Efforts to reduce the risk of opioid overdose deaths through co-prescribing and patient counseling

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Learning Objectives

1. Describe the basic profile of opioid mechanism of action
2. Describe the pharmacology of naloxone
3. Understand the benefits of coprescribing naloxone with opioids
4. Describe the reasons to have naloxone in the home
5. Know the laws protecting individuals from civil liability associated with naloxone administration and the reporting an overdose

Pain in America

- 20.4% of US citizens over the age of 18 suffer from chronic pain
- Chronic pain = pain lasting longer than three months
- One in five visits to outpatient clinics are related to pain
- Half of all patient visits to primary care are related to pain (not necessarily seeking pain relief but complaining of pain)
- 8% of US adults have chronic pain severe enough to limit quality of life or work activities
- Higher rates of chronic pain in women, the elderly, adults with lower socioeconomic status, public health insurance, low educational level

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
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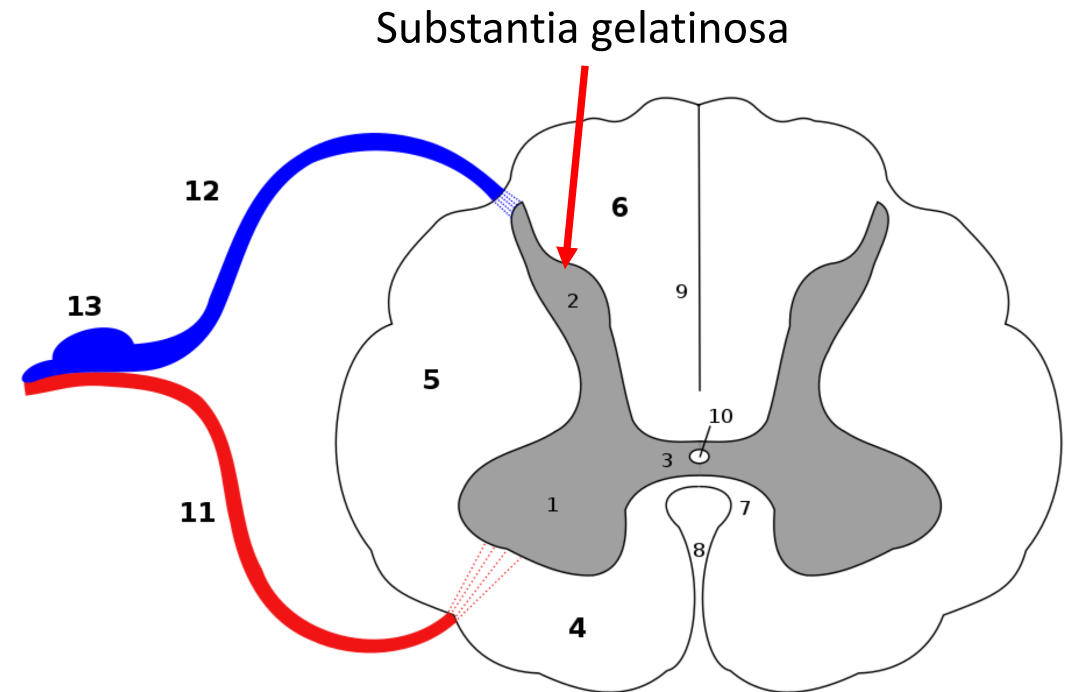
Comorbidities with Pain

- Depression
- Anxiety
- Chronic pain is associated increased risk for suicide
- Chronic pain can impact all facets of a patient's life

Gate Control Theory of Pain

- Transmission through three "gates" in the spinal cord
  1) Substantia gelatinosa in dorsal horn (*which contains opioid receptors*)
  2) fibers in the dorsal horn
  3) transmission cells in dorsal horn
- Current theory: negative state of mind may cause gates to stay open
  - Depression and anxiety may affect the gates
  - Unhealthy lifestyle may affect the gates



Challenges to Prescribing Pain Medications

- Risk of medical negligence with overprescribing/underprescribing
- Drug diversion activities by patients are leading to provider liability

Provider Knowledge Gap

- Understand addiction
- Populations at risk for opioid addiction
- Prescriptions vs. non-prescription opioid addiction
- Fallacious belief that addiction and dependence are synonymous

Terminology

- **Tolerance**: Lessened effect of a drug or need to escalate dose to achieve same effect
- **Dependence**: Physiological reliance resulting in withdrawal symptoms with cessation or reduction of drug administered
- **Pseudoaddiction**: Pursuit of additional medication due to poor pain control (cessation of drug seeking behavior with appropriate pain control)
- **Misuse**: Using a drug in a manner other than how it was prescribed
- **Abuse**: maladaptive pattern of substance use for non-medical purpose
- **Diversion**: Transferring a control substance from an authorized user to an unauthorized user

Definition of Addiction

- A treatable chronic disease
- Pursuit of a chemical substance to find relief or award
- Associated with diminished control over drug use, compulsive use, craving, and continued use despite harm
- Involves environmental pressures, genetics, an individual's life experiences
- Rewiring of the brain's circuitry: downregulating endorphin release
- Behaviors that become compulsive and result in dangerous consequences

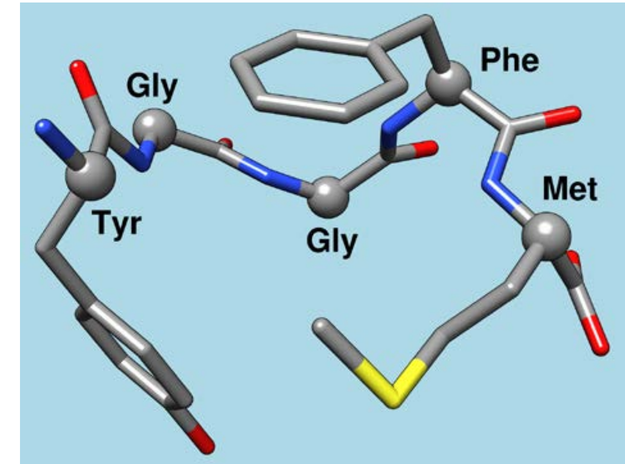
Characteristics of Addiction

- Craving for drug or positive reward
- Dysfunctional emotional response
- Failure to recognize significant problems affecting behavior and relationships
- Inability to consistently abstain
- Impairment of control behavior

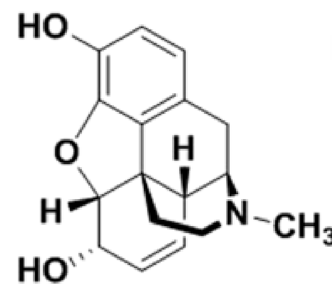
Opioid-related Analgesia

Opioids mimic an endogenous ligand for the μ opioid receptor

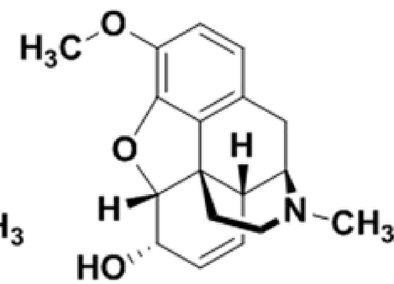
- Endorphins
  - Endogenous opioid peptides
  - Produce analgesia
  - “endogenous” + “morphine”
- Opium
  - Morphine: strong analgesic
  - Codeine: strong analgesic
  - Thebaine: stimulant, but main component in opium



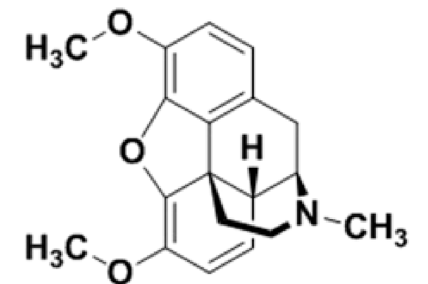
Met-enkephalin
Tyr-Gly-Gly-Phe-Met



Morphine



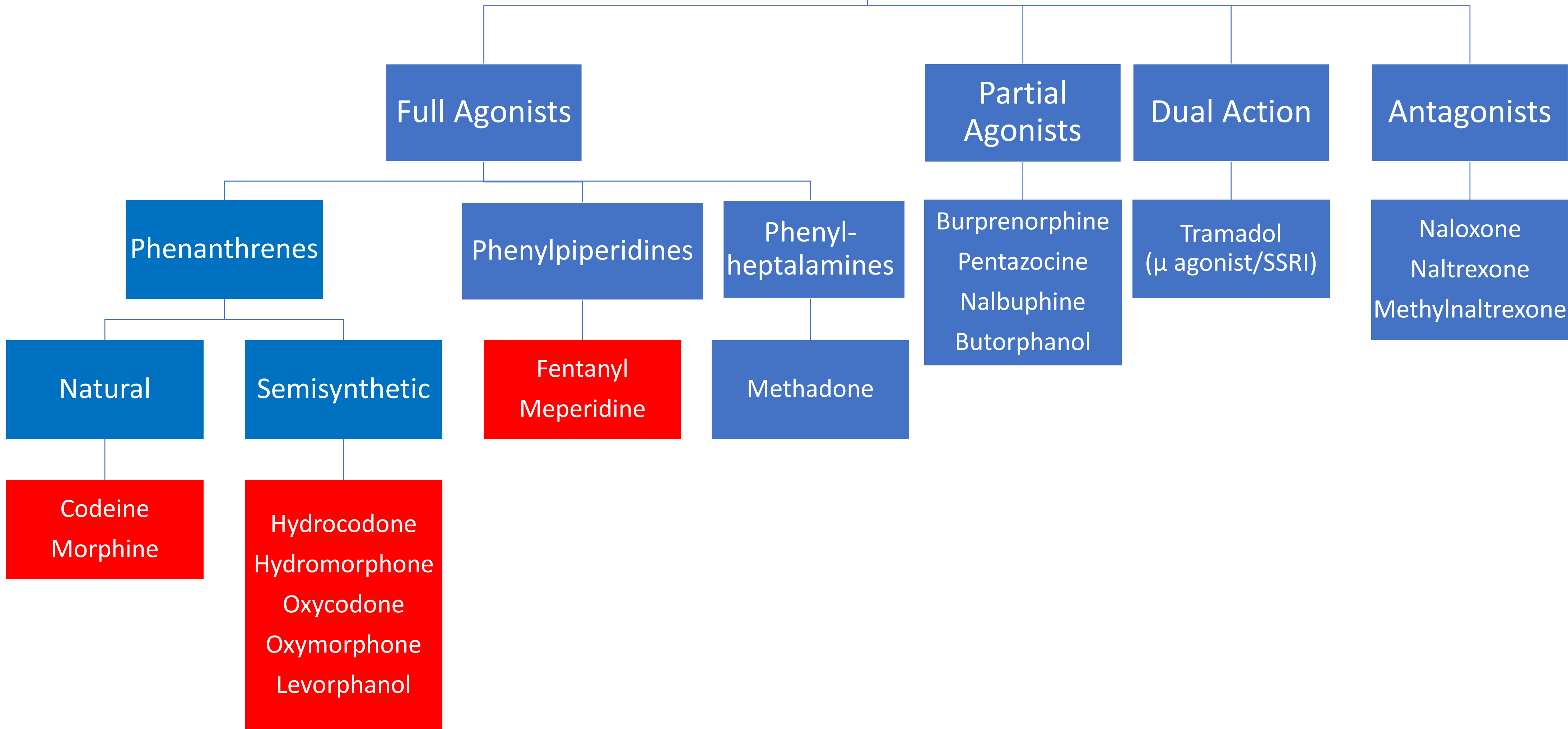
Codeine



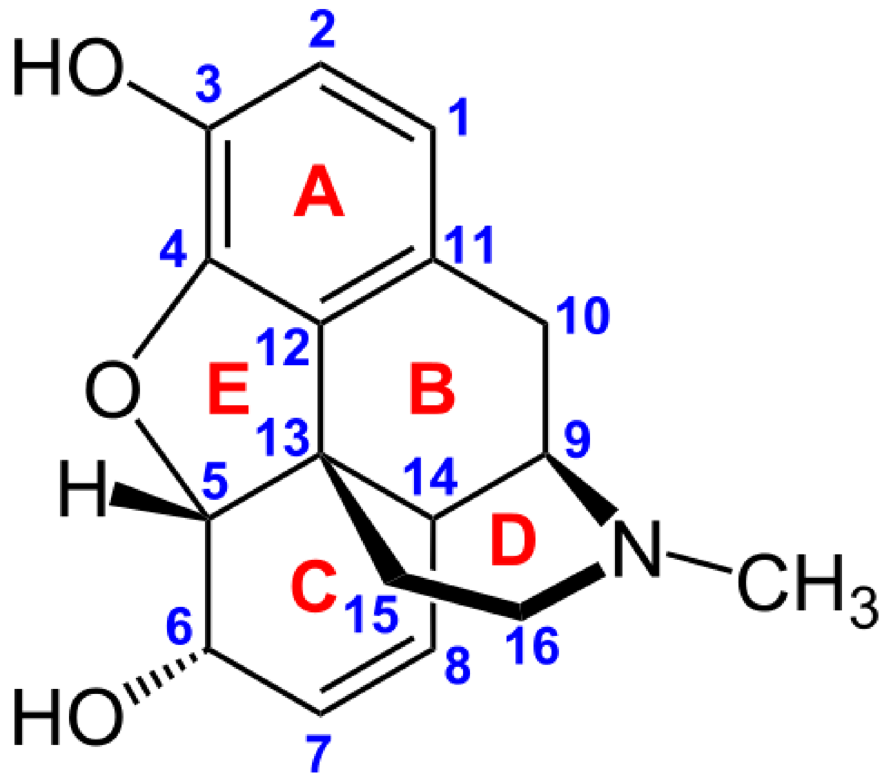
Thebaine

Opioid Receptors

	κ (kappa)	μ (mu)	δ (delta)
Location	Cerebral cortex Hypothalamus	CNS Vas deferens Myenteric gut neurons	Olfactory bulb
Physiological Roles	Analgesia Sedation Miosis Diuresis **Dysphoria**	Analgesia Euphoria Increased GI transit time Thermoregulation Respiratory depression (volume) Emetic effects Tolerance, physical dependence	Analgesia GI motility Olfaction Respiratory depression (rate)
Selective Agonists	Bremazocine Trifluadom Spiradoline	Morphine Hydrocodone Oxycodone	
Selective Antagonists	Buprenorphine	Naloxone Naltrexone	



Binds to
μ Receptor
Full Agonists
Partial Agonists
Dual Action
Antagonists
Phenanthrenes
Phenylpiperidines
Phenyl-heptalamines
Burprenorphine
Pentazocine
Nalbuphine
Butorphanol
Tramadol
(μ agonist/SSRI)
Naloxone
Naltrexone
Methylnaltrexone
Natural
Semisynthetic
Fentanyl
Meperidine
Methadone
Codeine
Morphine
Hydrocodone
Hydromorphone
Oxycodone
Oxymorphone
Levorphanol

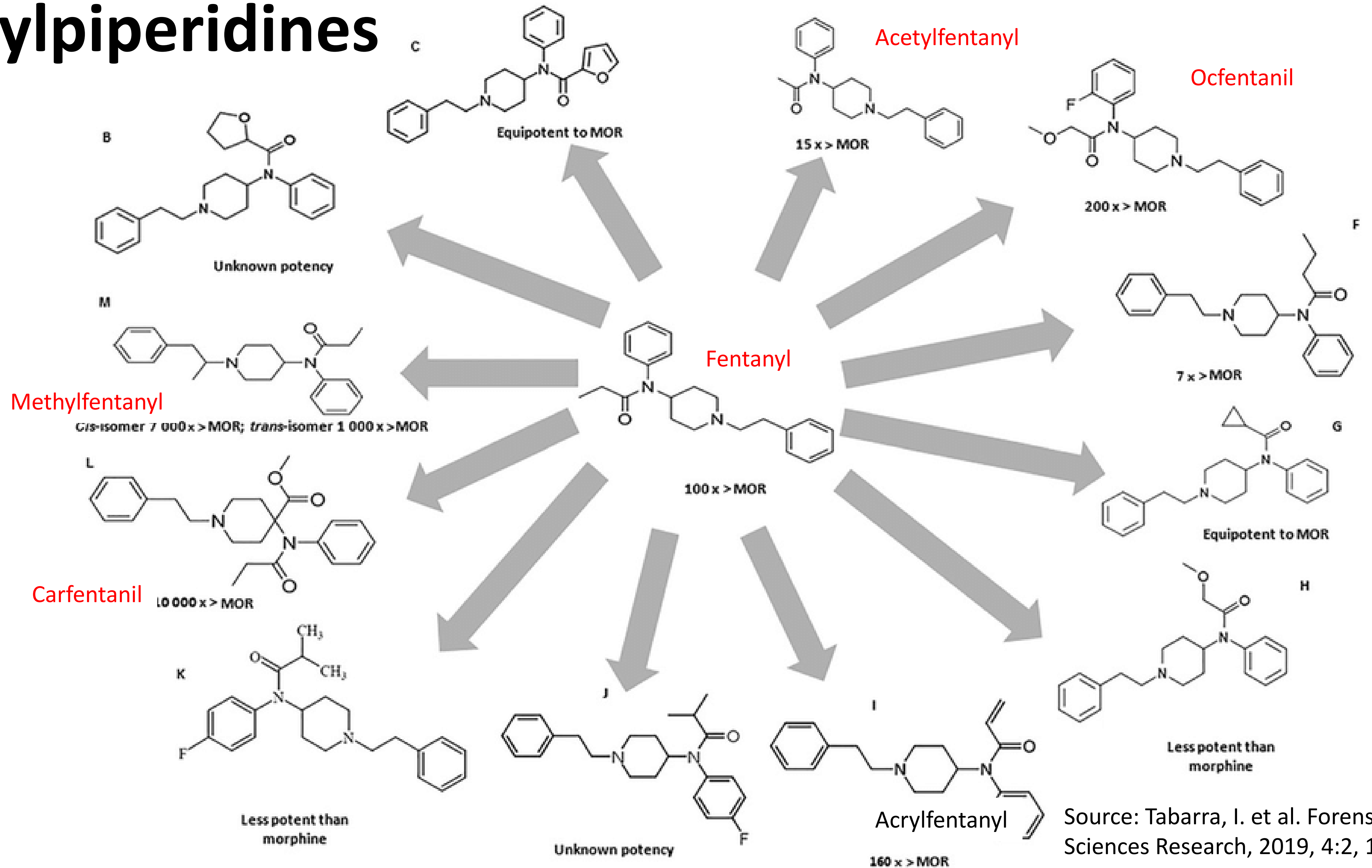


Morphine

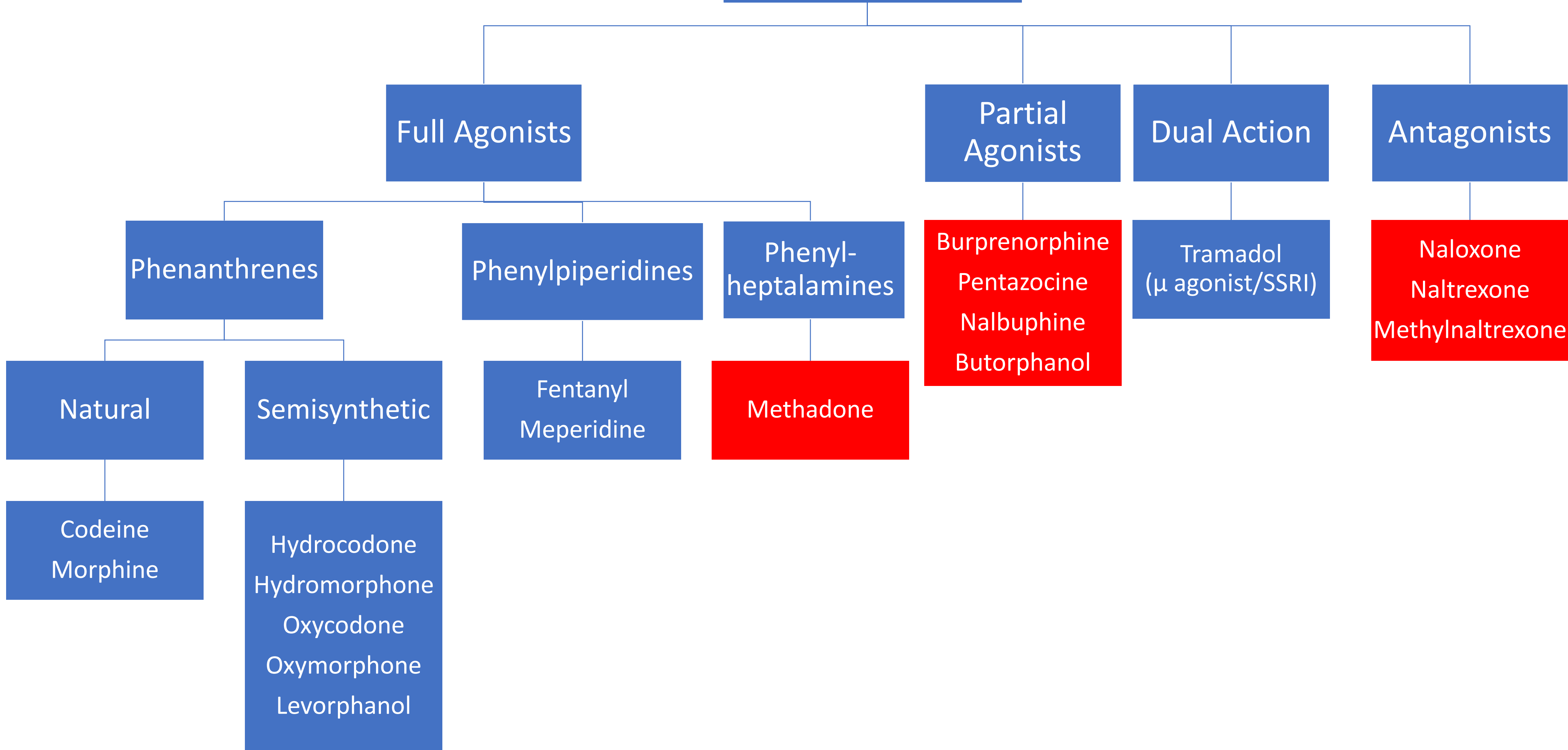
Phenanthrenes

Drug	N-17	C-3	C-6
Morphine	$-CH_3$	-OH	-OH
Codeine	$-CH_3$	$-O-CH_3$	-OH
Hydrocodone	$-CH_3$	$-O-CH_3$	=O
Hydromorphone	$-CH_3$	-OH	=O
Oxycodone	$-CH_3$	$-O-CH_3$	=O
Oxymorphone	$-CH_3$	-OH	=O
Levorphanol	$-CH_3$	-OH	
Heroin is acetylated at C_3 and C_6	Tertiary amine is essential	Hydroxyl improves binding; O-demethylation results in more active drug	Carbonyl increases potency; Hydroxyl associated with histamine release

Phenylpiperidines



Source: Tabarra, I. et al. Forensic Sciences Research, 2019, 4:2, 111-140



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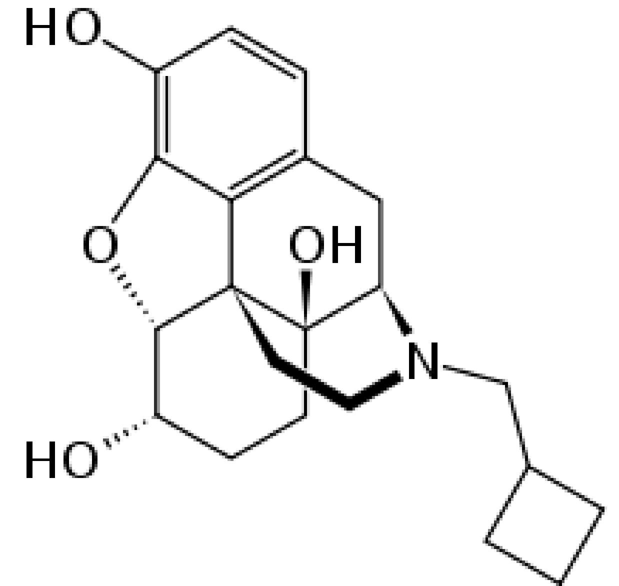
Tramadol
(μ agonist/SSRI)
Naloxone
Naltrexone
Methylnaltrexone
Natural
Semisynthetic
Fentanyl
Meperidine
Methadone
Codeine
Morphine
Hydrocodone
Hydromorphone
Oxycodone
Oxymorphone
Levorphanol

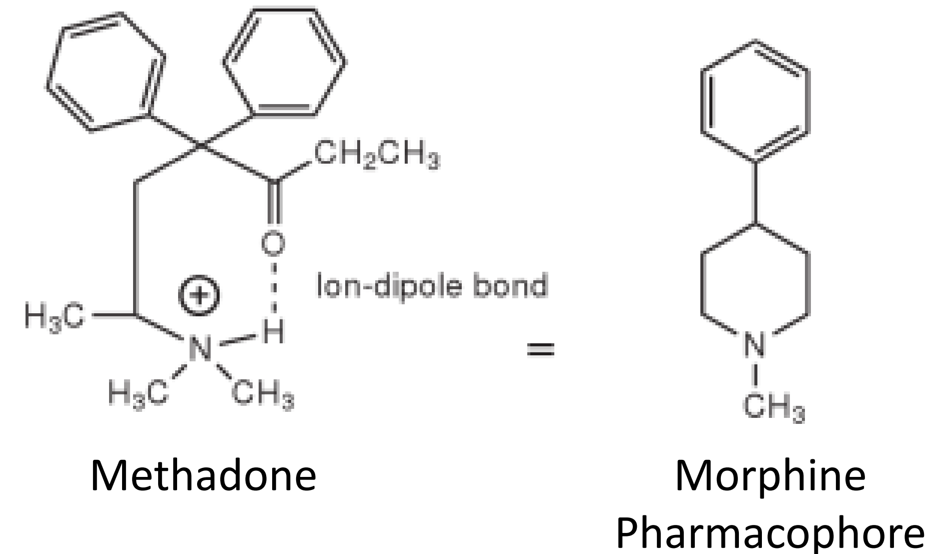
Alternates to Morphine Derivatives: Nalbuphine

- κ Agonist / μ Antagonist
- Subject to significant first pass effects, injectable use only
- Analgesia with less nausea and respiratory depression



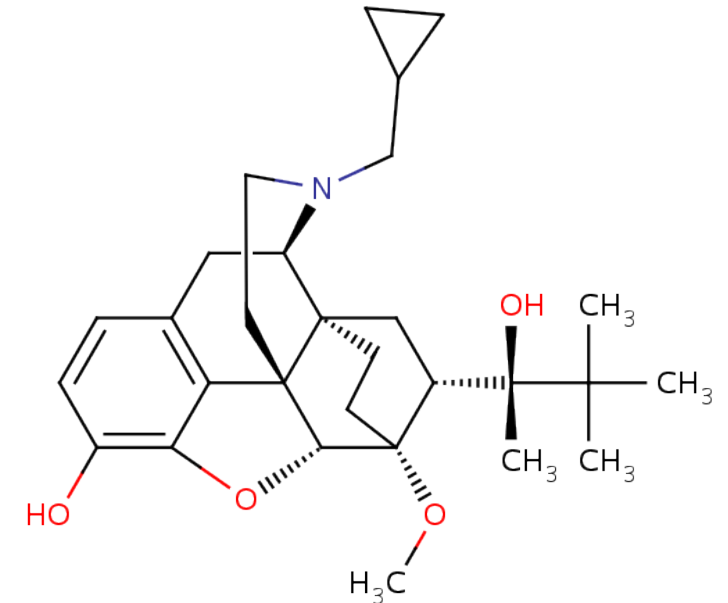
Medications for Opioid Use Disorder: Methadone

- Full agonist at μ opioid receptor, longer acting than morphine derivatives
- The highly flexible structure of methadone approximates the 4-phenylpiperidine pharmacophore of the phenylpiperidines
- Non-competitive antagonist to the *N*-methyl-d-aspartate (NMDA) receptor (neuropathic pain)
- As an MOUD, methadone is titrated to a higher daily dose, preventing withdrawal, but causing narcotic blockade to prevent euphoria from other shorter-acting opioids
- Due to the longer half-life of methadone (8 to 60 hours), the withdrawal time-course and symptoms are less severe



Medications for Opioid Use Disorder: Buprenorphine

- Can be prescribed for pain
- Partial agonist at μ opioid receptor
- Weak antagonist at κ opioid receptor
- High-affinity binding to the μ opioid receptors with slow-dissociation kinetics
- In OUD treatment, dose is titrated down slowly to allow withdrawal with less discomfort
- Withdrawal symptoms are much milder because it is a partial and not full agonist at the μ opioid receptor, and does not agonize the κ opioid receptor



Buprenorphine

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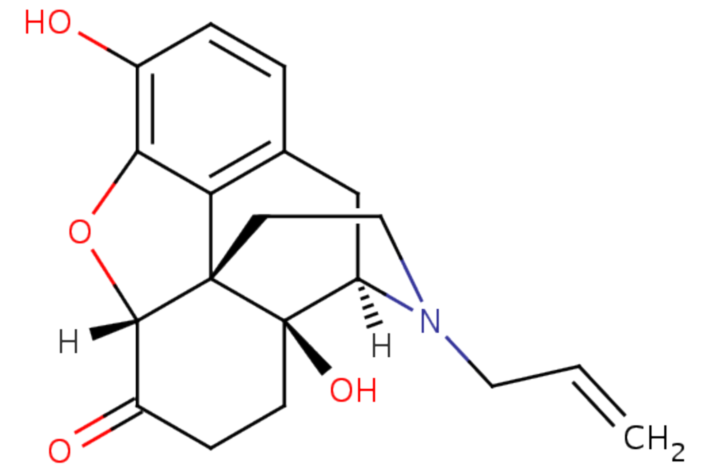
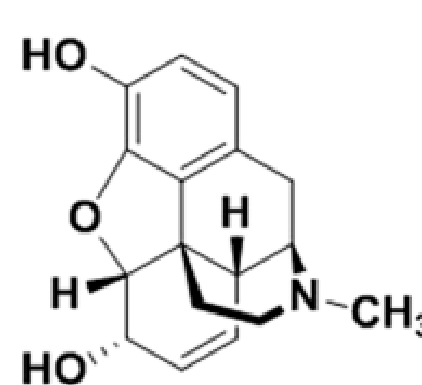
Medication for Overdose Reversal: Naloxone

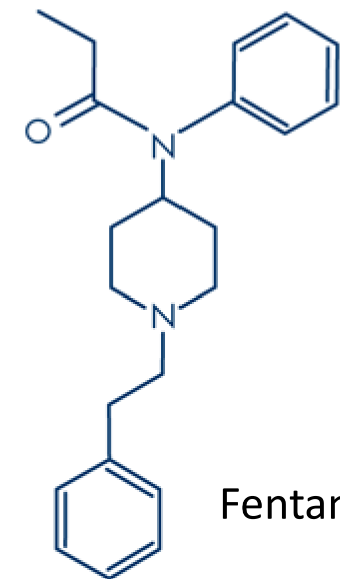
- µ Opioid Receptor Antagonist
- Antagonism due to hydroxyl at C14 and pi-electron density at N17
- Naloxone binds µ receptor with 200x more affinity than morphine
- Fentanyl binds µ receptor with only 2.6x more affinity than morphine (but is 200x more potent)
- Naloxone is an effective rescue agent for both morphine and fentanyl overdose



Naloxone



Morphine



Fentanyl

What is the chance an opioid prescription may be misused by your patient?

West Virginia Laws, Regulations, and Guidance Related to Opioids

- Opioid Reduction Act
  - Requires discussion of risks associated with opioid use and alternatives to opioid therapy
  - Limits amount of opioid that can be prescribed (4-day in emergency with addt'l 7 day Rx)
  - Non-emergency, 7-day Rx
- WV Code s 60A-9-5a
  - Prescribers of sched. II, III, or IV controlled substances register with Controlled Substance Monitoring Program
  - Document info obtained from CSMP in patient's medical record
  - Check CSMP database when issuing an initial Rx

Controlled Substance Agreement Forms

Pain Treatment with Opioid Medications: Patient Agreement*

I,____________________________, understand and voluntarily agree that
(initial each statement after reviewing):

______I will keep (and be on time for) all my scheduled appointments with the doctor and other members of the treatment team.

______I will participate in all other types of treatment that I am asked to participate in.

______I will keep the medicine safe, secure and out of the reach of children. If the medicine is lost or stolen, I understand it will not be replaced until my next appointment, and may not be replaced at all.

______I will take my medication as instructed and not change the way I take it without first talking to the doctor or other member of the treatment team.

______I will not call between appointments, or at night or on the weekends looking for refills. I understand that prescriptions will be filled only during scheduled office visits with the treatment team.

______I will make sure I have an appointment for refills. If I am having trouble making an appointment, I will tell a member of the treatment team immediately.

______I will treat the staff at the office respectfully at all times. I understand that if I am disrespectful to staff or disrupt the care of other patients my treatment will be stopped.

______I will not sell this medicine or share it with others. I understand that if I do, my treatment will be stopped.

______I will sign a release form to let the doctor speak to all other doctors or providers that I see.

______I will tell the doctor all other medicines that I take, and let him/her know right away if I have a prescription for a new medicine.

______I will use only one pharmacy to get all on my medicines:__________________________
Pharmacy name/phone#

______I will not get any opioid pain medicines or other medicines that can be addictive such as benzodiazepines (klonopin, xanax, valium) or stimulants (ritalin, amphetamine) without telling a member of the treatment team **before I fill that prescription**. I understand that the only exception to this is if I need pain medicine for an emergency at night or on the weekends.

*Adapted from the American Academy of Pain Medicine
http://www.painmed.org/Workarea/DownloadAsset.aspx?id=3203

_____I will not use illegal drugs such as heroin, cocaine, marijuana, or amphetamines. I nderstand that if I do, my treatment may be stopped.

_____I will come in for drug testing and counting of my pills within 24 hours of being called. I nderstand that I must make sure the office has current contact information in order to reach me, and ıat any missed tests will be considered positive for drugs.

_____I will keep up to date with any bills from the office and tell the doctor or member of the eatment team immediately if I lose my insurance or can't pay for treatment anymore.

_____I understand that I may lose my right to treatment in this office if I break any part of this greement.

ain Treatment Program Statement

Ve here at_____________________are making a commitment to work with you in your efforts to et better. To help you in this work, we agree that:

Ve will help you schedule regular appointments for medicine refills. If we have to cancel or hange your appointment for any reason, we will make sure you have enough medication to last ntil your next appointment.

Ve will make sure that this treatment is as safe as possible. We will check regularly to make ure you are not having bad side effects.

Ve will keep track of your prescriptions and test for drug use regularly to help you feel like you are eing monitored well.

Ve will help connect you with other forms of treatment to help you with your condition. We

ill help set treatment goals and monitor your progress in achieving those goals.

Ve will work with any other doctors or providers you are seeing so that they can treat you safely and ffectively.

Ve will work with your medical insurance providers to make sure you do not go without medicine ecause of paperwork or other things they may ask for.

f you become addicted to these medications, we will help you get treatment and get off of the edications that are causing you problems safely, without getting sick.

atient signature	Patient name printed	Date
rovider signature	Provider name printed	Date

*Adapted from the American Academy of Pain Medicine
http://www.painmed.org/Workarea/DownloadAsset.aspx?id=3203

https://nida.nih.gov/sites/default/files/SamplePatientAgreementForms.pdf

Patient Agreement Form

Patient Name:
Medical Record Number: **Addressograph Stamp:**

AGREEMENT FOR LONG TERM CONTROLLED SUBSTANCE PRESCRIPTIONS

The use of____(print names of medication(s)) may cause addiction and is only one part of the treatment for:___________________________________(print name of condition—e.g., pain, anxiety, etc.).

The goals of this medicine are:
☐ to improve my ability to work and function at home.
☐ to help my______________________(print name of condition—e.g., pain, anxiety, etc.) as much as possible without causing dangerous side effects.

I have been told that:

1. If I drink alcohol or use street drugs, I may not be able to think clearly and I could become sleepy and risk personal injury.
2. I may get addicted to this medicine.
3. If I or anyone in my family has a history of drug or alcohol problems, there is a higher chance of addiction.
4. If I need to stop this medicine, I must do it slowly or I may get very sick.

I agree to the following:

- I am responsible for my medicines. I will not share, sell, or trade my medicine. I will not take anyone else's medicine.
- I will not increase my medicine until I speak with my doctor or nurse.
- My medicine may not be replaced if it is lost, stolen, or used up sooner than prescribed.
- I will keep all appointments set up by my doctor (e.g., primary care, physical therapy, mental health, substance abuse treatment, pain management)
- I will bring the pill bottles with any remaining pills of this medicine to each clinic visit.
- I agree to give a blood or urine sample, if asked, to test for drug use.

Refills

Refills will be made only during regular office hours—Monday through Friday, 8:00AM-4:30 PM. No refills on nights, holidays, or weekends. I must call at least three (3) working days ahead (M-F) to ask for a refill of my medicine. **No exceptions will be made**. I will not come to Primary Care for my refill until I am called by the nurse.

I must keep track of my medications. No early or emergency refills may be made.

Pharmacy

I will only use one pharmacy to get my medicine. My doctor may talk with the pharmacist about my medicines.
The name of my pharmacy is____________________________________.

Prescriptions from Other Doctors

If I see another doctor who gives me a controlled substance medicine (for example, a dentist, a doctor from the Emergency Room or another hospital, etc.) I must bring this medicine to Primary Care in the original bottle, even if there are no pills left.

Privacy

While I am taking this medicine, my doctor may need to contact other doctors or family members to get information about my care and/or use of this medicine. I will be asked to sign a release at that time.

Termination of Agreement

If I break any of the rules, or if my doctor decides that this medicine is hurting me more than helping me, this medicine may be stopped by my doctor in a safe way.

I have talked about this agreement with my doctor and I understand the above rules.

Provider Responsibilities

As your doctor, I agree to perform regular checks to see how well the medicine is working.

I agree to provide primary care for you even if you are no longer getting controlled medicines from me.

_________________________________ ____________
Patient's signature Date

____
Resident Physician's signature

____
Attending Physician's signature

☐ This document has been discussed with and signed by the physician and patient. (A signed copy stamped with patient's card should be sent to the medical records department and a copy given to the patient.)

https://nida.nih.gov/sites/default/files/SamplePatientAgree

Does this form help you or your patient?

- How well does this assess the risk to your patient for medication misuse?
- Would it be appropriate to talk to your patient about opioid misuse and the risks of having opioids in the home?
- What about assessing the risks to opioid overdose with your patient?

NaloxONE West Virginia

- A program established with the West Virginia Drug Intervention Institute
- Trains pharmacists to engage with their patients at time of opioid fill to assess their risk to opioid misuse through counseling and assessment

Opioid Misuse Risk Assessment

Developed by the National Institute on Drug Abuse, the Opioid Risk Tool (ORT) is a brief, self-report screening tool designed for use with adult patients in primary care settings to assess risk for opioid abuse among individuals prescribed opioids for treatment of chronic pain. Patients categorized as high-risk are at increased likelihood of future abusive drug-related behavior. The ORT can be administered and scored in less than 1 minute and has been validated in both male and female patients, but not in non-pain populations.

Opioid Misuse Risk Assessment

Patient History	Score by Gender	
	Female	Male
Patient Aged between 16 - 45	1	1
History of Preadolescent Sexual Abuse	3	0
Family History of Substance Misuse		
Alcohol	1	3
Illegal Drugs	2	3
Prescription Medications	4	4
Personal History of Substance Misuse		
Alcohol	3	3
Illegal Drugs	4	4
Prescription Medications	5	5
Psychological Disorders		
ADD/ADHD, OCD, Bipolar	2	2
Depression	1	1
Total Score		

Administer test at initial visit prior to beginning opioid therapy for pain management.

- A score of 3 or lower indicates low risk for future opioid abuse,
- A score of 4 to 7 indicates moderate risk for opioid abuse, and
- A score of 8 or higher indicates a high risk for opioid abuse

Source: https://nida.nih.gov/sites/default/files/opioidrisktool.pdf

Accidental Overdose Risk Assessment

- Age of the patient: 16-25 (1), 26-44 (1), 45-64, greater than 64
- Medical History: (1 point for any issue)
- Asthma, Depression, Anxiety, COPD/Emphysema, Sleep Apnea, Liver Disease, Kidney Disease
- While using the opioid prescription, is there a chance that the patient may consume any of the following? (1 point for any med)
    1. Anxiety medication
    2. Muscle relaxation medication
    3. Sleep aids, both prescription or OTC
    4. Cough or cold medicine
    5. Alcohol
    6. Currently taking other opioid medications

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Prescription Medications	4	4
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Depression	1	1
Total Score		

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	Male	Female
0	28%	26%
1	10%	14%
2	1%	4%
3	1%	2%
4	1%	1%
5	1%	0.4%
6	1%	1%
7	0%	1%
8	1%	1%
9	0.4%	0%
10	0%	0.2%
11 - 19	1%	1%
20 - 25	1%	0.4%

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	Male	Female
0	19%	15%
1	9%	9%
2	8%	10%
3	4%	5%
4	3%	7%
5	3%	3%
6	1%	2%
7	0%	1%
8	0.2%	1%
9	0%	0%

0 – 2 Minimal risk of overdose

2 – 5 Moderate risk of overdose, co-prescribe naloxone

> 5 Significant risk of overdose, co-prescribe naloxone

Options for the Family Physician

- Fill opioid prescriptions in cases of severe pain (Two seven-day courses only, then referral to pain management clinic)
- Refer patients to pain management clinics as first response
- Refuse to fill opioid prescriptions
- Counsel patients on alternative pain mitigating therapies
- Work with your patient to ensure proper use of opioid medicines

Assessment Tools

- Screening to Brief Intervention
- Alcohol, Tobacco, Prescription Medication and Other Substances Use
- Opioid Risk Tool
- CRAFFT Substance Use Screening Tool for Adolescents
- Drug Abuse Screen Test