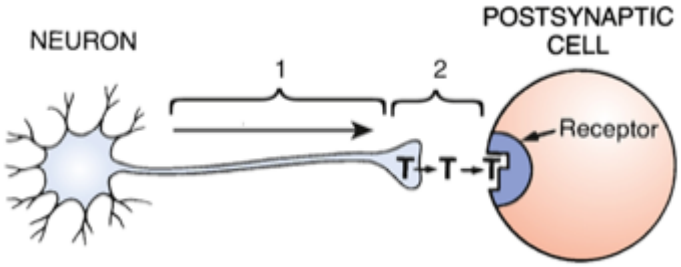
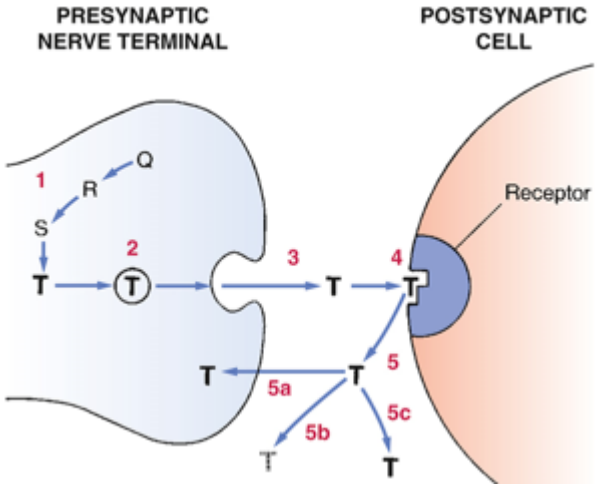
NeuroPharmacology (Ch. 12 & 20)

Neuropharmacologic Drug Action



2 main mechanisms that all drugs acting on the CNS/PNS share:

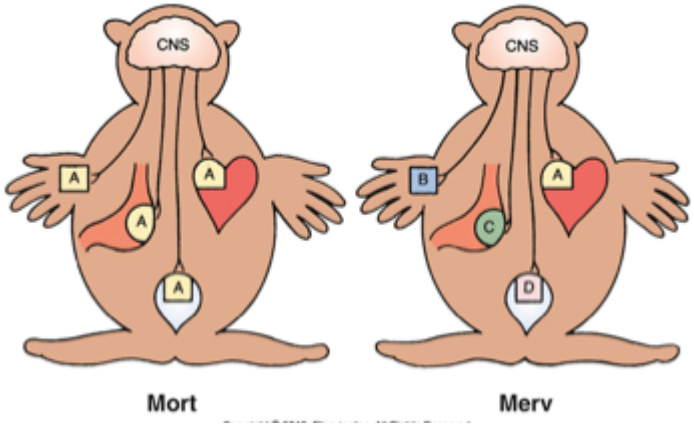
- They can either interact on the **axonal conduction (1)**: when the action potential is travelling from the cell body to the axon terminal.
- Or it can interact or interfere with the **synaptic transmission (2)** which is the process by which information is carried across the gap between the neuron and the post-synaptic cell
    - Most agents that we use today affect the synaptic transmission, either by increasing or decreasing the amount of NT, binding to the receptors of the NT…



There are several steps in which it can be altered:

1. Transmitter synthesis: altering or playing with that can either increase or decrease transmission. In the photo, steps Q,R, S produce transmitter (T)
2. Transmitter storage: putting the receptors in their little vesicles that then get released: can either increase or decrease transmission
3. Transmitter release: actual release of the vesicles with the NTs at the receptor on the other side of the synaptic cleft is triggered by the arrival of an action potential at the axon terminal

4. Receptor binding: transmitter molecules diffuse across the synaptic gap and then undergo reversible binding to receptors on the postsynaptic cell, initiating a cascade of events..
5. Termination of transmission by dissociation of transmitter from its receptors, followed by removal of free transmitter from the synaptic gap. Can be removed from the synaptic gap via different routes:
    a. 5a: Reuptake: axon terminal contains pumps that transport transmitter molecules back into the neuron from which they were released
    b. 5b: enzyme breakdown (happens following reuptake)
        i. NTs get broken down by enzymes or they get recycled… if you prevent 5a or 5b that means there are more NTs around increasing the effect.
    c. 5c: diffusion away from the synaptic gap
        i. Very slow and generally of little significance



This picture illustrates the fact that some of the receptors in the nervous system are more selective to certain types of NT. The picture is showing to contrast the scenario in which we only have one type of NT doing everything.

- Mort scenario: all the receptors are labelled as A, meaning all the receptors in our body are responding to a single NT. This means that whatever drug influenced your HR, would also affect your GI, bladder, skin, etc. This drug would have numerous amounts of adverse effects.
- Merv scenario: all the different targets have different receptors. If you give drug A, it should only affect the heart, etc.

In real life, we do not have either mort nor merv. We have certain NT that have more than one receptor. The more types of receptors we have to work with, the greater our chances of producing selective drugs.

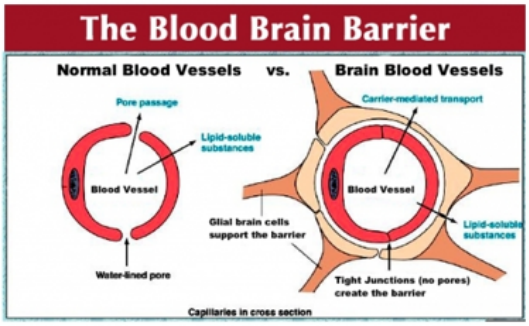
CNS Characteristics (Ch.20)

Drugs that we use that target the CNS usually target pain relief, seizure relief, anaesthesia, etc. But it is also the target for recreational drug use (stimulant/depressant; euphoria; hallucinations; etc).

Important to note, the effects on individual neurons: let's say I'm giving you a drug where its effects are to excite certain neurons, it shouldn't be translated as the overt functional effect (phenotype – what you're going to see), what we can see with our own eyes. It is possible that a drug has an excitatory effect on the neurons, but causes overt depression.

- Effects on individual neurons (ex: excitation/depression) DOES NOT EQUAL overt functional effects.

Ex: if you have neurons that act as a brake pedal, if the drug activates the brake pedal causing an excitatory effect on the neurons, but overt effect is that it will depress you.



- BBB separates the plasma from the brain with an extra protective layer to prevent harmful chemicals in reaching the CNS.
    - Protects against toxic substances: example a drug acting on the GI, you don't want it to also reach the brain and have some adverse effects. In this case, the BBB is good. Keep it in the blood, goes in other places.
    - Impairs therapeutic treatments: if you want it to reach the brain, the BBB would prevent that, your treatment would have a lower efficacy.
- Free lipid-soluble > ionized/protein-bound drugs
    - Most CNS drugs are lipid-soluble. They have an easy time crossing the BBB. They have a stronger effect on CNS.
    - Water soluble drugs don't go to the CNS, harder to treat or to cause adverse effects with them.
- Underdeveloped in infants.
    - BBB not matured yet, so vulnerable to CNS drugs.

Therapeutic Effects Disclaimer

- Limited CNS pathophysiology understanding → uncertainty of CNS agents action!
    - Mechanisms presented = plausible hypotheses/best educated guess
    - Almost always alters chemical synaptic transmission

    - This uncertainty is because of the high number of CNS transmitters (among other reasons). Their precise functional roles are unclear. The complexity of the brain clouds CNS drugs specific mechanism of action.
- High # of CNS transmitters
    - Unclear precise functional roles
    - Complexity clouds precise mechanism of action
- Affects psychotherapeutic R&D
    - Serendipitous findings - find something when we weren't looking for it
    - Poor animal models of psycho-pathologies
    - Small advances (ex: analog tweaking) vs. Major breakthrough (new molecules)
        - We try tweaking the drugs we already have rather than making new drugs from scratch.
    - Strong placebo component - either will enhance it or decrease the placebo effect
        - There is always a placebo effect in every drug, but with CNS drugs, the placebo effect is much higher.

<u>Chronic Exposure: CNS Adaptations</u>

Neuronal Plasticity!!

Because the brain is one of the organs that is very plastic (adjust/adapt), the effects of CNS drugs is much more likely to produce receptor up/downregulation, rebound effects, etc. The brain is particularly good at adjusting and creating a new state of homeostasis.

When a drug is taken chronically, their effects may differ from those produced during initial use. The brain's ability to adapt to drugs can produce alterations in therapeutic effects and side effects.

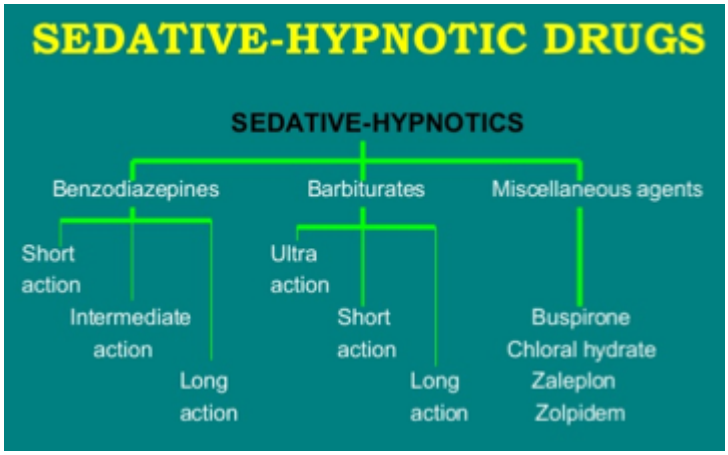
- Increased therapeutic effects (delayed onset)
    - Beneficial response from CNS adaptation rather than direct synaptic transmission alterations
        - Ex: antipsychotics & antidepressants
    - Some drugs have a delayed onset of the beneficial effects to appear, that's because it takes time for the brain to adjust to the presence of the drug. It is said that these beneficial effects are not coming directly from the drug itself, but from the brain readapting to the drug. The drug is there to create an incentive for the brain to do the work.
- Decreased adverse effects (habituation)
    - Phenobarbital sedation effect decreases over time while anti-seizure effects remain
    - Sometimes there are adverse effects when you start a medication, but once the brain has adjusted to its presence, the adverse effect will decrease over time.

- Tolerance & Dependence (review lecture 2)
    - Tolerance is a decreased response occurring of CNS adaptations
    - Physical dependence is a state in which abrupt discontinuation of drug use will precipitate a withdrawal syndrome. Withdrawal reactions continues until the adaptive changes have had time to revert, restoring the CNS to its pretreatment state.
    - Most drugs of abuse = CNS agents

SEDATIVE/HYPNOTIC DRUGS (Ch. 34)

Intro

- Family of CNS depressants - their main overt effect is to depress the brain
    - Hypnotics = promote sleep
    - Anxiolytics = decreases anxiety
- Most act on GABA receptors
    - Low dose → anti-anxiety
    - High dose → insomnia therapy
- Efficacy: benzodiazepine
- Safety: benzodiazepines >>> barbiturates
    - Both = "drugs of choice" for suicide → respiratory arrest
    - BZ: less tolerance and physical dependence, and less drug interactions >> barbiturates
    - Review table 34-1 for more details



Benzodiazepines (BZ)

Top 5 most prescribed benzos:

1. Alprazolam
2. Lorazepam

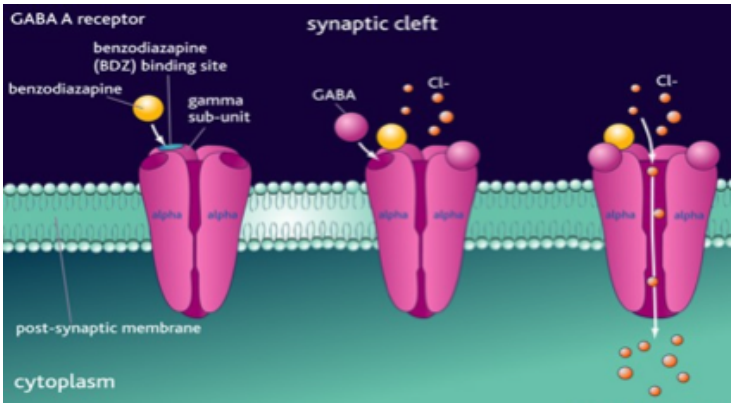
3. Clonazepam
4. Diazepam
5. Temazepam

Functions:

- Anxiolytic
- Antispasmodic
- Anticonvulsant
- Sedative-hypnotic
- Alcohol withdrawal management

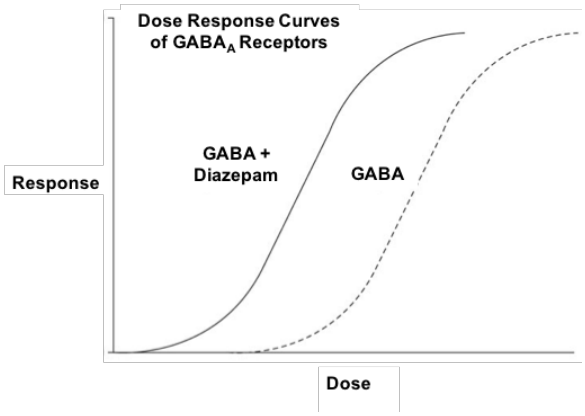
Mechanism of Action

Benzos bind to the GABA allosteric receptor. GABA is the brake pedal of the brain. Mainly inhibitory, depressing NT in the brain. On the picture below, GABA is the purple molecule and when it binds to its receptor (GABA receptor) it opens the receptor. GABA is a chloride ion receptor (ie. Chloride is negative ion). When the receptor opens, chloride goes into the neurons, hyperpolarizing it, making it more negative, making it more difficult to have an action potential in the neurons, thus decreasing the amount of activity in the neurons.
Benzos (yellow molecule in the picture), when it binds to GABA it binds to a different site, not competing with GABA. So when it binds to the receptor, the benzo increases the affinity of GABA for its own receptor.
*** benzos do not cause any action at GABA receptors by themselves. GABA binding is always required for channel opening. Benzos simply intensify the effects of GABA ***



The dotted curve is the normal dose-response of GABA alone.
When GABA combined with a Benzo, the curve shifts to the left, meaning that for the same amount of GABA in the body, you get a bigger response.

- This is a form of potentiation.



Kinetics & Usage

- Absorption: orally available
- Distribution: lipid-soluble → easy BBB crossing
- Metabolism:
    - CYP3A family hepatic enzymes → active metabolites
    - Parent drug half-life does not equal pharmacological effect half-life
    - Hepatic impairment → increased accumulation risk ++
        - Most metabolites are still active after liver metabolism.. It simply changes it into a different molecule. Therefore, you need to add up all the half lives of each molecule. Basically understand that it has a very long half life.

Nursing advice:

- Efficacy: there is not one better benzo than another. The choice of drug is based on the time course. If you want one for sleep, you'll choose one with a rapid onset, etc.
- Choice based on time course
    - Initiate sleep → rapid onset
    - Prolong sleep → slow-onset
    - Anxiety → intermediate
    - Repeated dosing → short half-life

Adverse effects/toxicity

- Common ADRs
    - Daytime drowsiness/decreased alertness
    - Anterograde amnesia → avoid triazolam
    - Sleep behaviors (ex. Sleep driving)
    - Paradoxical insomnia or anxiety
    - Respiratory depression → IV alone
    - Teratogenic → discontinue if pregnant or breast-feeding
- Tolerance

- Anxiety & hypnotic = low tolerance
- Antiseizure = high tolerance
- X-tolerance with other CNS depressants

- Dependence
  - Risk = very low
    - Have a high therapeutic index
  - Withdrawal Sx will resemble an anxiety disorder. You need to be weaned off
  - Alprazolam (xanax) > other BZ
- Serious Toxicity
  - BZ alone have a very low risk of toxicity
  - CNS depressant interaction (ex. Alcohol, opioids) → coma, respiratory arrest & death
  - 2% of IV admin (therapeutic doses!!) → severe hypotension; cardiac & respiratory arrest
  - Abrupt discontinuation of chronic use (especially short half life)

Barbiturates

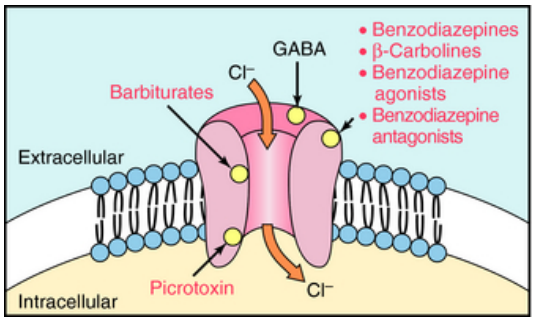
Used to be popular way back when. They are one of the oldest medications out there.

- 1864: founded by German chemist Adouf Von Baeyer
  - Used for anaesthesia at that time
- 1903: commercialized as veronal for its sedative and hypnotic effects
- 1911: phenobarbital synthesized and discovered to alleviate night seizures.

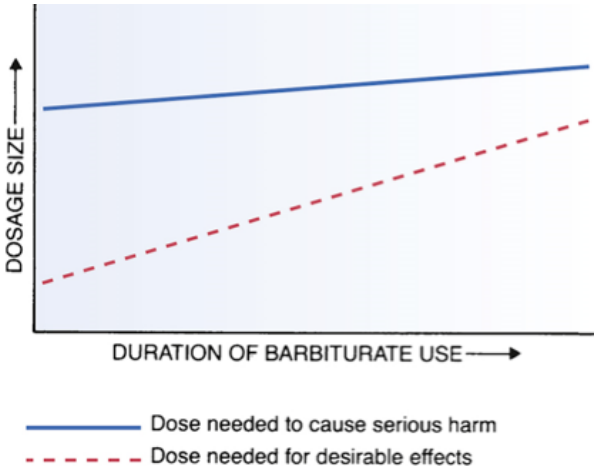
Mechanism & Effects

Barbiturates bind to the GABA receptor-chloride channel complex. By doing so, these drugs can enhance the inhibitory actions of GABA and directly mimic the actions of GABA. This is why it's much more dangerous than benzos. Because they directly mimic GABA, they have no ceiling

- Mostly used for:
  - ultra -short acting (ex: anesthesia)
  - Short to intermediate acting (ex: insomnia but rarely used anymore)
  - Long acting (ex: seizures)



- The blue line is the dose needed to get to the toxic effects
- Red dots are is the dose needed to get to the desirable effects of barbiturates.
- The graph shows that over time, the lines converge relatively quickly, becoming dangerous fast.



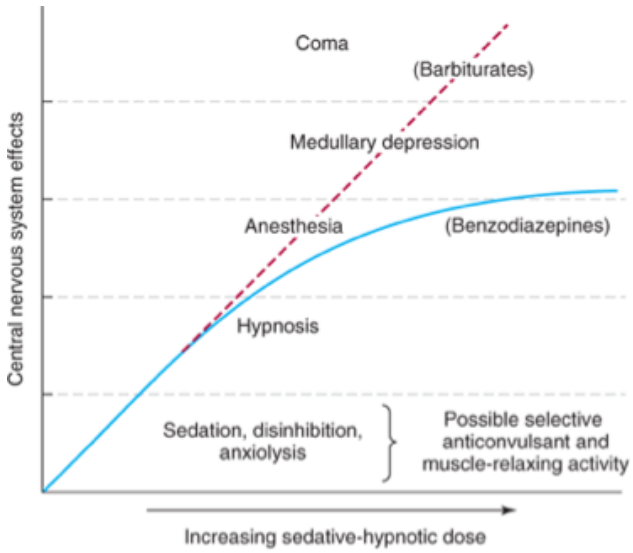
Effects:

- High risk of dependence & abuse
  - Cross-tolerance among barbiturates: this means that someone dependent on barbiturates can prevent withdrawal symptoms by taking any other CNS depressant.
- Powerful respiratory depressants → no tolerance develops against it
- Therapeutic tolerance > toxic tolerance
  - Tolerance develops to many - but not all - of their CNS effects. Specifically, tolerance develops to sedative and hypnotic effects and to other effects that underlie barbiturate abuse. However, even with chronic use, very little tolerance develops to toxic effects.
  - As tolerance builds, the doses need to be increased, causing the therapeutic dose to grow steadily closer to the lethal dose.

<u>Barbiturates vs. Benzodiazepines</u>

Nursing advices:

- Insomnia & anxiety: benzos >>> barbiturates
- Barbiturates usage: very rarely anymore



- Red line: the toxicity of the barbiturates increase almost proportionally
- Blue line: toxicity of the benzos tapers off (has a ceiling)

Benzodiazepine Receptor Agonists

	Zolpidem (Ambien)	Eszopiclone (Lunesta)
Usage Time	Short-Term	Unlimited (6-month safety study)
Therapeutic Usage	Sleep Induction & Maintenance	Sleep Induction & Maintenance
Other Infos	Peak [Plasma] ≈ 2 hours Half-Life ≈ 2.4 hours	Peak [Plasma] ≈ 1.5 hour Half-Life ≈ 6 hour Metabolism by CYP3A4

- These are drugs that are not benzo, and not barbiturates. They have a different chemistry. They bind only to alpha1-subunits of GABA receptors
    - Different GABA receptors have different subunits, and those subunits have different variations depending on genetics. Those with alpha-1 have hypnotic effects only. Because they are more selective for a specific unit, they have more selective effects.
- BRAs only have a hypnotic effect, without anxiolytic and anti-convulsive effects.
- ADRs/Toxicity Profile resembles BZ
    - Despite being more selective, the adverse effects are similar to those of benzos, same toxicity profile.

Nursing Capsule: Insomnia Management

- Insomnia = poor sleep quality → difficulty initiating/maintaining sleep
    - Common causes: disease; pain; anxiety
    - Common symptoms: daytime drowsiness; mood swings; concentration deficits
- Management

- Treat underlying cause if known medical condition
- 1st line treatment: non-drug therapies
  - lifestyle/sleep hygiene changes (ex. Decreased caffeine & nicotine; exercise; relaxation)
  - Cognitive behavioural therapy > drug therapy
- Hypnotic therapy → only if above methods failed
  - Discontinuation > dose escalation
  - Contraindication: pregnancy, respiratory diseases (COPD, sleep apnea)
  - Minimize dependency → lowest effective dose for shortest time period
  - Best choices = benzodiazepines (ex. flurazepam) & its agonists (ex. Zolpidem)

Nursing Capsule: Sedative-Hypnotic Administration

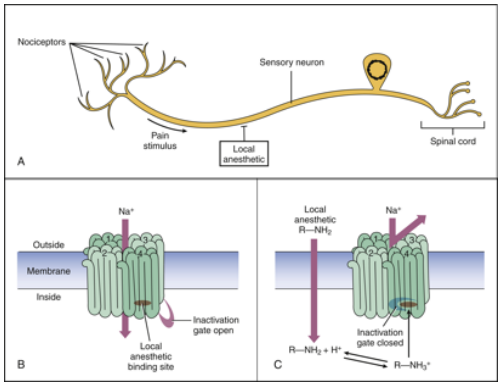
For insomnia treatment, all hypnotics should be taken shortly before bedtime.

- Benzodiazepines
  - Oral = preferred
  - IV = critical care & emergencies (ex. Alcohol withdrawal)
  - Avoid IM (except psychiatry)
  - Flumazenil = benzodiazepine antidote for sedation / Not for respiratory depression!
- Benzodiazepine agonists: all PO available

LOCAL ANESTHETICS (Ch. 26)

Mechanism of Action

The mechanism of action of local anesthetics are to block voltage-gated sodium channels which are found on the neuron's axon. By blocking the sodium channels, this prevents sodium from entering the cell, stopping the action potentials, and thereby blocking the conduction.



- Time course
  - Onset: membrane crossing properties (ex. polarity)
    - You want ideally a fast onset
  - Duration: crossing properties + regional blood flow
    - Duration is as needed depending on the procedure being done.
    - The more blood flow that goes to that region, the more quickly that drug can be "washed away" and metabolized by the liver more quickly =

shorter duration. Whereas, if the drug is in a region with low blood flow, the drug remains in the region longer, therefore being metabolized more slowly = longer duration.

- Combination with Epinephrine
    - Epi causes vasoconstriction of blood vessels. This causes the drug to remain in the region longer, decreasing its absorption, and therefore increasing its duration.
- Selectivity
    - Local anesthetics are nonselective modifiers of neuronal function. The only way to achieve selectivity is by delivering it to a limited area.
    - Blockade develops more rapidly in small unmyelinated neurons because those are usually the pain neurons. The larger myelinated neurons are typically the motor neurons, which can also be affected, it just takes longer for the effects to show.
    - Decreased pain > temperature > touch/pressure > motor

<u>Kinetics & Toxicity</u>

Pharmacokinetics

- Absorption: depends on blood flow at the site of administration
- Distribution: throughout systemic bloodstream
    - Concentration too low to have effects anywhere else than local site
- Metabolism: ester-types = in plasma vs. amide-types = hepatic enzymes
    - Metabolism of ester-types are metabolized in the plasma by plasma esterase, while amide-types are metabolized in the liver by hepatic enzymes
    - If absorption >> metabolism → toxicity increase
    - If metabolism >> absorption → decreased therapeutic success

Toxicity

- Distant effects > local effects
- CNS inhibition → coma; respiratory depression
- Heart inhibition → HR & SV decrease; cardiac arrest
- Vascular smooth muscle relaxation → hypotension
- Allergic reactions → esters > amides
- During delivery: increased labor + cross placenta
- Topical benzocaine in children → risk methemoglobinemia increase (a disorder in which Hb cannot release oxygen to its tissues)

History Capsule - Cocaine: the 1st local Anesthetic

- Excellent local anesthetic
  - Would block the sodium channels, just like the local anesthetic now (no pain)
  - Nowadays: we use lidocaine/procaine: cocaine that's modified to not give you a high and other adverse effects
- Substantial abuse potential
- CNS stimulant → risk of seizures
- CVS effects → increased HR & vasoconstriction

Esters vs. Amides

most are derivatives of cocaine with decreased CNS penetration

Procaine

- Injection only - ineffective topically
- Very low systemic toxicity
- Used to be 1st choice, replaced by amides due to **allergy risks**
- **Method of metabolism: plasma esterase**

Lidocaine

- Topical + injection
- Onset/duration/efficacy > procaine
  - Because it is metabolized by the liver, the duration is longer.
- **Allergy risk = 0**
- Systemic toxicity possible (ex. Liver failing)
- Useful for cardiac dysrhythmias - suppresses cardiac excitability
- **Method of metabolism: hepatic enzymes**

Clinical use of local Anesthetics

- Topical administration (lidocaine = preferred drug)
  - Relieve surface (ex. Burn, insect bites) or internal membrane (ex. Anal fissures) pain/irritations
  - Avoid large surface application + minimal effective dose = decreased systemic toxicity
  - EMLA patches → pediatric patients 1h prior to injections (ex. vaccines)
- Injection administration (choice of drug depends on duration and method)
  - Performed by a specialized HCP (ex. Anesthesiologist, dentist, NP)
  - Serious toxicity when IV injection → resuscitation equipment readily available
  - NEVER epinephrine combination at extremities (ex. Toes, nose, penis) → increases gangrene risk +++

- Contraindications
    - Use of any ester agents in patient with ester allergic reaction history
    - Topical benzocaine in children < 2 years old

GENERAL ANESTHETICS (Ch. 27)

Inhalation anesthetics

Goal: loss of all senses and consciousness

General anesthesia Discovery

1846 by William Morton

- Using Ether was applied on a piece of cloth and placed it on people's mouths

Before that….

- Strong men and straps holding you down
- Best butcher: fastest one = decreased bleeding = increased survival chance
- Allowed for: development of modern surgical procedure + increased patient safety & surgical success
- Surgeons can now take their time to operate

Basic Principles

Ideal properties

- Analgesia
- Unconsciousness
- Muscle relaxant
- Amnesia
- Large margin of safety
- Pleasant induction & emergence
- Efficient depth of anesthesia manipulations

Balanced anesthesia

- Combination of agents decreases effective dose → increased safety
- Most common agents and their best property
    - Induction → Propofol or short-acting barbiturates
    - Analgesia → opioids or nitrous oxide (NO)
    - Muscle relaxation → neuromuscular blockers

Hypothesized mechanism of action

- Old theory:
    - neuronal membrane dissolution → decreased transmission

    - Dismissed: same dissolution potential meant no anesthesia
    - Lipid-soluble would dissolve in cell membrane and disrupt action potential
- New theory
    - Increased inhibitory transmission + decreased excitatory
    - All potentiate GABA / except NO (NMDA inhibition) → blocking excitation and promoting inhibition
    - All depress, potentiate GABA, block excitation and promote inhibition.

<u>Pharmacokinetics & MAC</u>

Kinetic Properties

- Lung uptake proportional to
    - Inspired air concentration
    - Blood solubility & supply to lungs
- Distribution proportional to
    - Organ cardiac output (regional blood flow)
    - Ex: brain, liver, heart, kidney
- Export in expired breath
    - Same factors as uptake & distribution
    - Ex: decreased brain levels > skin & muscles
    - Hepatic metabolism = 0
    - No impact on time course of action

MAC = Minimum Alveolar Concentration

- Is the minimum concentration of drug in the alveolar air that will produce immobility in 50% of patients exposed to a painful stimulus.
- Potency index: small MAC = high anesthetic power
- Determines inspire air concentration for each agent
- Dose administered = 1.2-1.5x the MAC
- MAC influenced by external factors
    - Factors that decrease MAC (increase potency) - all some form of CNS depressant
        - Acute alcohol use
        - Advanced age
        - Anemia
        - Benzo
        - IV anesthetics
        - Hypotension
        - Hypothermia
        - Opiates

- Factors that increase MAC - CNS stimulants
  - Cocaine
  - Amphetamines

Major Inhalation Anesthetics

Nitrous Oxide

- Very low potency but very high analgesia
- Adjunct to primary anesthetic → decreases required dose
  - MAC is 105% and cannot work alone because it is impossible to give more than 100% (percentage is relative to atmospheric pressure). This means that there isn't enough pressure on the planet to induce anesthesia with this gas.
  - It is combined with other inhalational agents to enhance analgesia.
- Very safe for CNS, heart & respiration
- ADRs = postoperative nausea + vomiting

Isoflurane

- Very high potency (low MAC)
- Excellent depth of anesthesia management
- Elimination via expired breath = 100%
- ADRs = hypotension & respiratory depression
- Poor analgesic… needs to be combined

Serious ADRs of volatile anesthetics

- Respiratory & cardiac depression (almost all)
- Ventilation support almost mandatory
- Malignant hyperthermia (all except NO)
  - Muscle rigidity & severe increase in temperature
  - Risk factors: family history & when combined with succinylcholine

Nursing Capsule: Administration & Adjuncts

- Dosage & administration
  - Anesthesiologist (physician) & anesthetists (trained nurse) ONLY
  - LOTS of drugs combined + low therapeutic index = medical specialty
- Adjuncts → complement therapeutic effects or decrease adverse effects
  - Preanesthetics
    - Benzo (ex. IV midazolam) → decrease surgery anxiety & increased amnesia
    - Opioids (ex. fentanyl) → preoperative pain & cough suppression

- Alpha2-adrenergic agonists (ex. clonidine) → decreased anesthetic dose required + decreased anxiety
- Anticholinergic agents (ex. atropine) → decrease risk of anesthesia-induced bradycardia
- Neuromuscular blockers (ex. succinylcholine) → prevent muscle twitches & resistance
  - Flaccid paralysis state → risk of waking up with no way of letting the surgeon know!

- Post -anesthetics
  - Analgesics decrease post-op pain (ex. opioids)
  - Antiemetics decrease nausea & vomiting (ex. ondansetron)
  - Muscarinic agonists (decrease abdominal distension & urinary retention (ex. bethanechol)

IV anesthetics

Adjunct therapy or effects that cannot be achieved by volatile anesthetics

Propofol

- Actions & usage
  - Most popular (90% of anesthetic patients)
  - Increase GABA release → CNS depression
  - Uses: anesthesia induction & maintenance
  - Fast induction but short duration → low dose infusion
- Adverse Effects
  - VERY narrow therapeutic range!!!
  - Profound respiratory depression + hypotension
  - Lipid-soluble formulation → increased bacterial infection
  - Propofol infusion syndrome (rare): occurs if prolonged high dose infusion
    - Metabolic acidosis + Renal failure + cardiac failure + rhabdomyolysis
    - Monitor creatine PhosphoKinase (>5000/L = STOP)
- Nursing reality: propofol abuse
  - Not regulated substance → accessible
  - HCPs use it for quick naps
  - Activates brain reward center
  - Wake-up refreshed + elated
  - Overdose risk = very high

Benzodiazepines & Ketamine

- Diazepam
  - Large doses = unconsciousness + amnesia
  - Induction use; fairly safe
- Midazolam
  - Midazolam + opioid = conscious sedation
  - High risk of cardiorespiratory arrest
- Ketamine
  - NMDA blocker → dissociative anesthesia (when you see yourself from an out of body point of view)
  - Adverse psychological effects
    - Hallucination & delirium (=12% pts)
  - Controlled substance → drug abuse
  - Therapeutic usage
    - Minor surgeries/diagnostic procedures
    - In burn victims it is used to increase their cardiac output
  - Ketamine usage has increased due to the opioid crisis

OPIOIDS: CNS ANALGESICS (Ch. 28)

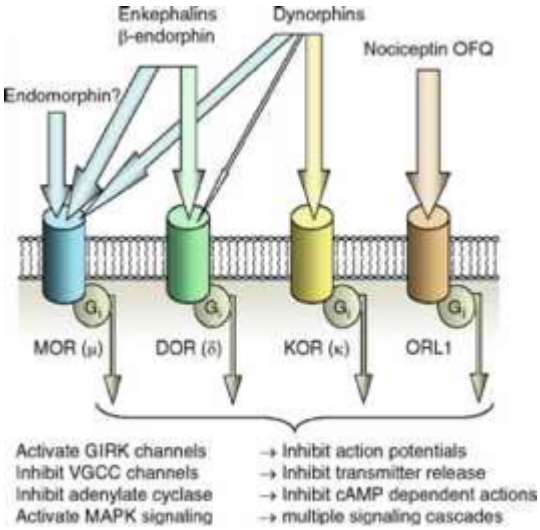
Opioids & Receptors

- Opioids are made from the opioid juices of the poppy plant
- They are classed based on their analgesic power, some are stronger than others.
  - Loperamide has no analgesic power, so they are not classified here
  - Strong analgesia: morphine and fentanyl
  - Moderate analgesia: codeine and hydrocodone
- The site of action are the different opioid receptors found in the brain, spinal cord and the GI. that is why the opioids cause constipation as a side effect.
- The receptor we are most interested in is the Mu receptor
  - Receptor that does everything (see picture below)
  - Especially responsible for the analgesia effect

Important Responses to Activation of Mu and Kappa Receptors

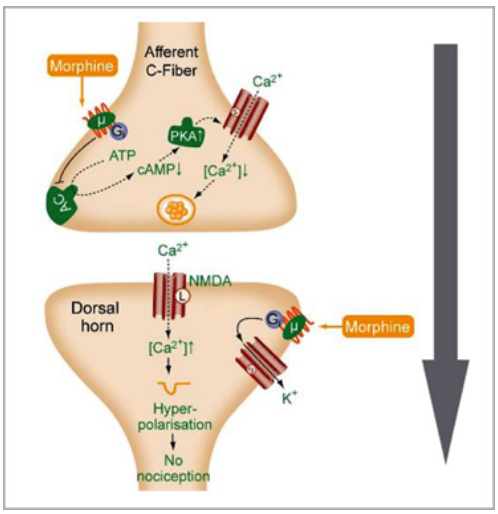
Response	Receptor Type	
	Mu	Kappa
Analgesia	✓	✓
Respiratory depression	✓	
Sedation	✓	✓
Euphoria	✓	
Physical dependence	✓	
Decreased GI motility	✓	✓

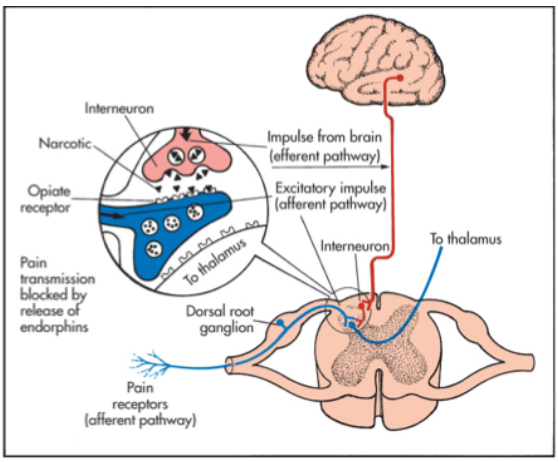
- Endogenous opioid peptides
    - We have a lot of endogenous opioid peptides which means they are peptides (proteins) similar to opioids. These are molecules released when you have pleasurable experiences or when you exercise.
    - They are called endorphins and enkephalons that are released by the brain. They also bind to the Mu receptors.



<u>Opioid Analgesic Action</u>

- Pain Modulation pathway → moderate to strong analgesia
    - They decrease the intensity of the pain signal, they don't block the pain signal at the site of the injury but rather in the spinal cord before it reaches the brain.
- No loss of consciousness & no other sense impairment
- One of the effects that opioids have that other analgesics don't have is that on top of modulating the pain response, they also change our interpretation of pain.
- Pain is a subjective measure for every individual.





Pathway:

- On the neuron, the morphine will bind to the Mu receptor on the presynaptic neuron and on the post synaptic neuron.
- On the presynaptic neuron, the binding of morphine will block the release of calcium into the presynaptic neuron (which in turn prevents the release of the vesicles on the post-synaptic). The end result is that you have barely any NT that are released towards the post-synaptic.
- At the same time, morphine binding to the post-synaptic neuron causes the opening of potassium channels, hyperpolarizing the cell, making it harder to stimulate (can't get an action potential).

<u>Other Opioid Effects</u>

- Respiratory depression
  - Most serious adverse effect
  - Tolerance develops long-term
  - Interaction with CNS depressants
  - Assess breathing frequency prior to giving the medication
  - Threshold = < 12breaths/min
  - Indirect ADR → increased intracranial pressure
- Constipation
  - Decreased gut mobility & fluid secretions
  - Management: exercises + fiber diet
  - Severe: laxatives + stool softener
  - Therapeutic effects:
    - Severe diarrhea therapy (1st usage)

        - Opioids that don't cross the BBB
        - Ex: loperamide
- Euphoria
    - Increased pain relief + risks of abuse
- Neurotoxicity
    - Decreased risk via opioid rotation
- Teratogen
    - Before conception + early pregnancy
- Sedation
    - Problematic for 'outpatients'
- Cough suppression
    - Risk of airway secretion accumulation
    - Therapeutic effect
        - Moderate agonists
        - Ex: codeine or hydrocodone

<u>Tolerance & dependence</u>

- Tolerance
    - Analgesia, euphoria, sedation and resp depression
    - cross -tolerance (and dependence!) between opioids
- No tolerance
    - Miosis (pupil constriction) & constipation
    - No cross-tolerance with CNS depressants (additive effect)
    - Cross-tolerance between opioid agonists
- **Environmental/Behavioral tolerance**
    - Environmental/behavioral tolerance: not only do you develop tolerance to a drug, but it seems that people who take drugs always consume them in the same location. For example, if someone usually takes a high dose of a drug in their home, but now they take the same dose but somewhere different, this can cause a shift in tolerance, leading to resp depression. It is believed that being in a different location causes a subconscious stress, making you more reactive to that same dose.
- Dependence/Withdrawal Syndrome
    - Intensity depends on half-life
    - Short (ex. morphine) = intense but brief
    - Long (methadone) = mild but prolonged
        - this is why it is used when someone is in withdrawal, it helps to cushion

- Withdrawal syndrome
    - Onset: ~ 10 hours after the last dose
    - About 7-10 days long
    - Symptoms: muscle spasms, GI distress, irritability
    - Almost only long-term users (>1month)
    - Extremely unpleasant but not lethal like CNS depressants
    - Gradual discontinuation decreases syndrome intensity (decrease the dose every 3 days)

Nursing Reality: Opioid Abuse

- People are hooked by the euphoria/sedation effect of it
- The use of opioids is maintained by the fear of withdrawal

Clinical Concerns

- Opioid under treatment by HCP = 75%
- Irrational fear of dependence/addiction
- Very rare in clinical setting
- Drug associated to painful experience
- Mostly acute treatment (< 3 weeks)
- Few cases = abuse-prone individuals
- Give benefit of the doubt to the patient!

<u>Strong Agonists: Morphine</u>

- Reference strong opioid agonist
- Extensive 1st pass effect → PO dosage compared to IV/IM/SubQ
    - It has a lot of 1st pass effect, that is why it is often given IV, IM or SC.
    - Still given orally, but in higher dosage
- Poor BBB crossing → increased toxicity in infants (immature BBB)
    - Even though it has poor BBB crossing, there is enough that gets across in infants, increasing the risk of toxicity.
- Therapeutic Usage: chronic severe pain
    - Subcut: most common on floors
    - Oral = administer every 4h
    - IM = only CR slow injection over 4-5 minutes
    - Epidural = long duration (about 24h) for spinal analgesia

Heroin:

- Heroin is morphine but more lipid-soluble (can cross the BBB).
- Has no therapeutic usage today, because it is too potent and highly addictive

Question: what is the origin of the names Morphine & Heroin?

- Morphine comes from the greek god's name Morphus which is the god of dreams
- Heroin comes from the soldiers that were given heroin to not feel fear and be less sensitive to pain in war, they were referred to as heroes.

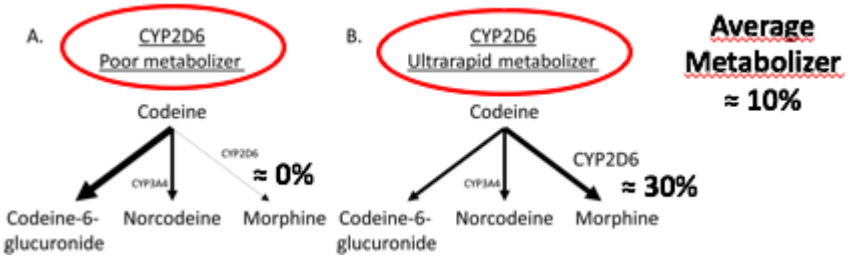
<u>Fentanyl</u>

- It's 100x more potent than morphine.
- Carfentanyl is 100x more potent than fentanyl.
- Metabolized by CYP3A4
- High risk of toxicity (ex: resp depression)
- Therapeutic usage:
    - IM or IV: surgical anesthesia induction/maintenance
    - Skin patch: persistent/severe pain in opioid tolerant patients
    - Transmucosal (ex: lollipop lozenge): Cancer breakthrough pain in very tolerant patients already on opioids around-the-clock

<u>Other Strong Opioid Agonists</u>

- HYDRO/OXYmorphone
    - Replaced morphine for most pain management
    - Among the most prescribed in clinical settings
- Meperidine
    - Not used very much anymore (safety issues)
    - Specific uses: post-anesthesia shivering
- Methadone
    - CYP3A4 metabolism
    - Longer duration than morphine
    - Used for opioid addiction therapy
        - Because of its longer half-life, it is safer and easier to control. Withdrawal symptoms are milder
    - Decreased withdrawal symptoms + suppressive therapy

Moderate Opioid Agonists



- Codeine is the most famous.
- Less pain relief but less chance for resp depression (as compared to morphine)
- Codeine: is sort of a pro-drug. In order to be active, it needs to be transformed into morphine. It's a weaker analgesic because not all the codeine is being transformed into morphine (only a percentage of the same response).
- Codeine is metabolized by CYP2D6, and there are people who are ultra-rapid metabolizers, meaning they metabolize more of the codeine into morphine. So they would need a smaller dose of codeine.
- While others have poor metabolizing CYP2D6 which means that the codeine they ingest, is metabolized into anything else but morphine because the CYP2D6 doesn't work.
    - The only way to find out is via trial and error.

Therapeutic usage of

- Codeine:
    - Alone or combined with NSAIDs for moderate analgesia
    - Excellent cough suppression
- Hydro & Oxycodone
    - Similar to codeine for analgesia
    - All available for PO
    - Oxy:
        - alone or combined
        - long acting controlled-release formulation available
        - CYP3A4 metabolism
    - Hydro:
        - Most prescribed drug in the US
        - Always combined to NSAIDs or antihistamines

Nursing capsule: Clinical Considerations of Opioids

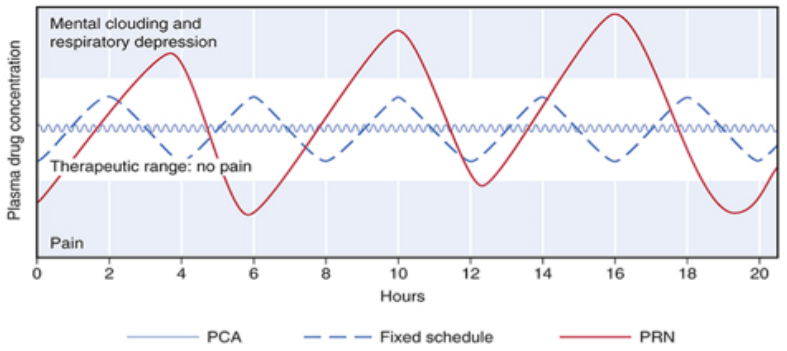
- High risk patients
    - Respiratory impairments: asthma, COPD
    - Head injuries → increases ICP

- Pregnant women → teratogen + baby dependence
- Infants & elderly → increases resp depression (dosage must be < adult dose)

- Pre-administration baseline
  - Respiratory rate, pulse & BP → withhold Rx if any decrease below baseline
  - Pain assessment → very subjective experience → risks of over-reporting & under-reporting
- Minimize abuse (real but small risk)
  - Smallest effective dose + switch to non-opioid analgesics ASAP
  - If abuse suspected: opioid/naltrexone tablets → antagonist works only if crushed or injected
    - When the naltrexone tabled is combine, it doesn't work PO. but when crushed or injected, it prevents the effects of the opioids from occurring.
- Minimize withdrawal reactions
  - Increased risk if high doses > 20 days → taper dosage over 3-10 days → decrease intensity of withdrawal symptoms.

<u>Administration Guidelines</u>

- Dosage determination
  - Open chest surgery > appendectomy
  - Adults > infants or elderly
  - Opioid tolerant > opioid naive
- Dosing schedule
  - Fixed 4 hour schedule = preferred
  - Decreases pain fluctuations & anticipatory anxiety
  - Subcutaneous on floors vs. IV in ICU
- Patient-controlled Analgesia (PCA)
  - Patient self-administration → device "lock-out timer" prevents overdose
  - Small doses at frequent intervals → decreases fluctuations → increased pain relief + decreased adverse effects
  - PCA associated with decreased hospital stay + increased physical therapy cooperation vs. fixed-schedule
  - Patient & family education = crucial for proper usage & success of PCA



Opioid Usage for Specific Pains

- Post-op
  - Decreased pain + increased movement autonomy & intentional cough
- Obstetric analgesia
  - drawback : fetal respiratory depression & decreased uterine contractions
  - Favor fentanyl and newer derivatives → short action + decreased feral impairments
- Myocardial infarcts
  - Decreased pain & BP = decreased cardiovascular demand = better cardiac recovery
- Head injuries
  - Very cautious due to increased ICP risks + hiding useful diagnosis signs (ex. Miosis, vomiting)
- Cancer-related pain (usually chronic)
  - Objective = maximize pain relief
  - Increased risks of dependence & tolerance = secondary concerns
- Chronic non-cancer pains
  - Balance 'patient rights vs. HCP concerns'
  - Try alternative pain relief first / monitor Rx & adherence more closely

Naloxone & Opioid Overdose

- Opioid Overdose Classic triad
  - Coma → profound/no arousal
  - Pinpoint pupils (miosis) → may dilate later with hypoxia
  - Respiratory depression → 2-4 breaths/min
- Opioid overdose treatment
  - Ventilatory support + Naloxone injection
- Opioid Antagonists: Naloxone
  - Given IV, IM or SubQ (not PO because of rapid 1st pass inactivation)
  - Reverses most effects of opioid agonists
  - A pt can be put in a state of acute withdrawal when naloxone is administered
  - Has a short-half-life → ~ 2 hours
    - might need to give repeated doses until pt gets to ER safely to be monitored
  - Other therapeutic uses: neonatal & post-op respiratory depression

N.B. Naloxone is an antagonist that has one of the highest affinities to the opioid receptors.