**Terminology**
- Narcotic = any substance that causes sleep, overtime associated with opioids
- Opiate = substances structurally related to products found in opium (morphine, codeine, oxycodone, heroin)
- Opioid = opiates & endogenous opioid peptides

**Opioid receptors:** μ, κ, δ
- Belong to rhodopsin family of G-protein coupled receptors
- Differ mainly in extracellular loops
- Capable of dimerization, affecting receptor response
- Widely distributed: CNS & peripheral tissues

**Endogenous opioids:** occur naturally in CNS & bind to opioid receptors
- Each family derived from distinct precursor
  - Proenkephalin → enkephalin
  - Pro-opiomelanocortin (POMC) → endorphins
  - Prodynorphin → dynorphins
- Most active opioid peptides share common terminal sequence = opioid motif: Tyr-Gly-Gly-Phe-(Met or Leu)
- Endogenous opioids function as neurotransmitters and/or modulators
  - Often coexist with other neurotransmitters

**Opioids (μ selective) mechanism of action:** peripheral, spinal cord & supraspinal

**Peripheral MOA**
- Blocks ongoing nociceptor sensitization (by chemical mediators released from tissue damage)
- Reduces firing of spontaneously active peripheral sensory fibers in inflammation
  - NO EFFECT W/O INFLAMMATION
- Inhibits release of substance P from peripheral nerve terminals (which usually acts on mast cells (histamine) or blood vessels (edema))
  - Not affected by naloxone
- Activates opioid receptors on peripheral nociceptive neurons → intracellular signalling events → activation of neuronal NO synthase & NO production → increase in $K_{ATP}$ currents → hyperpolarization = inhibits spike genesis & input to spinal dorsal horn

**Supraspinal MOA**
1. Binds to μ receptors on inhibitory GABA-ergic neurons at PAG
2. Prevents release of GABA = disinhibition
3. Activation of descending inhibitory pathways from PAG
4. Decreased nociceptive transmission

**Spinal cord MOA**
- Presynaptic: binds to mostly μ receptors on central afferent terminal (Aδ or C fibers) → inhibition of voltage-gated $Ca^{2+}$ channel opening in afferent fiber = reduced NT release (substance P)
  - Reversed by naloxone
- Postsynaptic: binds to μ receptors on 2nd order (postsynaptic) neurons in dorsal horn → opens $K^+$ channels = outward K conductance → hyperpolarization = dampens excitation by glutamate/substance P

**Spinothalamic tract:** nociceptive 1st order neurons release glutamate (Aδ, fast mild pain) & substance P (C fibers, slow intense pain) onto 2nd order neurons in dorsal horn of spinal cord (nociceptive-specific neurons or wide-dynamic range neurons) which synapse onto 3rd order neurons in thalamus, which further projects to other areas in the brain & cortex

**Altered pain reaction**
- Opioids activate receptors in basal ganglia (NA) & mesolimbic system
- Involved in reward (dopamine release), pleasure, mood
  - Patients know pain is present but are indifferent to it

## Side Effects

**CNS side effects**
- Sedation: shortened sleep onset, disrupt REM sleep
- Mental clouding
- Euphoria/dysphoria
- Dreams/hallucinations
- Miosis

**CV side effects**
- Minimal until toxic levels reached
- Orthostatic hypotension: peripheral vasodilation & inhibition of baroreceptor reflex

**GU side effects:** urinary retention
- Inhibits urinary voiding reflex
- ↑ external sphincter tone (μ and δ receptors)

**DERM side effects**
- Flushing: dilation of cutaneous blood vessels (partly histamine release)
- Pruritis: disinhibition of itch-specific neurons in dorsal horn
  - Reversed by naloxone

**GI side effects**
- N&V
  - Direct stimulation of chemoreceptor trigger zone
  - ↓ peristalsis
  - ↑ intestinal secretions
- Constipation
  - Opioid receptors on myenteric plexus & secretory cells
  - ↓ peristalsis
  - ↑ high-amplitude non-pulsatile phasic contractions (= ↓ food movement) + ↓ intestinal secretions = ↑ water absorption → "solidifying" intestinal content
  - ↑ anal sphincter
  - ↓ attention to defecation stimuli

**Respiratory side effects:** respiratory depression (dose-dependent)
- μ an δ receptors directly depress respiratory rhythm generation in medulla
- ↓ excitability of brainstem chemosensory neurons
  - Don't respond to high $CO_2$
- ↓ ventilation driven by hypoxia (affects carotid & aortic body chemosensors)
- ↑ chest wall rigidity & ↓ patency of upper airways

**Increased risk:** other drugs (depressants, interactions); sleep (↓ sensitivity of chemoreceptors, especially obstructive sleep apnea); age (newborns, elderly); disease (renal or cardiopulmonary – desensitized to high $CO_2$); relief of pain (pain stimulates respiration)

## Opioid overdose & toxicity

**Terminology**
- Tolerance: ↓ in apparent effectiveness of a drug; different physiological responses develop tolerance at different rates
- Physical dependence: state of adaptation w/ prolonged use of drug → withdrawal syndrome
- Addiction: compulsive use & obsession with drug; high relapse rate

**S/S of acute opioid toxicity/overdose:** stupor, comatose, pinpoint pupils (dilated if severe hypoxia), low RR or apnea, cyanosis, cold & clammy skin, hypothermia, hypotension, shock

**Triad of opioid poisoning:** coma, miosis & respiratory depression

REVERSE WITH NALOXONE (μ antagonist)

**Opioid withdrawal**
- Mood: craving, restlessness, irritability, anxiety, insomnia, dysphoric mood
- Physical sx: nausea, muscle aches, increased sensitivity to pain
- Physical signs: mydriasis, sweating, piloerection, yawning, fever, tachycardia, increased BP, vomiting, diarrhea

## Various opioid characteristics

**Pentazocine:** κ agonist, weak μ antagonist (or partial agonist)
- Dysphoric & psychomimetic effects (high doses)
- Doesn't block respiratory effects of other opioids
- Ceiling effect to analgesia
- Can precipitate withdrawal in μ-agonist dependent patients
- Can be used in morphine allergic pts

**Nalbuphine:** κ agonist, μ antagonist
- Less dysphoric effects than pentazocine

**Oxycodone:** μ and κagonist
- CYP3A4 interactions significant

**Morphine:** strong μ agonist
- Morphine-6-glucoronide metabolite is toxic
  - → Accumulation of toxic metabolite in renal dysfunction

**Hydromorphone:** strong μ agonist
- Safe in renal dysfunction (palliative care, near-death care)
- Less side effects in some patients (sedation, NC)
- Given po, sc, im, iv, pr

**Methadone:** μ and δ agonist; NMDA antagonist; blocks reuptake of 5-HT & NE
- Treatment of opioid dependence
- Actions at sites other than opioid receptors = works better in "difficult to treat pain" (cancer or neuropathic pain)
- Long half-life
- Respiratory depression possible
- SEs: usual opioid side effects + QT prolongation, arrhythmias, MI, anticholinergic effects, seizures
- Interactions
  - Contraindicated with amiodarone
  - Cleared through CYP3A4
  - Is a CYP2D^ inhibitor

**Buprenorphine:** partial μ agonist
- Respiratory depression not major (but may have ceiling effect)
- Can cause withdrawal if receiving μ-agonist long-term or if drug is stopped
- Analgesic (injection) or treatment of opioid dependence (sublingual)
- Metabolized by CYP3A4

**Codeine**: weak opioid converted to morphine by CYP2D6
- Genetic variations in CYP2D6 = ultra-rapid or slow metabolizers
- Drug interactions with CYP2D6
- Antitussive at dose > 15 mg q4-6h
- Chronic use in renal dysfunction → toxic metabolites

**Tramadol:** weak μ agonist; blocks re-uptake of 5-HT & NE
- Centrally acting analgesic
- Reduces seizure threshold
- Tramadol (parent) = serotonergic effect
  - → Serotonin syndrome; risk increased if on SSRIs and CYP2D6 inhibited
- Tramadol → active metabolite by CYP2D6 which has opioid activity
- Contraindicated with MOAIs
- Decrease dose if CrCl < 30 mL/min
- SEs: dizziness, NVC, headache, somnolence

**Meperidine:** μ agonist, NMDA antagonist, blocks re-uptake of 5-HT
- Rapid onset, short duration = NOT for chronic pain
  - Used for acute pain
  - Alternative in cases of morphine allergy
- Toxic metabolite (normeperidine) accumulates over time, especially in renal dysfunction (= DON'T USE)
  - CNS toxicity: tremor, seizures
- Serotonin syndrome if also taking antidepressants (TCAs, SSRIs, SNRIs)
- Contraindicated with MAOIs
- Antimuscuarnic effects: can cause tachycardia
- Negative inotropic effects on heart

**Fentanyl:** potent μ agonist (transdermal)
- Initial onset delayed; NOT for opioid naïve or acute pain
- Heat increases absorption from patch; if irritates skin can use steroid spray or wait 1 min for alcohol to evaporate