جامعة تكريت – كلية الطب البيطري

الدراسات العليا \ فرع الادوية والفسلجة والكيمياء الحياتية

ماجستير أدوية

أ د حسام الدين النجار

First Term \ 2024-2025

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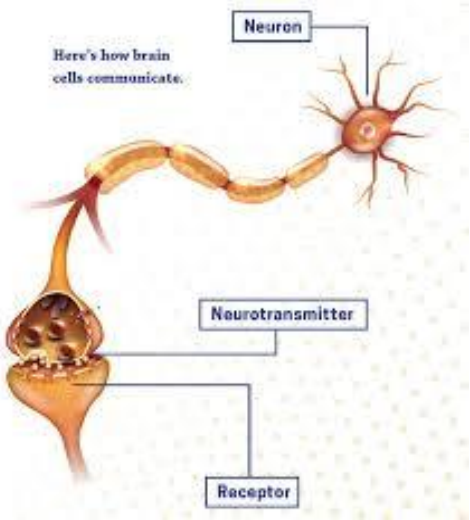
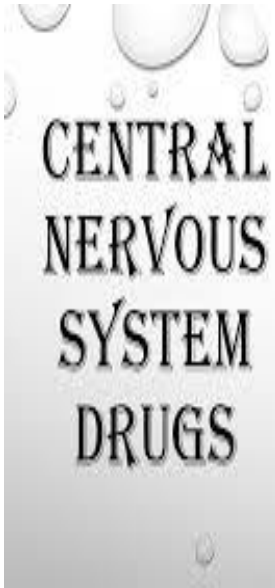
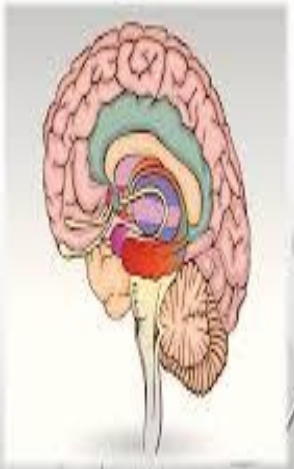


Advanced Pharmacology

Opioids

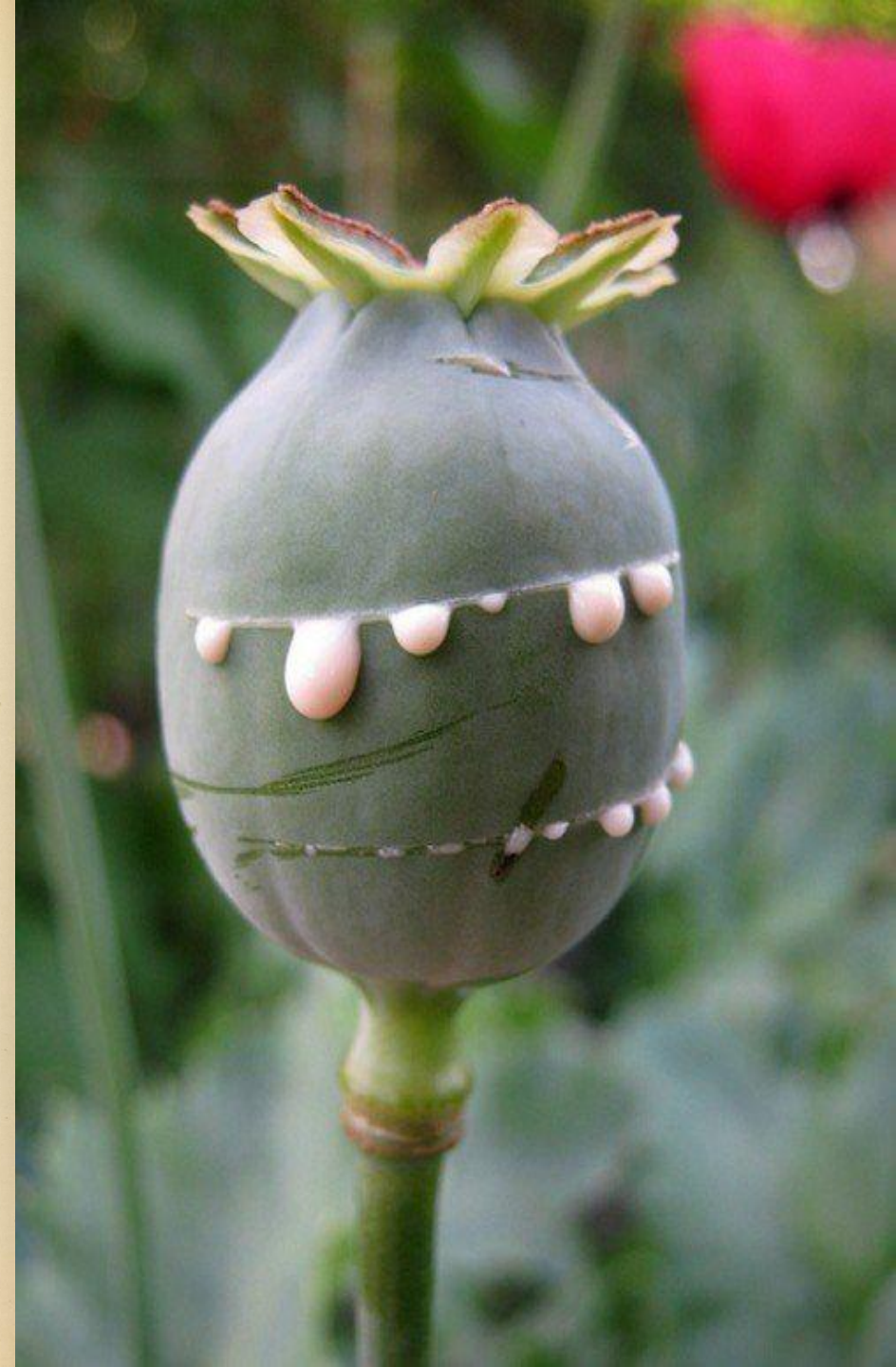




History of Opioids

- Opium is extracted from poppy seeds (Paper somniforum)
- Used for thousands of years to produce:
  - Euphoria
  - Analgesia
  - Sedation
  - Relief from diarrhea
  - Cough suppression

259. *Papaver somniferum* L. **Schlaf oder Saatmohn.**



- Invention of the hypodermic needle in 1856 produced drug abusers who self administered opioids by injection
- Controlling the widespread use of opioids has been unsuccessful because of the euphoria, tolerance and physiological dependence that opioids produce.

<u>Terminology</u>

- “opium” is a Greek word meaning “juice,” or the exudate from the poppy
- “opiate” is a drug extracted from the exudate of the poppy
- “opioid” is a natural or synthetic drug that binds to opioid receptors producing agonist effects

Natural opioids occur in 2 places:

- **1) In the juice of the opium poppy (morphine and codeine)**
- **2) As endogenous endorphins**

All other opioids are prepared from either morphine (semisynthetic opioids such as heroin) or they are synthesized from precursor compounds (synthetic opioids such as fentanyl)

Pharmacological Effects

- Sedation and anxiolysis
  - Drowsiness and lethargy
  - Apathy
  - Cognitive impairment
  - Sense of tranquility
- Depression of respiration
  - Main cause of death from opioid overdose
  - Combination of opioids and alcohol is especially dangerous
- Cough suppression
  - Opioids suppress the “cough center” in the brain
- Pupillary constriction: in the presence of analgesia is characteristic of opioid use
- Nausea and vomiting
  - Stimulation of receptors in an area of the medulla called the chemoreceptor trigger zone causes nausea and vomiting
  - Unpleasant side effect, but not life threatening
- Gastrointestinal symptoms
  - Opioids relieve diarrhea as a result of their direct actions on the intestines
- Other effects
  - Opioids can release histamines causing itching or more severe allergic reactions including bronchoconstriction
  - Opioids can affect white blood cell function and immune function

Mechanism of action

- **Activation of peripheral nociceptive fibers causes release of substance P and other pain-signaling neurotransmitters from nerve terminals in the dorsal horn of the spinal cord.**

- **Release of pain-signaling neurotransmitters is regulated by endogenous endorphins or by exogenous opioid agonists by acting presynaptically to inhibit substance P release, causing analgesia.**

Primary Effect of Opioid Receptor Activation

- Reduction or inhibition of neurotransmission, due largely to opioid-induced presynaptic inhibition of neurotransmitter release
- Involves changes in transmembrane ion conductance
  - Increase potassium conductance (hyperpolarization)
  - Inactivation of calcium channels

- Three Opioid Receptors
  - Mu
  - Kappa
  - Delta

Mu-Receptors: Two Types

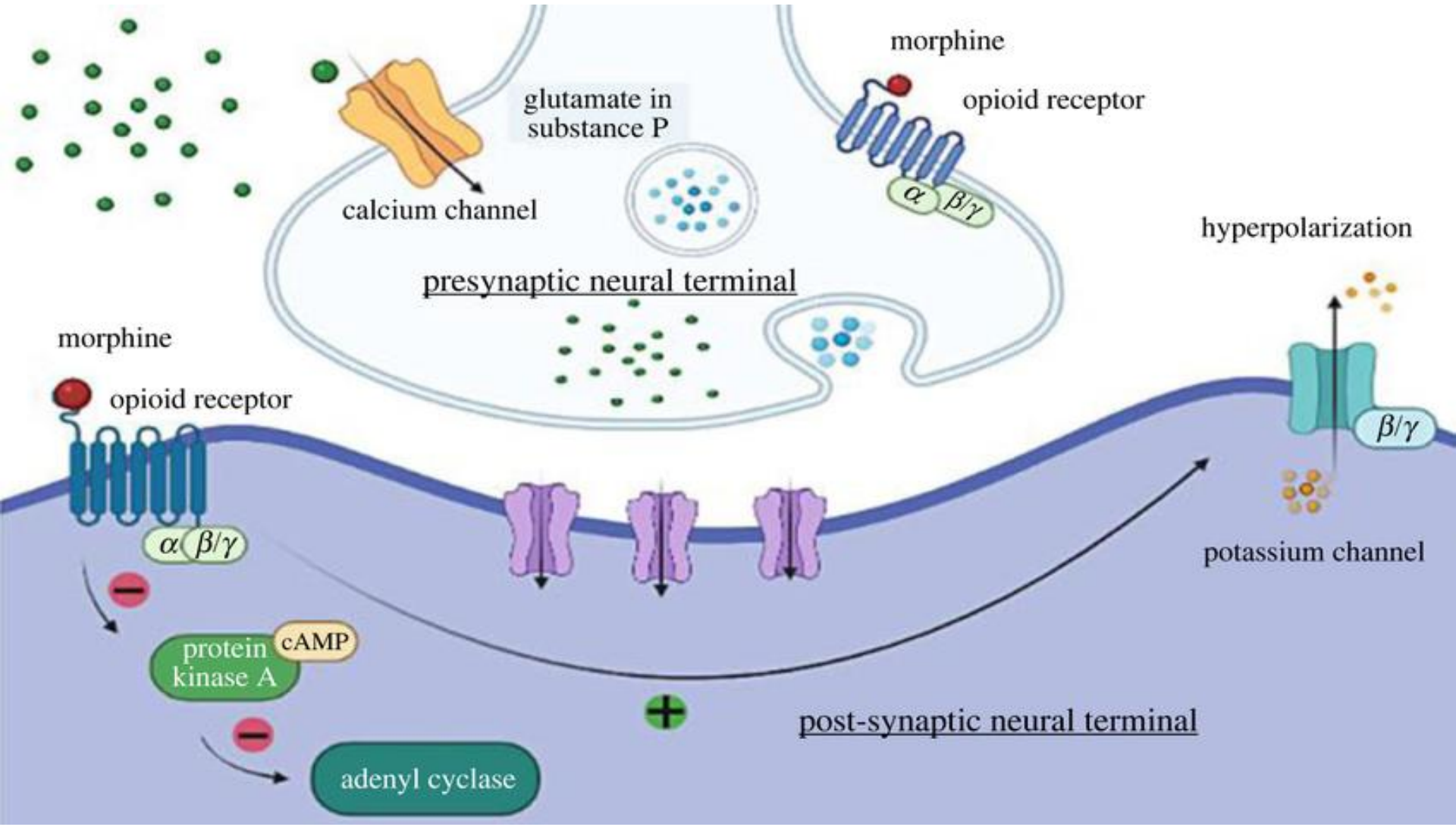
- Mu-1
  - Located outside spinal cord
  - Responsible for central interpretation of pain
- Mu-2
  - Located throughout CNS
  - Responsible for respiratory depression, spinal analgesia, physical dependence, and euphoria

Kappa Receptors

- Only modest analgesia
- Little or no respiratory depression
- Little or no dependence
- Dysphoric effects

Delta Receptors

- It is unclear what delta's responsible for.
- Delta agonists show poor analgesia and little addictive potential
- May regulate mu receptor activity



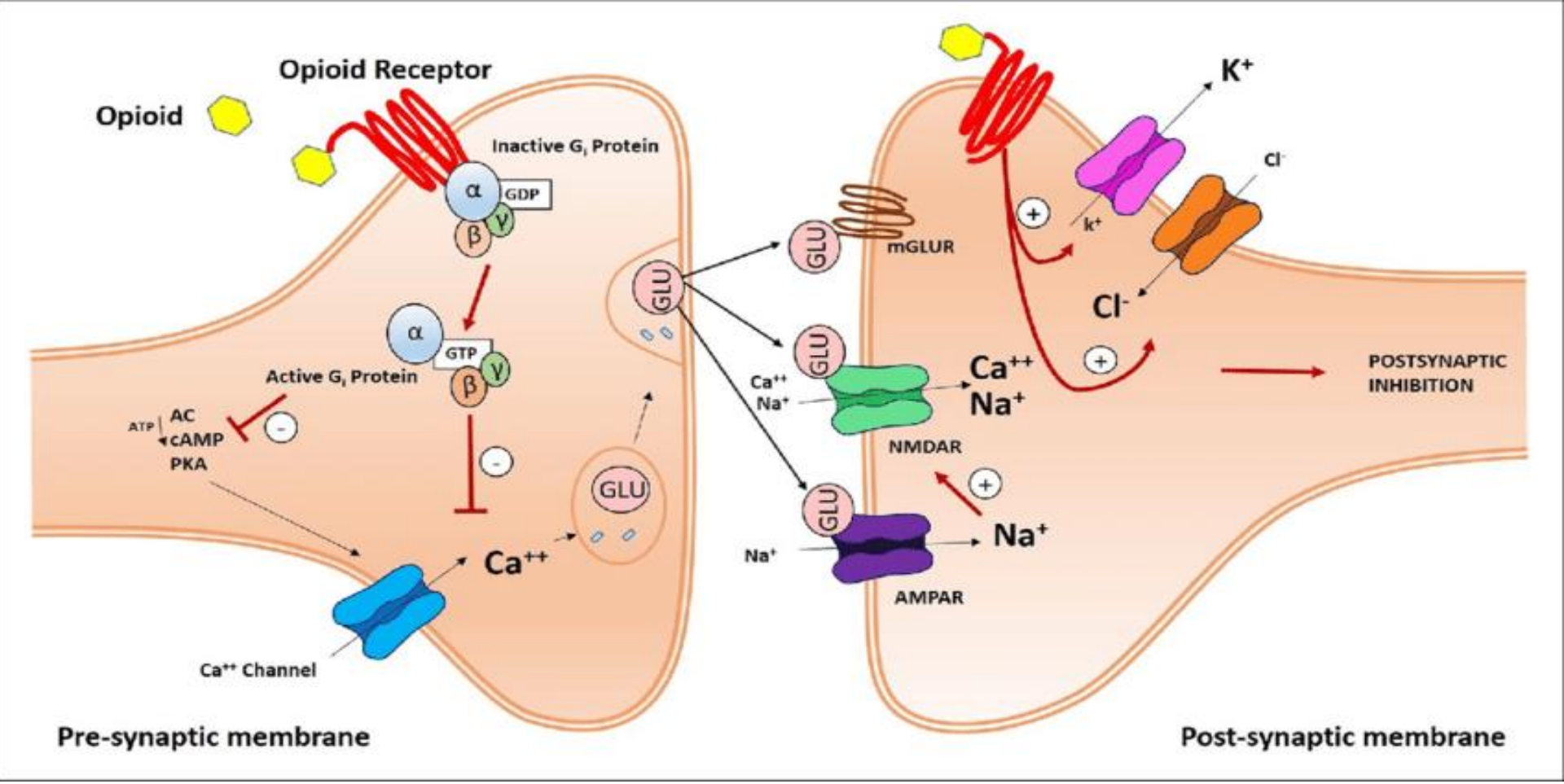
Mechanism of opioid binding to the target Mu opioid receptor at neural terminal

Mu and Kappa Receptor Activation

Response	Mu-1	Mu-2	Kappa
Analgesia	★	★	★
Respiratory Depression		★	
Euphoria		★	
Dysphoria			★
Decrease GI motility		★	
Physical Dependence		★	

Mu and Kappa Receptors

DRUGS	MU	KAPPA
Pure Agonists	Agonist	Agonist
Agonist-Antagonist	Antagonist	Agonist
Pure Antagonists	Antagonist	Antagonist



Schematic illustration of an opioid receptor-mediated synaptic pain pathway. In the presynaptic membrane, opioid peptides bind opioid receptors and activate G-proteins, thereby inhibiting Calcium (Ca ++) influx. G-βγ subunits then directly bind and inhibit Ca ++ influx. Activated G proteins can have the same effect by inhibiting adenylyl cyclase (AC) and, as a consequence, cyclic AMP (cAMP) and protein kinase A (PKA) activity. Ca ++ channel inhibition blocks glutamate (Glu) release from presynaptic vesicles and fast and slow excitatory transmission between primary and secondary neurons. Fast transmission is mediated by ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptors; slow transmission by metabotropic glutamate receptors (mGluR). Moreover, opioid receptors mediate postsynaptic inhibition of pain, by enhancing chloride (Cl −) influx and potassium (K +) efflux.

- Pure Agonist: has affinity for binding plus efficacy
- Pure Antagonist: has affinity for binding but no efficacy; blocks action of endogenous and exogenous ligands
- Mixed Agonist-Antagonist: produces an agonist effect at one receptor and an antagonist effect at another
- Partial Agonist: has affinity for binding but low efficacy

AGONISTS

- *Morphine
- *Heroin
- *Hydromorphone
- *Fentanyl
- *Codeine

- Antagonists

Naloxone

Naltrexone

Agonist–antagonist opioids

The best known agonist–antagonists are :

- buprenorphine
- pentazocine

Morphine

PHARMACOKINETICS

- Routes of administration (preferred)
  *Oral latency to onset (15 – 60 minutes)
- * it is also sniffed, swallowed and injected.
- * duration of action up to 6 hours.
- * First-pass metabolism results in poor availability from oral dosing.
- * 30% is plasma protein bound

EFFECTS AND MEDICAL USES

- *symptomatic relief of moderate to severe pain
- *suppression of severe cough (rarely)
- *suppression of severe diarrhea
- *AGONIST for mu, kappa, and delta receptors.

Hydromorphone

PHARMACOKINETICS

- *Routes of administration (Preferred) *Oral
- *latency to onset (15 – 30 minutes)
- *can be given Intravenous
- *Duration of Action (3-4 hours)
- *Peak effect (30-60 minutes)
- PROPERTIES AND EFFECTS
- * 7 times more potent analgesic as morphine.
- *used frequently in surgical settings for moderate to severe pain (cancer, bone trauma, burns, renal colic.)

Fentanyl

Pharmacokinetics

- Routes of Administration
  * Oral, and transdermal (possibly intravenous)
  *Highly lipophilic
  *latency to onset (7-15 minutes oral; 12-17 hours transdermal
  *duration of action (1-2 hours oral; 72h. transdermal)
  *80 – 85% plasma protein bound
  *90 % metabolized in the liver to inactive metabolites

Other properties

* 80 times the analgesic potency of morphine and 10 times the analgesic potency of hydromorphone.
*high efficacy for mu 1 receptors.
*most effective opiate analgesic

Naltrexone

PHARMACOKINETICS

- *latency to onset (oral tablet 15-30 min.)
- *duration of action 24-72 hours
- *peak effect (6-12 hours)

STRUCTURAL DISTINCTION

- *Differs from naloxone in structure.

EFFECTS

- *Reverses the psychotomimetic effects of opiate agonists.
- * Reverses hypotension and cardiovascular instability secondary to endogeneous endorphins (potent vasodilators)
- *inhibits Mu, Delta, and Kappa receptors.

Tolerance

- Tolerance is a diminished responsiveness to the drug's action that is seen with many compounds
- Tolerance can be demonstrated by a decreased effect from a constant dose of drug or by an increase in the minimum drug dose required to produce a given level of effect
- Physiological tolerance involves changes in the binding of a drug to receptors or changes in receptor transductional processes related to the drug of action
- This type of tolerance occurs in opioids

Dependence

- Physiological dependence occurs when the drug become necessary for normal physiological functioning – this is demonstrated by the withdrawl reactions
- Withdrawl reactions are usually the opposite of the physiological effects produced by the drug

Withdrawl Reactions

Acute Action

- Analgesia
- Respiratory Depression
- Euphoria
- Relaxation and sleep
- Tranquilization
- Decreased blood pressure
- Constipation
- Pupillary constriction
- Hypothermia
- Drying of secretions
- Reduced sex drive
- Flushed and warm skin

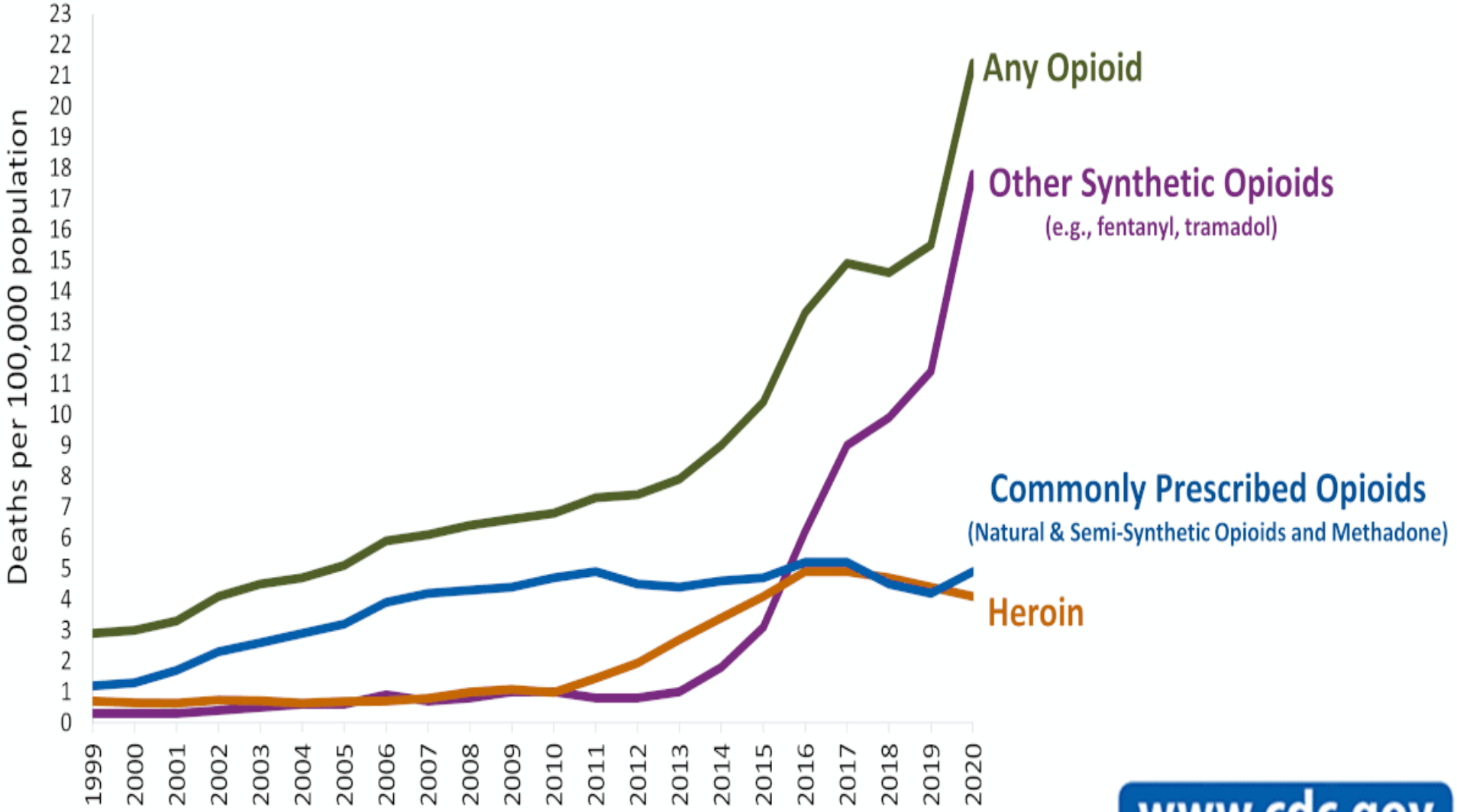
Withdrawl Sign

- Pain and irritability
- Hyperventilation
- Dysphoria and depression
- Restlessness and insomnia
- Fearfulness and hostility
- Increased blood pressure
- Diarrhea
- Pupillary dilation
- Hyperthermia
- Lacrimation, runny nose
- Spontaneous ejaculation
- Chilliness and “gooseflesh”

Dependence ...continued

- Acute withdrawl can be easily precipitated in drug dependent individuals by injecting an opioid antagonist such as *naloxone* or *naltrexone* – rapid opioid detoxification or rapid anesthesia aided detoxification
- The objective is to enable the patient to tolerate high doses of an opioid antagonist and undergo complete detoxification in a matter of hours while unconscious
- After awakening, the person is maintained on orally administered *naltrexone* to reduce opioid craving

Overdose Death Rates Involving Opioids, by Type, United States, 1999-2020



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.

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