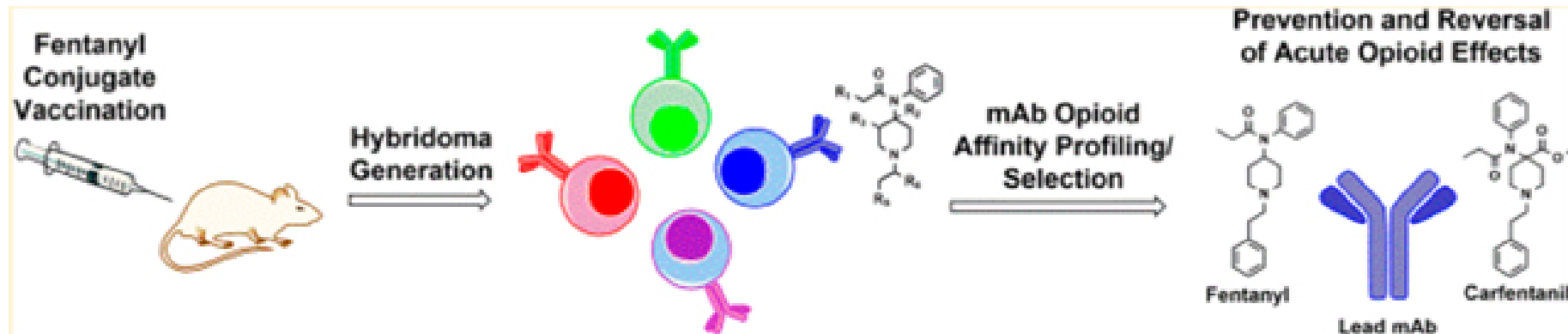
# In the Pipeline

- Lorcaserin
  - ▣ Reduced opioid seeking behavior in a rodent model, but removed from the market in February 2020 secondary to increased risk of cancer
- Vaccines targeting heroin and prescription opioids
  - ▣ Create antibodies that prevent opioids from entering the CNS
  - ▣ Passive immunity to mitigate substance use disorder
  - ▣ 2 preclinical trials in mice have shown benefit in targeting heroin



# In the Pipeline

- Monoclonal antibodies
  - ▣ Target the synthetic opioid fentanyl and its derivatives
  - ▣ Currently being studied as an antidote to acute intoxication in murine models



# Polling Question for Pharmacists/Nurses #3

Which of the following therapeutic modalities is under investigation as a treatment to combat opioid addiction?

- A. Monoclonal antibodies
- B. Vaccines
- C. Abuse-deterrent formulations of existing opioids
- D. All of the above

# Correct Response for Pharmacists/Nurses #3

Which of the following therapeutic modalities is under investigation as a treatment to combat opioid addiction?

- A. Monoclonal antibodies
- B. Vaccines
- C. Abuse-deterent formulations of existing opioids
- D. **All of the above**

# LEGISLATION & OUD



# Federal Initiatives

- National Guidelines
  - ▣ 2016 CDC Guidelines for Prescribing Opioids for Chronic Pain
  - ▣ Emphasis on multi-modal analgesia
- Food and Drug Administration (FDA)
  - ▣ Can regulate/remove drugs from the market
  - ▣ Supports development of potent, non-opioid analgesia and abuse-deterrent formulations of existing opioids
- Drug Enforcement Agency (DEA) and Justice Department
  - ▣ Prescribing requirements
  - ▣ Prosecution of illegal prescribing and pill mills

# SUPPORT for Patients & Communities Act

- 215 item bill addressing to combat the opioid epidemic signed into law October 2018
  - ▣ Expanded federal anti-kickback laws for patients seeking substance use disorder treatment to include patients covered under private insurance and those who are self paying
  - ▣ Loosened restrictions on the electronic prescribing of controlled substances for Medicare beneficiaries

# State Initiatives

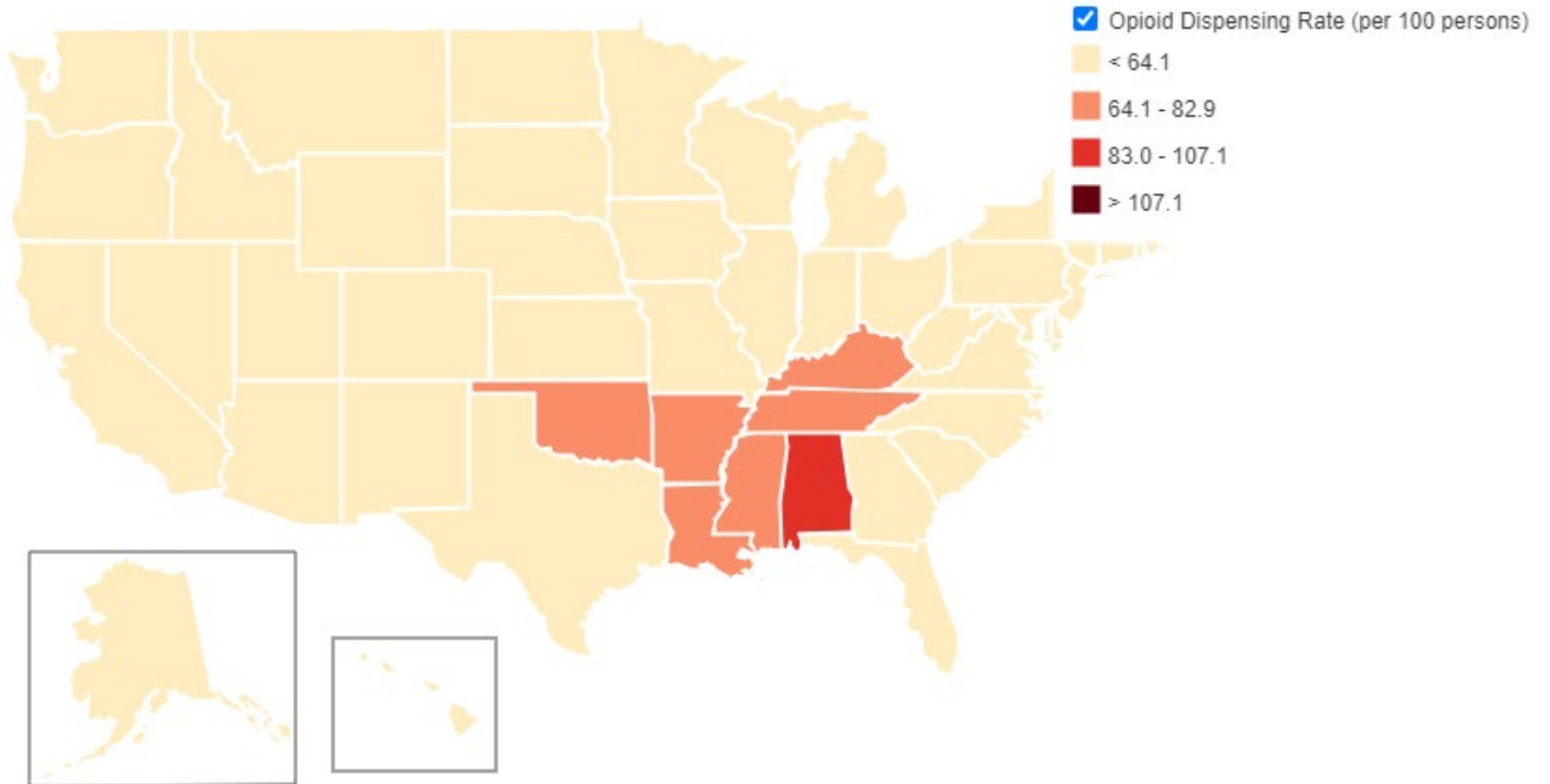
- Prescribing restrictions in addition to federal law
- Prescription Drug Monitoring Programs
- Insurance industry regulation
- Expansion of social support programs and decriminalization laws

# Opioid Prescribing

- Number of opioid prescriptions peaked in 2012
  - ▣ 255 million prescriptions
  - ▣ 81.3 prescriptions per 100 persons
- The rate in 2018 is the lowest rate in 13 years
  - ▣ 168 million prescriptions
  - ▣ 51.4 prescriptions per 100 persons



# 2019 Opioid Prescribing Rates by State



# Prescription Restrictions Codified in Law

- Day supply limitations for opioid naïve patients
  - ▣ 7 days: AK, HI, CO, UT, OK, LA, MO, IN, WV, SC, PA, NY, MA, CT, MA
  - ▣ 5 days: AZ, NC, NJ
  - ▣ 3-4 days: TN, KY, FL, MN (for dental/ophthalmic pain only)
- Maximum morphine milligram equivalents (MME)
  - ▣ MA limits to 100 MME/day
  - ▣ NV/AZ limits to 90 MME/day
  - ▣ RI/TN limits to 50 MME/day
- Additional risk control requirements for prescriptions written for minors
  - ▣ AL, CT, IN, LA, MA, NE, PA, WV

# Polling Question for Pharmacy Technicians #3

How many states have enacted new legislation regulating the prescribing and dispensing of opioid medications?

- A. 15
- B. 26
- C. 38
- D. 50

# Correct Response for Pharmacy Technicians #3

How many states have enacted new legislation regulating the prescribing and dispensing of opioid medications?

- A. 15
- B. **26**
- C. 38
- D. 50

# Prescription Drug Monitoring Programs (PDMPs)

- Allow healthcare providers to access patient history and prescription fill patterns for select medications
  - ▣ Controlled substances
  - ▣ Naloxone
- 49 states, D.C. and Guam have implemented a PDMP
  - ▣ Missouri is the only state without a PDMP requirement
  - ▣ Requirements for use and reporting by healthcare professionals vary by state
- States may have limited data sharing agreements with surrounding states

# Social Support & Illicit Drug Decriminalization

- Public health initiatives have been undertaken in a variety of states to limit the damage of the opioid crisis
  - ▣ Medicaid expansions to cover more persons
  - ▣ Needle exchange programs
- Decriminalization for possession of illicit drugs
  - ▣ Oregon became the first state to decriminalize all drugs in November 2020
  - ▣ Makes possession a civil violation rather than a criminal one
  - ▣ Violation may result in a fine or court-ordered therapy

# Effects of Legislation Targeting Opioid Use

- A total of 26 states have enacted some form of legislation regulating the prescribing or dispensing of opioids for acute pain
- 33 states have enacted prescribing guidance for opioid medications
- There is no data on what extent these laws and guidelines impact opioid-related morbidity and mortality
- The SUPPORT for Patients and Communities Act provides support for data collection and analysis

# CONCLUSION





# Key Points

- Opioid addiction in the United States is a complex public health crisis
- Strategies to combat the opioid crisis are multifaceted and involve expanded access to overdose prevention and treatment, increased availability of treatment programs and multimodal analgesia
- The impact of legislation on OUD and opioid-related deaths remains uncertain
- Opportunities to reduce opioid use and misuse are available to all healthcare professionals

# Additional Reading

- 2016 CDC Guideline for Prescribing Opioids in Chronic Pain
- 2018 SAMSHA Guidelines: Medications for opioid use disorder: for healthcare and addiction professionals, policymakers, patients and families
- 2019 APS Consensus Statement: Challenges with Implementing the Centers for Disease Control and Prevention Opioid Guideline

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**THANK YOU!**

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