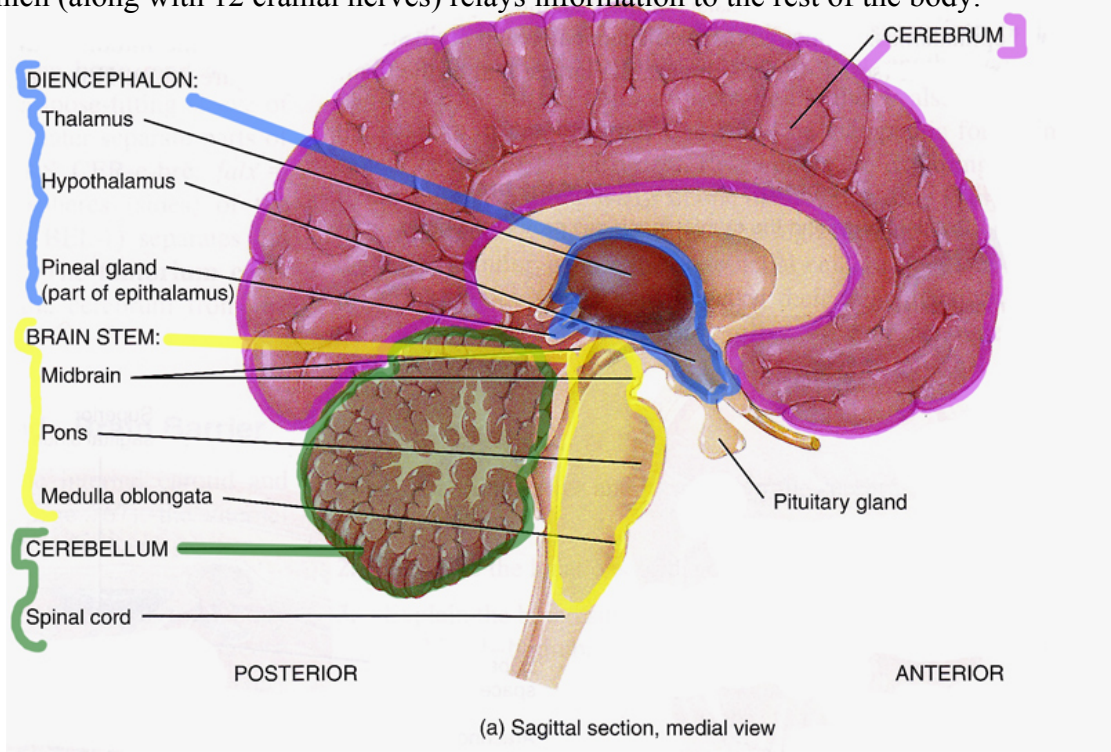
CNS REVIEW

Anatomy

(See my video "Brain Anatomy for Intro to Pharm")

The "higher order" thinking part of the brain (the cerebrum) surrounds a more primitive part of the brain (the diencephalon) that surrounds the most primitive "just stay alive" part of the brain (the brain stem). Sitting behind the brain is the cerebellum. All of this sits atop the spinal cord, which (along with 12 cranial nerves) relays information to the rest of the body.



(a) Sagittal section, medial view

THE CEREBRUM

Cerebral Cortex (Grey Matter): brain cell bodies + **Cerebral Medulla** (White Matter): all the connections between the cells in the grey matter

Contains areas important **for voluntary actions**, thinking, speaking, reading, memory, personality, intelligence and such "higher order" human thinking-type things.

Also contains or contributes to the

Basal ganglia - also called the **EPS** (extra pyramidal system): coordinates gross muscle movements, some unconscious movements, starting/stopping movements and muscle tone

Amygdala (part of the "**Limbic System**") - regulates emotional and behavioral response to stress and threats to survival. i.e. fear, rage, anxiety.
Also **linked to addictive behavior.**

THE DIENCEPHALON

Pineal gland - **Circadian Rhythms** and sleep cycles (secretes melatonin)
- very important in dealing with insomnia

Hypothalmus - Controls and **regulates activities of the Autonomic Nervous System**
-Regulates mood, emotional patterns, appetite and the pineal gland

-Body temperature and osmolarity of blood
-Helps maintain the waking state
-Contains part of the **reticular activating system** (regulates wakefulness)
-**Produces hormones** like oxytocin and **ADH** (antidiuretic hormone)
(ADH is crucial to regulation of the volume of blood in the body)
-Regulates the pituitary gland (will be important with endocrine drugs)

Thalamus *"The Relay Station":* Relays almost all sensory input to the cerebral cortex
-Important for crude touch, pressure, pain, temperature
-Movement planning and control

THE BRAIN STEM

Because of its position, part of the function of all portions of the brainstem is to relay information from the spinal cord and other parts of the brainstem and cerebellum to and from the cerebrum and diencephalon. Also, the brainstem is where most of the cranial nerves originate.

The **reticular activating system (RAS)** is part of the **reticular formation,** which runs throughout. This is a series of activating and inhibitory fibers that regulate your degree of wakefulness. It is inhibited by CNS depressants (i.e. alcohol, barbiturates, benzodiazepines), and is excited by stimulants (i.e. amphetamines, caffeine).

1. Midbrain -moves eyes in response to visual and motion stimuli
-moves head and trunk in response to auditory stimuli
-**substantia nigra/red nucleus** important in controlling movement
(this is the area that disappears in Parkinson's patients)
2. Pons -Helps medulla oblongata with breathing control

3. **Medulla Oblongata** –regulates the reticular activating system and therefore consciousness and arousal.
- **cardiovascular** centers: heart beat, blood vessel constriction/dilation (blood pressure)
- **breathing** center
- **vomiting center** and **chemoreceptor trigger zone**
- larynx, tongue, swallowing, coughing, sneezing, hiccups
- cranial nerves IX, X (**vagus nerve**), XI, XII

"Medullary depression" is fatal in cases of overdose of CNS depressants such as alcohol, opiates, or any drug that mimics the actions of GABA such as benzodiazepines or barbiturates.

CEREBELLUM: This hot-blooded little beast with its tent-like *tentorium cerebelli* is always on the job.

Regulates **posture and balance** (screwed up by alcohol)
Coordinates complex and skilled movements
Compares intended movements with what is actually happening
(**Proprioception**-the body's ability to know where it is in space)

How Brain Connections Work

The brain is like a computer, using simple "on" and "off" switches in an *extremely* complicated array.

Between the switches are other nerves that transmit the messages over long distances called relay neurons.

The way the systems remains balanced (homeostasis!) is by feedback loops. We know that nerve conduction is transmitted by a wave of depolarization and ions (Na^+, K^+, Cl^-, Ca^{++} etc)… how then are the nerves switched on and off?

Ion channels in the membranes of the nerves that are controlled either by voltage or receptors for molecules called neurotransmitters. These ion channels are called "gated channels". They can be hooked up with a variety of receptors and enzymes that will open and close them, allowing ions to flow through the membrane and depolarize them. There are also "go-betweens" called G-proteins that act as little switches in their own right.

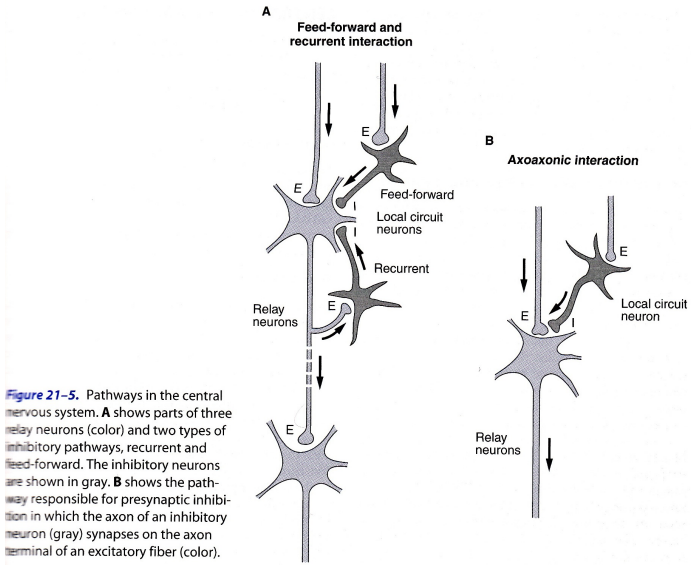


Figure 21–5. Pathways in the central nervous system. **A** shows parts of three relay neurons (color) and two types of inhibitory pathways, recurrent and feed-forward. The inhibitory neurons are shown in gray. **B** shows the pathway responsible for presynaptic inhibition in which the axon of an inhibitory neuron (gray) synapses on the axon terminal of an excitatory fiber (color).

A. Channels opened by voltage. Example: pacemaker cells in the heart.

B. Channel opened by agonist. Example: Nicotinic Acetylcholine Receptor - lets sodium through.

C. Most neurotransmitters work like this – the receptor is hooked to the channel with a G-protein switch. Example: Muscarinic ACh Receptor

D. Receptor and switch and another enzyme make the reaction last longer. Example: NE beta-receptor works with an enzyme to make a messenger called cyclic AMP (cAMP).

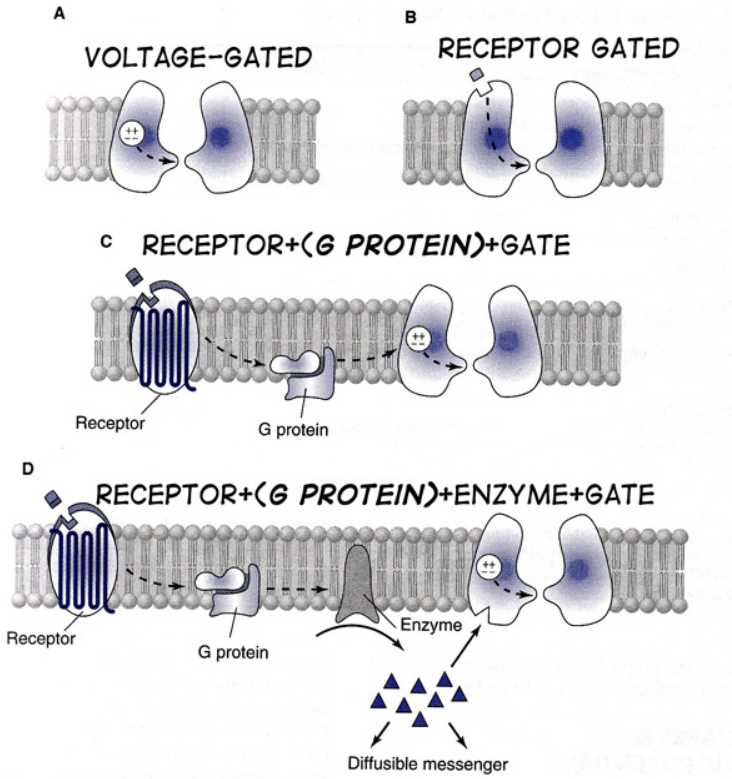
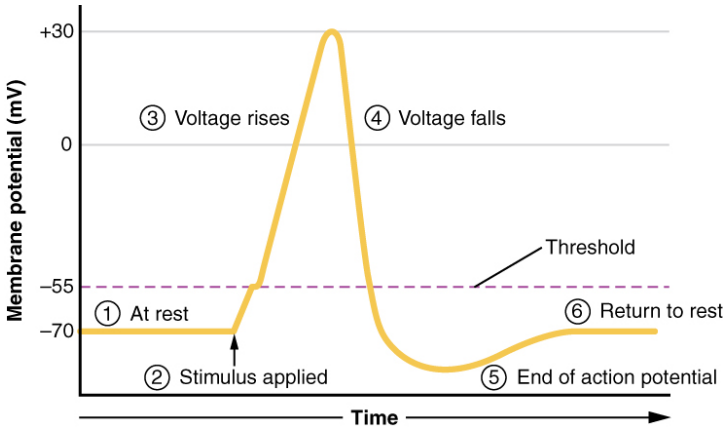


Figure 21–1. Types of ion channels and neurotransmitter receptors in the CNS.

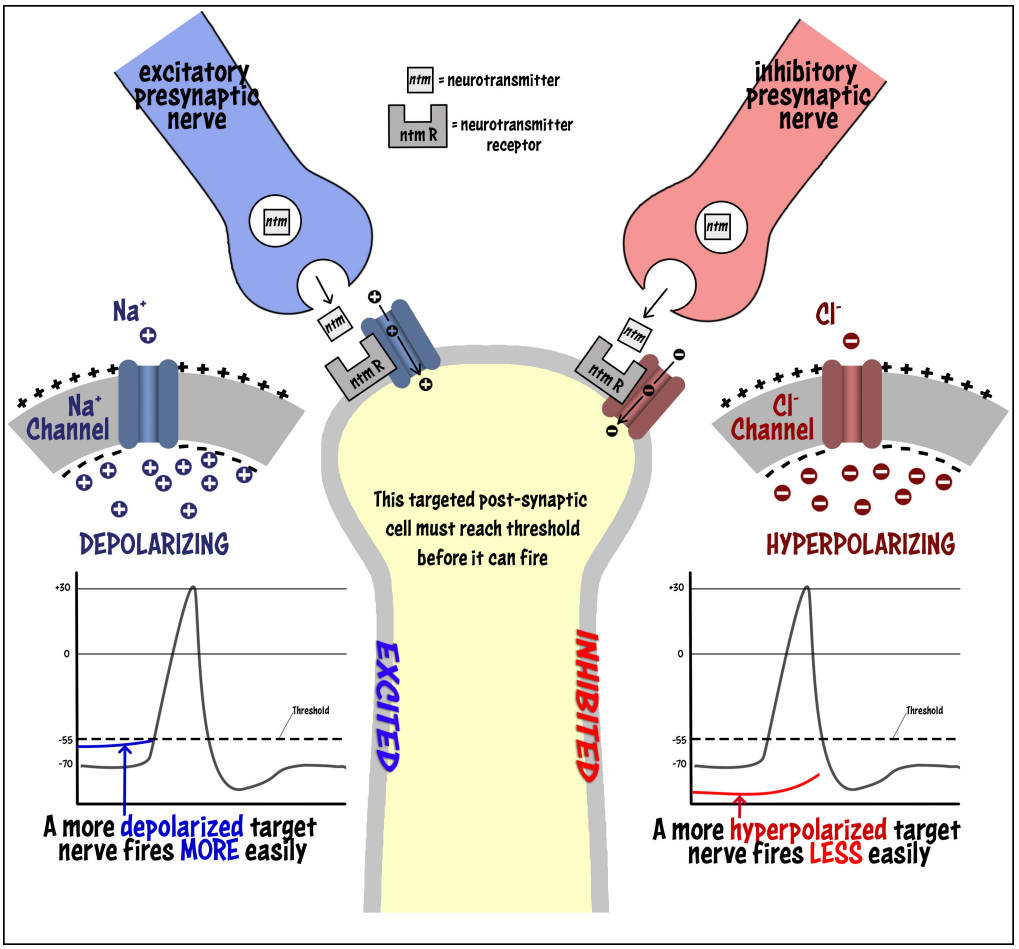
So how are nerves triggered to fire in the brain? From Bio231 you will recall that a nerve membrane must be **depolarized** to fire. **Hyperpolarization** of the membrane makes it *less* likely to fire.



If you don't ***immediately*** remember all of this, and the sodium and potassium channels involved, go watch Crash Course A&P #9 about action potentials. GO WATCH.

In the brain, many, many neurons synapse with any single nerve. So it is the SUM of the depolarization or hyperpolarization that determines if the target nerve will fire.

Neurotransmitters in the brain are either excitatory or inhibitory based **on what type of ion channel they are attached to**: if the receptor is attached to a positive ion channel (like sodium or calcium), triggering that receptor will cause depolarization and be excitatory. If negative ion channel is opened, like chloride, then it will be inhibitory. That's how one neurotransmitter might be excitatory in one area, but be inhibitory in a different area of the brain. Note that **inhibiting an inhibitory nerve** will allow excitatory nerves to cause the target nerve to fire. *(I drew this graphic; it's important!)*



Knowing all this, some terms we mentioned before might make more sense now:

Drug **Sensitization**: increasing effect
Example: a drug causes prolonged release of a presynaptic neurotransmitter over time

Drug **Tolerance**: decreasing effect over time
Example: down-regulation of neurotransmitter receptors in the brain

Considering that in the brain, neurotransmitters' main effect is to open ion channels, note that CNS conditions fall into two categories:

Too much activity: seizures, psychosis
End result: areas of the brain that are either too excited
or not inhibited enough
or just firing on their own for no good reason

Too little activity: Major Depression, Parkinson's
End result: areas that are degenerated from disease, or too inhibited,
or there isn't enough neurotransmitter to bind receptor,
or not enough receptors to begin with

If we know which neurotransmitter is involved, and we know what receptor it binds, we can target a drug to try to fix the problem!

And remember, your body always tries to fight the actions of drugs, and because of homeostasis, drugs that are hyperpolarizing will tend to cause a reactive increase in depolarization by the brain. Similarly, depolarizing drugs will cause the brain to compensate by increasing hyperpolarization as much as possible. Of course you keep upping the dose until you override the homeostasis.... BUT THEN...

WITHDRAWAL from a stimulatory drug: leaves only homeostatic inhibitory nerves firing, and you get overall depression of brain function (sleepiness, difficulty thinking, stumbling)

WITHDRAWAL from an inhibitory drug: leaves only homeostatic excitatory nerves firing, and you get overall overstimulation of brain function (insomnia, hallucinations, seizures)

Make sense? Not yet? That's okay. Let's keep going.

1.) Pharmacodynamic theory for one neurotransmitter works for the others.

So, you already know the direct- and indirect- situation with Acetylcholine (ACh).
If you understand that process for one neurotranmitter, you understand the concept behind any neurotransmitter.

For instance, with **dopamine,** we'll learn the drugs **bromocriptine** (a dopamine direct agonist), **haloperidol** (a dopamine direct antagonist) and **talcapone** (an indirect agonist that works by enzyme blockade) that all bind the dopamine D2 receptor.

So, you can automatically predict from what you already know in the table on the left what is true in the table on the right.

The enzyme AChE breaks down **ACh** Physostigmine blocks AChE. Atropine blocks **ACh (M) Receptors**
How does physostigmine treat an atropine overdose?
Physostigmine blocks AChE, so **Ach** levels rise. Higher levels of **Ach** compete with atropine for binding at the **ACh (M) Receptors**.

The enzyme COMT breaks down **Dopamine (DA)** Tolcapone blocks COMT Haloperidol blocks **DA (D_2) Receptors**
How does tolcapone treat a haloperidol overdose?
Tolcapone blocks COMT, so **DA** levels rise. Higher levels of **DA** compete with haloperidol for binding at the **DA (D_2) Receptors**.

See how that works?

In real life, the easiest solution for an overdose of any direct-acting dopamine **antagonist** like **chlorpromazine** is to give a direct-acting **agonist** like **bromocriptine.** And vice versa.

2) If you know the physiology, you know the actions and side effects.

Just as with NE and ACh, if you know the actions of the neurotransmitter, you can guess what at least some of the effects of the various drugs are based on the receptors they bind.

You know there are indirect cholinergic agonist drugs for Alzheimer's and that anticholinergics make people confused... it makes sense, right?

Another example: dopamine tends to make people vomit and become psychotic. So it shouldn't be surprising that drugs that block the dopamine receptor are good for treating vomiting and psychosis.

GABA is inhibitory. So it should make sense that drugs like zolpidem *(Ambie*n), a GABA agonist, can be used to make you sleepy.

Serotonin (5HT) is a neurotransmitter important for feeling content. So it should make sense that drugs that are serotonin agonists are good for alleviating depression and anxiety.

...Get it?...

Some Neurotransmitters
MONOAMINES: NE, DA, 5HT

Norepinephrine (NE)

Binds **adrenergic alpha and beta receptors** out in the autonomic NS & in the CNS
Important in the reticular activating system (the thing that keeps you awake) and attention, body temperature, pituitary regulation
Implicated in **Depression, ADHD, narcolepsy, appetite control**
broken down by **MAO & COMT**

Dopamine (DA)

Binds "D" receptors (D_1-D_5);
D_2 mostly inhibitory (hyperpolarizing), D_1 mostly excitatory (depolarizing)
Controls movement, thoughts, emotions, **reward response (addiction)**
Important in - **Parkinson's** – too little DA activity in the basal ganglia
- limbic areas (**psychosis** – too much DA activity in the limbic system)
- medulla: **vomiting** center - too much DA causes vomiting
(drugs like prochlorperazine, promethazine, metoclopromide)
- hypothalamus (in regulation of **prolactin** release in pituitary)
inhibition of DA release disinhibits prolactin release
-**galactorrhea** in patients taking anti-dopamine drugs

Emerging evidence that show it plays an important role in **major depression** & **ADHD**
Like NE, it is **degraded by MAO** and **COMT**

Serotonin (5HT)

(5-Hydroxytrypamine, also called 5HT)
7 main different types of 5HT receptors, some excitatory, some inhibitory
$5HT_1$, $5HT_2$ (and maybe 4,6 and7?) receptors important in depression
$5HT_3$ type receptors in GI tract specifically important in nausea and vomiting.
The illicit drug LSD is a potent 5HT agonist and causes hallucinations
Overdose causes "serotonin syndrome"
5HT has a role in mood (**depression**, **anxiety**) appetite, temperature, **nausea/vomiting,** migraines, ADHD, insomnia...
broken down by MAO

Acetylcholine (ACh)

In the peripheral nervous system: Nicotinic receptors: in muscle
Nicotinic direct-acting agonist: depolarizing paralyzing agents like **succinylcholine**
Nicotinic direct-acting blocker: nondepolarizing paralyzing agents like **pancuronium**
Nicotinic indirect-acting blocker: **botox** (inhibits ACh release)

Muscarinic receptors: in autonomic organs and **brain**
Important in learning and **memory (Alzheimer's disease)**
Important to **movement control (Parkinson's)**

Muscarinic direct-acting blockers: **atropine** (see ANS handout)
Muscarinic indirect-acting agonist: **physostigmine** (see ANS handout)

Adenosine (yes, it's that adenosine also found in ATP!)

Causes sleepiness and dilates brain vasculature
Used IV as a drug to stop certain heart arrhythmias, more on that later...
At least 5 receptor subtypes
antagonist: caffeine *So... by what mechanism of action does caffeine keep you awake?*

Histamine

H_1 and H_2 receptors. Histamine has roles in wakefulness, nausea and possibly psychosis.

PEPTIDES

Peptides = Small Proteins

Examples:

Substance P: Related to **pain** regulation, mood, **nausea**, stress, others
Levels influenced by hormones and many other factors, binds **NK1 receptors**
neurokinin receptor (**NK1)** antagonists commonly used in chemo-related nausea

Endorphins (see "**opiates**" below), enkephalins, dynorphins: regulate pain and euphoria
Other peptides: ACTH, MSH, Growth Hormone, CCK, many *many* others

Endocannibinoids

Tetrahydrocannabinol (THC) and cannibidiol (CBD) in marijuana
Binds CB1 receptor in various brain regions
Effects on pain tolerance and vomiting center
anandamide is a cannibinoid found in normal brain (also found in chocolate!)
Drug agonist **dronabinol**: **anti-emetic** role in chemotherapy and AIDS
CBD in cannibidiol (approved June 2018) may be useful for drug-resistant seizures

ENDORPHINS (Opiates/Opioids)

Endorphins are the "natural opiates" found in the brain
responsible for the **"natural high**" as experienced by runners and thrill seekers)

Bind three types of opiate receptors (called **Mu**, Delta and Kappa.)
Found in gray matter of the cerebral cortex (and throughout the body, including GI tract!)

*Note on terminology: The term "**opiate"** originally referred to a naturally occurring drug derived from opium like morphine, heroin or codeine, whereas "**opioid"** meant a synthesized drug such as oxycodone. Nowadays, almost everyone uses the terms interchangeably.* ☺

This is a good drug class to introduce the term: "**partial agonist"** & "**agonist-antagonist**"
a **partial agonist** drug has only partial efficacy compared to the natural ligand
example: buprenorphine
agonist-antagonist drugs stimulate one subtype of receptor but block another.
example: pentazocine: blocks Mu but stimulates Kappa

Agonist drugs: **morphine**
codeine,
hydrocodone (in *Vicodin*® & *Norco*® with acetaminophen),
fentanyl,
meperidine *(Demerol),* heroin, methadone, oxycodone *(Oxycontin)***,** others

Antagonists: **naloxone** *(Narcan):* direct-acting antagonist. blocks opiate mu receptors
naloxone is used for **opiate overdose** and **is available OTC** (ask pharmacist)

Therapeutic Effects:

1. **Block pain mostly centrally** (in the brain)
by changing whether your brain decides the pain is mild or severe.

2. ***stop*** **coughing** (**dextromethorphan**) – **DM** in cough medicine
commonly abused by misinformed teenagers "robotrippin'"
cross-reacts with NMDA receptors to cause **dissociative state** much like ketamine

3. ***stop*** **diarrhea (by causing constipation**): block Mu receptors in gut
examples: diphenoxylate *(Lomotil),* **loperamide** *(Imodium)*)
Do not cause euphoria or relieve pain
To combat **opiate-caused constipation,** newer **opiate antagonists that do not cross the BBB** bind mu receptors in the GI tract to reverse constipation caused by opiate pain medications. Example: methylnaltrexone (*Relistor)*

Side effects: miosis (small pupils), urinary retention, vomiting, euphoria
orthostatic hypotension (induces histamine release which dilates blood vessels)

Current opioid epidemic (prescription, heroin and designer fentanyl derivatives) has led to a political and federal mandates reduction in opioid production in US, leading to shortages in hospitals and pharmacies, as well as prosecution of doctors who prescribe opiates to patients. Meanwhile, opioid abuse is now the **leading** cause of injury-related death in the US.

Opioids, continued: Usual cause of overdose death: **<u>Respiratory (Medullary) Depression</u>**:
This is why **you pay attention to respiratory rate (RR) while giving IV opioids!**

Prescription opioids (often obtained illegally) cause more deaths than car accidents

Outpatients MUST NOT take opiates with other respiratory depressants
(like alcohol, benzodiazepines, barbiturates, anesthetics)

mechanism of respiratory depression: **via inhibition of the medulla oblongata**
1) **limits the amount you can give** a patient to control pain, and
2) **causes death** when patients **abuse** the drug (i.e. do not use it as directed)

Some abusers crush PO opiate medications to inject or inhale in an attempt to get a rush of euphoria but get a fast very high blood level, which can lead to death via respiratory depression.

Newer formulations to deter patients from crushing pills to get high: Newly approved 2016: *Troxyca* is a combination of the opiate oxycodone with beads containing the antagonist naltrexone that is released if the pill is crushed, making the oxycodone ineffective and saving the patient's life!

Because of euphoria, morphine and other **fast-acting** opioids have high abuse potential

Tolerance (loss of effect over time) develops quickly to euphoria, pain, sedation (and luckily respiratory depression), so patients require **higher and higher doses,** leading to patients requiring high doses that prescribers are reluctant to give (because of prosecution of prescribers seen to be prescribing too much opioids). Patients acquire illegal sources that are not regulated, and take unknown doses, leading to tragedy.

Tolerance and dependence occurs in almost all **chronic** pain patients. (It's a myth that you won't get dependent if you take the drugs for pain.) Remember dependence is NOT addiction.

Opioids have fairly **high first-pass metabolism,** so PO doses are higher than by other routes

Critical thinking: An Italian study in the late1990s showed that most people who died from opioid overdose had abstained from opioid use for the four months preceding their deaths. Why did that happen?

Pharmacokinetics are variable as different opiates are broken down by different P450 enzymes
e.g. **codeine**, a prodrug, is biotransformed by CYP2D6 into **morphine**

Question: CYP2D6 absent in some people, and superfast in other people…*How will that affect those patients' response to the drug?*

"Neonatal Abstinence Syndrome" occurs in babies born to mothers addicted to opiates, amphetamine, cocaine, marijuana, barbiturates or benzodiazepines. In the case of opiates the symptoms show up 24-48 hours after birth. **Unlike opiate withdrawal in adults, withdrawal in an infant can be fatal.** The infants sometimes have to be given methadone (a opioid agonist) and weaned off over the course of a *month*.

***Robotrippin'** is the term for people trying to get "high" from cough syrups like Robotussin. Although **dextromethorphan** is an opiate derivative, in moderate overdose it causes very unpleasant **ketamine-like dissociative anesthesia symptoms** *(see anesthesia section later),* and not the morphine high the users were hoping for.

AMINO ACID NEUROTRANSMITTERS: Glutamate, Glycine & GABA

IMPORTANT: It is important to realize that most neurotransmitters can be excitatory or inhibitory, depending on what type of ion channel its receptor is sitting on. At this stage in your training, keep this in mind especially for dopamine and serotonin... depending on the location in the brain and which receptors they bind, these two neurotransmitters are sometimes excitatory, sometimes inhibitory. However:

Glutamate is almost always **excitatory**, and
Glycine and **GABA** are usually **inhibitory.**

Glutamate

The most common excitatory transmitter. Important in those relay neurons
Binds **glutamate receptors** as well as **NMDA receptor**
(NMDA = N-methyl-D-aspartate, another amino acid)
agonist binding opens sodium channels and excite nerves in the CNS
NMDA antagonists (e.g. **ketamine**) cause a **dissociative state**
(see General Anesthesia drugs)
Many areas of CNS, important in the pain response.
Possible links to autism, schizophrenia, obsessive-compulsive disorder, depression

Glycine

Almost always **Inhibitory neurotransmitter**
Found mostly in those local inhibitory interneurons (see page 3)
bind **glycine receptors** to let **chloride** ions through (and hyperpolarize/inhibit)
also binds NMDA receptors to allow glutamate to work *(weird)*
Blocked by the **glycine antagonist strychnine** -> causes convulsions
(Why? Well, if glycine is inhibitory to the motor cortex, and you inhibit that inhibitor, what do you get?)

GABA (Gamma-AminoButyric Acid)

Inhibitory neurotransmitter
Bind $GABA_A$ and $GABA_B$ receptors which increase **chloride** movement into cells
Binding to GABA receptors are facilitated by other nearby receptors that bind
barbiturates, benzodiazepines and other hypnotics.
propofol also works via GABA; **alcohol** also has an effect on GABA receptors
halogenated hydrocarbons like **isoflurane** are hypothesized to work via GABA

GABA-type inhibition is important in treating:
seizures, anxiety, insomnia, **agitation** and is exploited in some anesthetics
GABA-like drugs **depress the medulla oblongata** by inhibition/hyperpolarization

OTHER STUFF:
Hormones like oxytocin, ADH (a.k.a.vasopressin or AVP), histamine, tryptophan, tyramine, aspartate, and lots of other molecules.

CNS DRUGS (from Lippincott 7th Edition)

The drugs you'll be responsible for are in bold face in the handout, you will not have to memorize all of these drugs for this class.

BENZODIAZEPINES
- ***Alprazolam*** XANAX
- ***Chlordiazepoxide*** LIBRIUM
- ***Clonazepam*** KLONOPIN
- ***Clorazepate*** TRANXENE
- ★ ***Diazepam*** VALIUM, DIASTAT
- ***Estazolam*** GENERIC ONLY
- ***Flurazepam*** GENERIC ONLY
- ★ ***Lorazepam*** ATIVAN
- ★ ***Midazolam*** GENERIC ONLY
- ***Oxazepam*** GENERIC ONLY
- ***Quazepam*** DORAL
- ***Temazepam*** RESTORIL
- ***Triazolam*** HALCION

BENZODIAZEPINE ANTAGONIST
- ★ ***Flumazenil*** GENERIC ONLY

OTHER ANXIOLYTIC DRUGS
- **Antidepressants** VARIOUS (SEE CHAPTER 10)
- ★ ***Buspirone*** GENERIC ONLY
- ***Meprobamate*** GENERIC ONLY

BARBITURATES
- ***Amobarbital*** AMYTAL
- ***Pentobarbital*** NEMBUTAL
- ★ ***Phenobarbital*** GENERIC ONLY
- ***Secobarbital*** SECONAL

OTHER HYPNOTIC AGENTS
- **Antihistamines** VARIOUS (SEE CHAPTER 37)
- ***Doxepin*** SILENOR
- ***Eszopiclone*** LUNESTA
- ★ ***Ramelteon*** ROZEREM
- ***Suvorexant*** BELSOMRA
- ***Tasimelteon*** HETLIOZ
- ★ ***Zaleplon*** SONATA
- ★ ***Zolpidem*** AMBIEN, INTERMEZZO, ZOLPIMIST

ANTI-SEIZURE DRUGS
- ***Brivaracetam*** BRIVIACT
- ★ ***Carbamazepine*** TEGRETOL
- ***Clobazam*** ONFI
- ***Clonazepam*** KLONOPIN
- ★ ***Diazepam*** VALIUM
- ★ ***Divalproex*** DEPAKOTE
- ***Eslicarbazepine*** APTIOM
- ***Ethosuximide*** ZARONTIN
- ***Felbamate*** FELBATOL
- ***Fosphenytoin*** CEREBYX
- ★ ***Gabapentin*** NEURONTIN
- ***Lacosamide*** VIMPAT
- ***Lamotrigine*** LAMICTAL
- ★ ***Levetiracetam*** KEPPRA
- ★ ***Lorazepam*** ATIVAN
- ***Oxcarbazepine*** TRILEPTAL
- ***Perampanel*** FYCOMPA
- ★ ***Phenobarbital*** GENERC ONLY
- ★ ***Phenytoin*** DILANTIN
- ***Pregabalin*** LYRICA
- ***Primidone*** MYSOLINE
- ***Rufinamide*** BANZEL
- ***Tiagabine*** GABITRIL
- ***Topiramate*** TOPAMAX
- ***Vigabatrin*** SABRIL
- ***Zonisamide*** ZONEGRAN

PREOPERATIVE MEDICATIONS
- ★ **Analgesics**
- ★ **Antacids**
- ★ **Antiemetics**
- ★ **Benzodiazepines***

ANALGESICS
- ★ ***Acetaminophen*** TYLENOL, OFIRMEV
- ***Celecoxib*** CELEBREX
- ★ ***Gabapentin*** NEURONTIN
- ★ ***Ketamine*** KETALAR*
- ★ **Opioids (see Chapter 14)**

GENERAL ANESTHETICS: INHALED
- ***Desflurane*** SUPRANE
- ★ ***Isoflurane*** FORANE
- ***Nitrous oxide*** GENERIC ONLY
- ***Sevoflurane*** ULTANE

GENERAL ANESTHETICS: INTRAVENOUS
- ***Dexmedetomidine*** PRECEDEX
- ***Etomidate*** AMIDATE
- ***Methohexital*** BREVITAL
- ★ ***Propofol*** DIPRIVAN

NEUROMUSCULAR BLOCKERS (see Chapter 5)
- ***Cisatracurium, mivacurium,***
- ★ ***pancuronium, rocuronium,***
- ★ ***succinylcholine, vecuronium***

LOCAL ANESTHETICS: AMIDES
- ***Bupivacaine*** MARCAINE
- ★ ***Lidocaine*** XYLOCAINE
- ***Mepivacaine*** CARBOCAINE
- ***Ropivacaine*** NAROPIN

LOCAL ANESTHETICS: ESTERS
- ***Chloroprocaine*** NESACAINE
- ***Tetracaine*** GENERIC ONLY

PSYCHOMOTOR STIMULANTS
- ★ ***Amphetamine*** ADDERALL, DYANAVEL, MYDAYIS
- ***Armodafinil*** NUVIGIL
- ***Atomoxetine*** STRATTERA
- ★ ***Caffeine*** CAFCIT, NO DOZ, VIVARIN
- ★ ***Cocaine*** GENERIC ONLY
- ***Dexmethylphenidate*** FOCALIN
- ***Dextroamphetamine*** DEXEDRINE, ZENZEDI
- ***Lisdexamfetamine*** VYVANSE
- ***Methamphetamine*** DESOXYN
- ★ ***Methylphenidate*** CONCERTA, COTEMPLA, DAYTRANA, RITALIN
- ***Modafinil*** PROVIGIL
- ★ ***Nicotine*** NICODERM CQ, NICORETTE, NICOTROL
- ★ ***Theophylline*** ELIXOPHYLLIN, THEO-24, THEOCHRON
- ***Varenicline*** CHANTIX

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)
- ★ ***Citalopram*** CELEXA
- ***Escitalopram*** LEXAPRO
- ★ ***Fluoxetine*** PROZAC
- ***Fluvoxamine*** LUVOX
- ★ ***Paroxetine*** PAXIL
- ***Sertraline*** ZOLOFT

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)
- ***Desvenlafaxine*** PRISTIQ
- ***Duloxetine*** CYMBALTA
- ***Levomilnacipran*** FETZIMA
- ★ ***Venlafaxine*** EFFEXOR

ATYPICAL ANTIDEPRESSANTS
- ★ ***Bupropion*** WELLBUTRIN, ZYBAN
- ***Mirtazapine*** REMERON
- ***Nefazodone*** GENERIC ONLY
- ***Trazodone*** GENERIC ONLY
- ***Vilazodone*** VIIBRYD
- ***Vortioxetine*** TRINTELLIX

TRICYCLIC ANTIDEPRESSANTS (TCAs)
- ★ ***Amitriptyline*** GENERIC ONLY
- ***Amoxapine*** GENERIC ONLY
- ***Clomipramine*** ANAFRANIL
- ***Desipramine*** NORPRAMIN
- ***Doxepin*** SILENOR
- ***Imipramine*** TOFRANIL
- ***Maprotiline*** GENERIC ONLY
- ***Nortriptyline*** PAMELOR
- ***Protriptyline*** VIVACTIL
- ***Trimipramine*** SURMONTIL

MONOAMINE OXIDASE INHIBITORS (MAOIs)
- ***Isocarboxazid*** MARPLAN
- ★ ***Phenelzine*** NARDIL
- ★ ***Selegiline*** EMSAM
- ***Tranylcypromine*** PARNATE

DRUGS USED TO TREAT MANIA and BIPOLAR DISORDER
- ★ ***Carbamazepine*** TEGRETOL, EQUETRO, CARBATROL
- ***Lamotrigine*** LAMICTAL
- ★ ***Lithium*** LITHOBID
- ★ ***Valproic acid*** DEPAKENE, DEPAKOTE

FIRST-GENERATION ANTIPSYCHOTIC (low potency)
- ★ ***Chlorpromazine*** GENERIC ONLY
- ***Thioridazine*** GENERIC ONLY

FIRST-GENERATION ANTIPSYCHOTIC (high potency)
- ***Fluphenazine*** GENERIC ONLY
- ★ ***Haloperidol*** HALDOL
- ***Loxapine*** GENERIC ONLY
- ***Molindone*** GENERIC ONLY
- ***Perphenazine*** GENERIC ONLY
- ***Pimozide*** ORAP
- ★ ***Prochlorperazine*** COMPRO, PROCOMP
- ***Thiothixene*** GENERIC ONLY
- ***Trifluoperazine*** GENERIC ONLY

SECOND-GENERATION ANTIPSYCHOTIC
- ★ ***Aripiprazole*** ABILIFY, ARISTADA
- ***Asenapine*** SAPHRIS
- ***Brexpiprazole*** REXULTI
- ***Cariprazine*** VRAYLAR
- ***Clozapine*** CLOZARIL, FAZACLO
- ***Iloperidone*** FANAPT
- ***Lurasidone*** LATUDA
- ★ ***Olanzapine*** ZYPREXA
- ***Paliperidone*** INVEGA
- ***Pimavanserin*** NUPLAZID
- ***Quetiapine*** SEROQUEL
- ***Risperidone*** RISPERDAL
- ***Ziprasidone*** GEODON

ANTI-PARKINSON DRUGS
- ★ ***Amantadine*** GOCOVRI
- ***Apomorphine*** APOKYN
- ***Benztropine*** COGENTIN
- ★ ***Bromocriptine*** PARLODEL
- ★ ***Carbidopa*** LODOSYN
- ★ ***Entacapone*** COMTAN
- ★ ***Levodopa (w/ Carbidopa)*** SINEMET
- ***Levodopa (w/ Carbidopa+ Entacapone)*** STALEVO
- ***Pramipexole*** MIRAPEX
- ***Rasagiline*** AZILECT
- ***Ropinirole*** REQUIP
- ***Rotigotine*** NEUPRO
- ***Safinamide*** XADAGO
- ★ ***Selegiline (Deprenyl)*** ELDEPRYL, ZELAPAR
- ***Tolcapone*** TASMAR
- ***Trihexyphenidyl*** GENERIC ONLY

ANTI-ALZHEIMER DRUGS
- ***Donepezil*** ARICEPT
- ***Galantamine*** RAZADYNE
- ***Memantine*** NAMENDA
- ★ ***Rivastigmine*** EXELON

OPIOIDS

STRONG AGONISTS
- ***Alfentanil*** ALFENTA
- ★ ***Fentanyl*** ABSTRAL, ACTIQ, DURAGESIC, FENTORA, IONSYS, LAZANDA, SUBSYS
- ***Heroin*** GENERIC ONLY
- ★ ***Hydrocodone*** HYSINGLA, LORTAB*, NORCO*, VICODIN*, ZOHYDRO ER
- ***Hydromorphone*** DILAUDID, EXALGO
- ***Levorphanol*** GENERIC ONLY
- ***Meperidine*** DEMEROL
- ***Methadone*** DOLOPHINE, METHADOSE
- ★ ***Morphine*** ARYMO ER, KADIAN, MORPHABOND, MS CONTIN
- ★ ***Oxycodone*** OXAYDO, OXYCONTIN, PERCOCET*, ROXICODONE
- ***Oxymorphone*** OPANA
- ***Remifentanil*** ULTIVA
- ***Sufentanil*** SUFENTA

MODERATE/LOW AGONISTS
- ★ ***Codeine*** GENERIC ONLY

MIXED AGONIST–ANTAGONIST AND PARTIAL AGONISTS
- ***Buprenorphine*** BELBUCA, BUPRENEX, BUTRANS, PROBUPHINE
- ***Butorphanol*** GENERIC ONLY
- ***Nalbuphine*** GENERIC ONLY
- ***Pentazocine*** TALWIN

ANTAGONISTS
- ★ ***Naloxone*** EVZIO, NARCAN
- ***Naltrexone*** VIVITROL

OTHER ANALGESICS
- ***Tapentadol*** NUCYNTA
- ***Tramadol*** CONZIP, ULTRAM

DRUGS FOR MIGRAINE

TRIPTANS
- ***Almotriptan*** AXERT
- ***Eletriptan*** RELPAX
- ***Frovatriptan*** FROVA
- ***Naratriptan*** AMERGE
- ***Rizatriptan*** MAXALT, MAXALT-MLT
- ***Sumatriptan*** IMITREX, ONZETRA, ZEMBRACE
- ***Zolmitriptan*** ZOMIG

ERGOTS
- ***Dihydroergotamine*** DHE 45, MIGRANAL
- ***Ergotamine tartrate*** ERGOMAR

NSAIDs
- ★ ***Aspirin*** BAYER, BUFFERIN, ECOTRIN
- ★ ***Ibuprofen*** ADVIL, MOTRIN
- ***Indomethacin*** INDOCIN
- ***Ketorolac*** GENERIC ONLY
- ★ ***Naproxen*** ALEVE, ANAPROX, NAPROSYN

PROPHYLACTIC AGENTS
- ★ **Anticonvulsants**
- ★ **β-Blockers**
- ★ **Calcium channel blockers**
- ★ **Tricyclic antidepressants**

Practice Critical Thinking: Neurotransmitters

Note: There may be more than one correct answer!

1. Why do you think medications made for diseases of the CNS might have unpredictable side effects?
   ___A. the brain is too complicated; we don't really understand how it works
   ___B. there are over 100 natural neurotransmitters that we know of
   ___C. neurotransmitters have more than one function that we know of

2. If you develop an agonist or antagonist to any of the CNS neurotransmitters, what pharmacokinetic properties will be the most relevant to their effectiveness?
   ___A. lipid solubility
   ___B. water solubility
   ___C. ability to penetrate tight junctions
   ___D. ability to be well absorbed

3. Consider some mechanisms by which drugs of abuse might make a user "high".
   ___A. stimulate endorphin receptors
   ___B. depolarize neurons
   ___C. inhibit inhibitory neurons
   ___D. stimulate feelings of love

4. Why is it that receptors that open chloride channels are inhibitory, but receptors that open sodium channels are excitatory?
   ___A. sodium is a positive ion, chloride is a negative ion
   ___B. sodium and chloride are found in salt
   ___C. sodium has fast and slow channels, chloride only has slow channels
   ___D. this is a trick question, receptors don't open channels

Answers: 1: A, B, C 2: A, C 3: A, B, C, D 4: A

And some more critical thinking questions *(Yay!)*:
Local anesthetics block sodium channels. Why would this block the perception of pain?
(Hint: Remember action potentials back in A&P1?)

Why would combining synergistic inhibitory drugs increase your chances for coma or death?
(Hint: think hyperpolarization)

Why would combining excitatory/depolarizing drugs lower the brain's threshold for seizure?
(Hint: think depolarization)

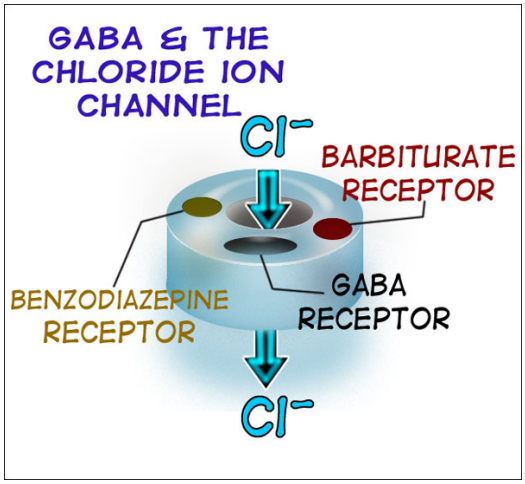
CNS DRUGS

Before we launch into the CNS drugs, be warned that many drugs are used for a variety of disorders. So if you start to feel a little confused about which drug treats which disease, you are probably not alone. Many of the discoveries of new drugs to treat CNS conditions were discovered by accident; that means memorizing the indications is tough to do in a systematic way. On the other hand, they are all similar in some ways; i.e. a lot of them have to be tapered to prevent withdrawal.

BENZODIAZEPINES (& friends)

(Chapters 18, 12, 13, 16)

Benzodiazepines have a variety of uses that are tied to the fact that they bind near the **GABA receptor**. Drugs that act in similar ways, barbiturates, and sedatives like zolpidem (*Ambien*) and zaleplon (*Sonata*) bind different portions of that receptor, sometimes in different areas of the body, which accounts for the difference in action of the classes of drugs.



GABA (gamma-aminobutyric acid) is an *inhibitory* neurotransmitter in the CNS, which acts to hold open a **chloride ion channel** (see page 5), and as you might predict, benzodiazepines and barbiturates act as depressants in the central nervous system.

Their main uses are in anesthesia, anxiety, seizure control, and as sedatives (hypnotics), but are also indicated as centrally-acting muscle relaxants. For example, diazepam (Valium) is used as a muscle relaxant in some cases.

Drugs that work in a GABA or GABA-like mechanism **cause general depression of activity** of the **whole** brain. Part of your brain is the medulla oblongata (see page 3). **If the medulla oblongata gets too inhibited, you stop breathing.** And die.

The most common benzodiazepine **antagonist** (and antidote for overdose) is **flumazenil.** There is no antagonist for barbiturates.

SEDATIVES and HYPNOTICS

A sedative is used to calm down an agitated person
A hypnotic puts an awake person to sleep
Obviously, many sedatives also make folks sleepy.

Humans MUST sleep, and sleep occurs in several stages, including 4 stages of NREM and REM sleep. REM (Rapid Eye Movement) sleep is the sleep in which dreams occur, the body is essentially paralyzed, and normal male erections occur. REM sleep is required to maintain your sanity and also important for memory. Some sleep disorders include narcolepsy (falling asleep

uncontrollably: see the section on stimulants for treatment of this), sleep apnea (stopping breathing while sleeping), sleepwalking (more common in kids), night terrors (kids) and insomnia (inability to sleep or remain asleep).

We'll concentrate on **insomnia** here as a representative condition.

Drugs that induce sleep act on the **reticular activating system** in the hypothalamus and medulla oblongata. Patients can become used to (tolerant to) ***any*** sleeping aid and **no sleeping aid should be used for more than 3-4 weeks;** they should only be used long enough to repair **sleep hygiene.**

Sleep hygiene is the practice of regular, quality sleep: Going to bed and waking at the same time daily, refraining from excessive or erratic naps, having a dark and quiet bedroom, not drinking caffeine close to bedtime, having a nightly routine, having regular exposure to daylight etc.

Poor sleep hygiene worsens symptoms of every disorder of the CNS. This cannot be overstressed.

Drugs used for insomnia can:
initiate sleep via a melatonin agonist or a very short-acting drug
maintain sleep via use of something that is generally inhibitory the brain that is longer-acting.

<u>BENZODIAZEPINES</u>.
Benzodiazepines are preferred over barbiturates as hypnotics because of *less* REM interference and less hangover.
Benzos come in short-, medium- and long-acting versions.
Examples of benzodiazepines used in sleep are **diazepam** (*Valium*) triazolam (*Halcion*), and flurazepam (*Dalmane*). Pregnancy **Category X.**

PO benzodiazepines have high TI **when given <u>alone</u>** but
extremely hazardous if mixed with alcohol, opiates or barbiturates *(Why?)*
Withdrawal from long-term hi-dose benzodiazepines can cause seizures and long-term benzo users can have a seizure if you give them a large dose of a benzo antagonist. *(Why? And then what do you do with the seizing person?!)*

Benzos have a cross-tolerance with alcohol. **Diazepam** (*Valium*) and **lorazepam** (*Ativan*) in particular, are also used to treat **alcohol withdrawal**.

Those two drugs are also excellent fast-acting sedatives for **violently agitated patients**.
(What do you do if a patient is violently agitated because they are extremely drunk?)

<u>Barbiturates</u>. **Phenobarbital** (*Luminal*), secobarbital (*Seconal*), pentobarbital (*Nembutal*).
Barbiturates are rarely used these days for sleep because **they reduce REM sleep,** have lots of **P450 interactions,** cause **hangover** and rebound nightmares. Additionally, barbiturates cause **automatism**, in which the patient forgets whether or not they've taken their pill. This can be overcome with **labeled pill dispensers**, but is particularly problematic in the elderly and a lot of

old people overdose on them. Like benzodiazepines, with barbiturates comes the possibility of addiction and **life-threatening withdrawal.**

Newer **non-benzodiazepine GABA agonist** *(also a lie)* drugs:

zaleplon (*Sonata*)
zolpidem (*Ambien*): women need **half the dose of men,** also available as a mouth spray. May cause sleep-walking, sleep-driving and anterograde amnesia
eszopiclone (Lunesta)
Bind a subset of benzodiazepine receptors, don't seem to reduce REM
relatively safer for pregnant women
So far are Category B & C
Less side effects and patients take longer to develop tolerance to them.
indicated for sleep, but NOT anxiety or seizures

1st generation *(aka old-timey)* Antihistamines: block **Histamine H_1** receptors in the CNS
diphenhydramine *(Nytol, Sominex*, also packaged as *Benedryl)*
doxylamine *(Nyquil)*, hydroxyzine
can have a **paradoxical reaction** in some elderly or very young patients (the patients become more agitated with the drug)
Available in many OTCs (buy generics!) some have anticholinergic effects (dry mouth)
interfere with REM sleep slightly

Melatonin
melatonin, ramelteon (*Rozerem*), **tasimelteon** *(Hetlioz)*].
Bind the melatonin MT_1 and MT_2 receptors

Melatonin is a **hormone**. It is NOT inhibitory to the brain. Think of it as a reset button that tells the brain what time it is every day. It is regulated by light hitting the retina. Melatonin of our ancestors (l00 years ago) was regulated by the rising of the sun.
(Note: melatonin as a supplement is unregulated, so check for that USP symbol)

Melatonin is **only good for *falling* asleep,** not *staying* asleep.
tasimelteon *(Helioz)* Indicated for non-24-hour-sleep-disorder:
In-the-dark blind patients need the drug to function well.

Other hypnotic drugs:
suvorexant *(Belsomra):* Orexin antagonist (orexin is a peptide neurotransmitter that works at RAS to keep you awake) [approved 2014]
off-label trazodone (an atypical antidepressant, blocks H_1-receptors, causes priapism)
low-dose doxepin (old timey TCA)
propofol: not for insomnia! (Used only in anesthesia or in ICU for medical coma)

ANXIOLYTICS

(Anti-anxiety drugs): Chapter 13

Anxiety and related symptoms seem to be related to over-action of the **sympathetic nervous system** and **limbic system**. Included anxiety diagnoses would be generalized anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder or a phobic disorder that might only require one-dose treatment (i.e. claustrophobia when having an MRI done, or one dose given for fear of flying).

Common drugs for anxiety include:

Benzodiazepines: At low doses, benzodiazepines are good anxiolytics. Examples of benzodiazepines used for anxiety would be **lorazepam** *(Ativan*), alprazolam (*Xanax*), **diazepam** (*Valium*), clonazepam (*Klonopin*). Because of cross-tolerance with alcohol, and the fact that alcohol is used by some anxiety patients as a "self-medication", benzodiazepines should not be used in a patient who is dependent on or is using alcohol.

Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants
What is the mechanism of action of these drugs? What neurotransmitter(s) are raised/lowered by these drugs?
The SSRIs **paroxetine** (*Paxil*), sertraline (*Zoloft*) or **escitalopram** (*Lexapro*) and others are sometimes also used for chronic anxiety disorders. These take several weeks to start working, so sometimes the patient gets a benzo for the first few weeks until the SSRI kicks in.

Selective Serotonin Reuptake Inhibitor (SSNRI) Antidepressants:
What is the mechanism of action of these drugs? What neurotransmitter(s) are raised/lowered by these drugs?
The SSNRIs **venlafaxine** *(Effexor)* and **duloxetine** *(Cymbalta): Used like the SSRIs.*

Azapirones are $5HT_{1A}$ antagonists, $5HT_{2A}$ agonists, and dopamine D_2 agonists. (?!) So... for now just remember the example drug **buspirone** (*Buspar*). Buspirone does not interact with alcohol but can also take a few weeks to work, but it is just about as good as benzos at treating generalized anxiety disorder so yay!

Beta-blockers such as **propranolol**: used to control extreme social phobia ***symptoms*** like tachycardia (rapid heart beat) or stage fright *symptoms* (it slows the heart rate). Since it blocks beta-2 receptors centrally, it also reduces tremor.

Note: **Barbiturates** definitely *could* be used for anxiety but since there are way better drugs they are rarely ever used for anxiety nowadays.

Note: the fact that the most effective anxiolytics bind some GABA and/or Serotonin receptors tells us that anxiety is somehow controlled by GABA and Serotonin... or even DA or Norepi?...

ANTI-SEIZURE DRUGS

A **seizure** is an abnormal discharge of electrical signal in the brain. This leads to abnormal firing of various centers of the brain, leading to false information being sent to the rest of the body. What the patient experiences can be anything from a sensory disturbance (such as an odor or feeling of euphoria or a loss of consciousness) to signals being sent to muscles resulting in spasms of muscles.

Generalized seizure: a seizure that involves the whole brain
Main classes of generalized seizures:
Petit mal (absence) seizure: a generalized seizure without convulsions
Grand mal (tonic-clonic) seizure: a generalized seizure with convulsions
Atonic (loss of muscle tone) and Myoclonic (rapid jerks often in one body part)

Partial seizure: (partial or complex) a seizure that involves only part of the brain
This can precede a generalized seizure

Status epilepticus: A seizure that lasts more than five minutes, or two seizures that occur without regaining consciousness, a medical emergency

Some causes of seizures: hypoglycemia, tumors, infections (meningitis), alcohol withdrawal, toxins, head injuries, birth defects. Also fevers in babies.

Drugs used for seizures are classified as *either*:
Anticonvulsant: used emergently to stop a seizure in progress or
Antiepileptic: used by patients daily to prevent seizures and are aimed at increasing GABA, decreasing glutamate or blocking Na^{+} or Ca^{++} ion conductance in some way.
Make sense?

Benzodiazepines: Great as anticonvulsants
In the US, the most commonly used anti-convulsant benzodiazepines you'll run across will be **diazepam** *(Valium)* and **lorazepam** ***(****Ativan****)***; in fact these two drugs are the **first-line treatment for status epilepticus.**

Other common benzodiazepines used for seizures are: clonazepam *(Klonopin)* (used for absence seizures) and clorazepate *(Tranxene)* (used for partial seizures).

The benzodiazepines **diazepam** and **lorazepam** are the most commonly used drugs for the seizures associated with **alcohol withdrawal syndrome**, a potentially lethal syndrome in alcoholic patients which you will occasionally see in the hospital.

Fun fact: Diazepam *(Valium)* is also available as a PR formulation.

Barbiturates: **Phenobarbital** is both anticonvulsant and antiepileptic. The side effect of **sedation wears off** (drug tolerance) and so can be used in a patient long term. Useful in generalized and partial seizures. When stopping the drug it must be tapered to prevent withdrawal.

Other Antiseizure drugs

levetiracetam (*Keppra*): focal, myoclonic, generalized seizures
Few drug interactions but can increase suicidal ideation/behavior. Cat C
gabapentin *(Neurontin) :* used for partial seizures (and certain kinds of **pain**), Cat C
works by inhibiting glutamate release
Non-linear pharmacokinetics because actually transported in the gut
Few drug interactions, pretty safe for old people, used for shingles pain
lamotrigine *(Lamictil):* used for general, absence, partial seizures and bipolar Cat C
Drug interactions common with other antiseizure drugs
topiramate (*Topamax*): used for generalized or partial seizures and migraine, Cat D
Can cause sleepiness, weight loss, tingling, kidney stones
ethosuximide *(Zarontin):* absence seizures, Cat C
works via decreasing calcium transport
can cause lupus or blood dyscrasias
lacosamide: focal seizures
eslicabazepine: focal seizures
brivaracetam *(Briviact):* focal seizures
felbamate: broad spectrum of action but causes aplastic anemia
oxycabazepine: focal seizures, causes hyponatremia
perampanel: focal and generalized seizures, might make you homicidal (?!)
...

Three Other Very Common Anti-Seizure Drugs (for generalized or partial seizures):
-all work on sodium channels of seizing brain areas

Note: All 3 of these (phenytoin, carbamazepine & valproic acid) cause 10-20% FETAL MALFORMATIONS. ¡Category D! All three have drug interactions via P450 enzymes

1. **phenytoin** *(Dilantin)*: weird side effects of dizziness and **overgrown gums.**
Half-life increases as dose increases
Black box warning: **If giving IV, don't inject i.v. too fast (causes arrhythmias)**
an also cause **Stevens-Johnson syndrome**: (skin and mucous membranes fall off)
Competes with Vitamin K (causes bleeding… see blood thinner handout)
used as second-line drug to stop status epilepticus (if benzodiazepines fail)
Do not mix in 5% dextrose (will cause crystal formation)

2. **carbamazepine** *(Tegretol):* is related to TCAs (antidepressants) but good antiepileptic
Also used in **bipolar disorder** and trigeminal neuralgia (a type of facial pain)
contraindicated in absence seizures
induces lots of P450 enzymes (1A2, 2C8, 2C9, 2C19, 3A4, UGTs)
so drug interactions common.
Black box: **aplastic anemia risk** (idiosyncratic)
Stevens-Johnson in patients **with HLA-B*1502 allele**

3. **valproic acid** *(Depakote, Depakene):* another GABA drug
Works for *all* kinds of epilepsy (**also used in mania**, see below)
Black box: **Liver toxicity**, pancreatitis, do not use in babies under 2 or in children with mitochondrial diseases

*Critical thinking question on benzos and other inhibitory type CNS drugs: If you take a drug like diazepam every day for a year, for any reason, and then **suddenly** stop taking it without tapering the dose, you might experience insomnia, anxiety or even seizures, for days, or even weeks, long after the drug has left your system. Why? (Hint: think homeostasis...)*

GENERAL ANESTHESIA
(Chapter 18):
The mechanism of action of most general anesthetics isn't understood, but they work.

Stages of General Anesthesia
Stage I. Stage of Analgesia - loss of pain
Stage II. Stage of Excitement – controlled by hypothalamus. Patient seems delirious or drunk, they are amnesic (forget what is happening), ↑Heart rate, ↑breathing rate
***Stage III. Stage of Surgical Anesthesia** – apnea (stop spontaneous breathing), heart still beats, lose responsiveness to pain (pinching or shock)
Stage IV: Stage of Medullary Depression: - die without circulatory and breathing support

Induction of general anesthesia: bringing the patient to Stage III.
Maintenance of General Anesthesia: keeping the patient at Stage III.

"Procedural" sedation is minimal anesthesia used for short procedures
"**Conscious" sedation** is sedation where the patient is awake, but forgets what happened

Drugs used in General Anesthesia:
Halogenated Hydrocarbons (halothane, enflurane, **isoflurane**)
Inhaled by lungs, distribute to CNS and fat stores, very low MAC (1-4%)
Used for maintenance

Effects: Anesthesia, muscle relaxation, myocardial & respiratory depression, low blood pressure

Side Effects:
malignant hyperthermia
when combine halogenated hydrocarbons with **succinylcholine**
(recall succinylcholine is a depolarizing nicotinic-binding muscle relaxant)
- caused by Calcium trapping inside muscle cells
- ⇑BP, ⇑HR, ⇑Temp, ⇑[K+], acidosis, severe muscle rigidity
- can occur up to 24 hours later!
- treat with muscle relaxant **dantrolene**

Other side effects: lung irritation (secretions, coughing), nausea, vomiting
isoflurane is the least toxicity on liver and kidney
Isoflurane Increases Intracranial pressure: contraindicated in head trauma

Ketamine: short-acting NMDA antagonist; also abused as a street drug
10-12% of adults given ketamine report terrible nightmares and hallucinations when they wake up (a.k.a. "emergence reactions"), less if post-op area is quiet and calm

Dissociative Anesthetic State: amnesia, analgesia, catatonia
-so no pain, no memory, but look awake (really weird)
related chemically to PCP, currently studied for use in acute depression
weirdly, **dextromethorphan**, an opiate derivative, also binds NMDA receptors and early overdose can look like ketamine overdose.

midazolam (*Versed*), a short-acting benzodiazepine
Used in "**conscious sedation**"
usually in combination with opioid **fentanyl** for pain (see opiates) and
propofol, a hypnotic inducing agent (see below)

Midazolam is famous for its **anterograde amnesia** effect (patient forgets anything that happens while drug is in the body). It also is used in some emergency situations to rapidly sedate an agitated person.
Midazolam also cannot be combined with certain anti-HIV drugs.
Don't forget it is a benzodiazepine so you have got to watch the patient's respiratory rate (medullary depression!)

Other short-acting drugs used for short procedures or conscious sedation:

propofol *(Diprivan)*:
used IV only for induction (puts patients to sleep really fast (hypnotic))
super fast half-life; wears off in minutes
looks like milk (lipid emulsion)
bacteria like to grow in it
burns going in, turns your pee green
used for medical comas in an ICU
killed Michael Jackson

etomidate: for induction, can cause transient reduction in cortisol levels, reduces ICP

fentanyl: for pain. a short-acting opioid, also reduces cough, safe in heart procedures

dexmedetomidine: sedative, similar to clonidine (see Heart/BP lectures)

Also:

Nitrous oxide *(Laughing gas):* Good for pain relief but even highest doses only put about half of all people to sleep, so not useful for general procedures. Used more commonly in dentistry. Mechanism unknown, but NMDA, GABA and 5HT receptors implicated.

It is important to remember that any drug that affects something in the CNS has the potential to interact with other drugs in the CNS.
This definitely includes recreational drugs!

STIMULANTS:

"Stimulants": Cause excitement, euphoria, increase wakefulness and motor activity

Amphetamines: **amphetamine**, **dextroamphetamine**, (illegals: methamphetamine, MDMA)
First developed & used in WWII to keep troops awake; 1950s-1960s used as OTC dieting aid

Mechanism of action: **increased release** of norepinephrine, serotonin and dopamine
and also inhibits NE 5HT DA reuptake a little *and* inhibits MAO a little *Yikes!*

Actions: Increases focus, reduces appetite, increase wakefulness.
Indications:

ADD/ADHD: Attention Deficit Disorder/ Attention Deficit Hyperactivity Disorder
medications normalize brain function in ADHD, do not make patient "hyper"
lisdexamfetamine *Vyvanse:* a prodrug converted by red blood cells into dextroamphetamine
amphetamine/dextroamphetamine: *Adderall*
methylphenidate (*Ritalin, Concerta*): Blocks DA & NE reuptake onlyy.
(DA-reuptake more than NE)
atomoxetine (*Strattera):* blocks NE-reuptake more than DA; not considered habit-forming

Obesity: amphetamines suppress appetite via hypothalamic feeding center
phentermine, diethylpropion: chemical structures similar to amphetamine
Example *Qsymia*® (phentermine + topiramate)
(topiramate is antiseizure drug with side effect of appetite reduction)

Narcolepsy: (condition where patient falls asleep without warning)
so drugs that stimulate reticular formation will help
methylphenidate *(Ritalin)*
modafinil (*Provigil*)
armodafinil (*Nuvigil*) } ?mechanism - something with NE and DA

Warnings: Because of action on NE and Dopamine, amphetamines can cause stroke or sudden cardiac death.
High doses cause extreme **agitation**, **psychosis**, diarrhea, nausea, **stroke, sudden cardiac death**
Even low doses cause increase in BP and reflex bradycardia
Recommended doses can cause irritability, insomnia
Can cause "**amphetamine psychosis**" (should make sense because dopamine)

Note: Amphetamines are widely abused by students to help them "focus" and stay awake. All studies thus far have shown no improvement in academic performance in students (other than those with ADHD)

Abuse of amphetamines is based on the action of these drugs to reduce fatigue and appetite and change mood. After stopping the drug patient sleeps deeply but awakens feeling depressed ("crash"). Tolerance is common.

Methylxanthenes: found in tea (theophylline), cocoa (theobromine), and coffee (**caffeine**)

Caffeine: mechanism: **adenosine antagonist** *(inhibiting inhibitor, right?)*, works thru Ca^{++}, cAMP?

Effects: Stimulates cortex to increase alertness
Increases heart rate and contractility
Increases acid production in the stomach
constricts brain vessels (may be how it helps migraine) but dilates peripheral vessels
Suppresses ADH release and acts therefore as a **diuretic** (makes you pee).
No evidence that high doses or regular caffeine use improves academic performance

Withdrawal: lethargy, headache, irritability

Therapeutic uses: **headache**, caffeine withdrawal, and as a **stimulant** (off-label)

20 oz venti Starbucks Blonde Roast	475 mg
12 oz tall Starbucks Pike Place Roast	235 mg
14 oz medium Dunkin' Donuts Coffee	210 mg
2 oz 5 h Energy	200 mg
1 caplet NoDoz	200 mg
16 oz Rockstar Energy	160mg
17 oz Honest Tea Organic Lemon	90 mg
16 oz grande Starbucks Green Tea Latte (reg or iced)	80 mg
8 oz Green Mountain Breakfast Blend Keurig cup	75 mg
12 oz Pepsi Zero Sugar	69mg
12 oz Mountain Dew (reg or diet)	54 mg
8 oz brewed black tea	47 mg
12 oz Barq's Root Beer	22 mg
9 Hershey's Milk Chocolate Kisses	9mg
12 oz most Root Beer	0 mg
12 oz water	0 mg

Nicotine: stimulates N receptors. It is in cigarettes (~12-24 mg ea.) and ENDS (electronic nicotine delivery systems) (variable) - both derived from tobacco

increases: euphoria, relaxation, wakefulness, attention, **heart rate**, GI activity

reduces: reaction time, **appetite** and **coronary blood flow**

Toxic doses: *blockade* of N receptors, medullary paralysis, shock, death

Withdrawal: irritibility, insomnia, headache

Drugs for withdrawal:

buproprion *(Wellbutrin, Zyban)*: atypical antidepressant, reduces cravings

varenicline *(Chantix):* partial N-agonist, reproduces many of the effects of nicotine but doesn't stimulate the same subclass of N receptors in the brain that cause euphoria. Helps with withdrawal.

cocaine: used as a topical anesthetic in some Ear Nose Throat procedures

blocks reuptake of DA, NE and 5HT

increased DA in limbic system causes euphoria and potential for addiction

chronic use depletes DA and increases cravings

like amphetamines, dopamine activity can cause psychosis at high doses

use causes: euphoria, wakefulness, excitedness.

If used nasally, topical vasoconstriction may cause necrosis/perforation of sinus/palate

withdrawal: irritability, anhedonia, sleepiness, paranoia

You do not need to recite these criteria for me. But be able to differentiate between a depressed, manic or schizophrenic (psychotic) patient (should have been covered in your psych course)

DSM-V (Diagnostic and Statistical Manual of Mental Disorders) Criteria
(See also "Crash Course: Psychology #30 on Affective Disorders:
https://www.youtube.com/watch?v=ZwMlHkWKDwM

DEPRESSION: Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; significant impairment in social, occupational, education functioning. (Rule out medical problem or grieving)

- depressed mood or irritability most of the day, nearly every day
- markedly diminished interest or pleasure in all, or almost all, activities nearly every (anhedonia)
- significant weight loss when not dieting or weight gain (>5% of body weight in a month)
- insomnia or hypersomnia nearly every day
- psychomotor agitation or retardation nearly every day
- fatigue or loss of energy nearly every day
- feelings of worthlessness or excessive or inappropriate feelings of guilt
- diminished ability to think or concentrate, or indecisiveness
- recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

MANIA: A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week. During the period of mood disturbance, three (or more) of the following:

-inflated self-esteem or grandiosity
-decreased need for sleep
-more talkative than usual or pressure to keep talking
-flight of ideas or subjective experience that thoughts are racing
-distractibility
-increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
-excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

In DSM-V: For children there is similar diagnosis called “Disruptive Mood Dysregulation”
Also in DSM-V: you can have some manic features in depression in which case the diagnosis changes slightly to “depression with mixed features”. This was done to emphasize that depression and mania describe diseases that lie along a spectrum of symptoms.

SCHIZOPHRENIA: Two or more of the following, each present for a significant portion of time during a one-month period or less if successfully treated.

-Delusions – Strange beliefs such as delusions of grandeur or persecution, ideas of reference (e.g., believing that TV newscaster is delivering a secret coded message).
-Hallucinations – Auditory, visual, tactile, gustatory, or olfactory
-Disorganized speech – Frequent derailment or incoherence
-Grossly disorganized behavior (e.g. wearing inappropriate clothing; inappropriate affect) or catatonic behavior (rare).

NOTE: Items 1-4 are considered ‘positive symptoms’ and are easier to treat than negative symptoms. DSM-V requires at least one of these for diagnosis

-Negative symptoms (alogia, avolition, affective flattening).

AFFECTIVE DISORDERS

Major Depression is a medical affective disorder characterized by changes in mood, appetite, sleep, and concentration accompanied by feelings of hopelessness and thoughts of death or suicide.

Mania is another affective disorder characterized by an elevated, expansive, irritable or agitated mood, associated with need for less sleep, and behavior that can lead to painful consequences

Either of these diagnoses are diagnoses of exclusion; that is, other medical causes should be ruled out (eg. Thyroid disorder)

Bipolar Affective Disorder is a disorder where a patient cycles between Depression and Mania.

The **monoamine hypothesis** suggests that depression is due to too little Norepinephrine (NE) and Serotonin (5HT) (and possibly dopamine), and that mania is caused by too much of those neurotransmitters in the brain. So, the major drugs used to deal with these problems deal with those neurotransmitters.

Be aware: **<u>All</u> currently approved antidepressants take 3-4 weeks to start lifting mood.**

Be aware: **If a patient says he/she is suicidal, they need to be evaluated in an ER or office by a qualified psychiatric professional.**
-a good clue to risk is if the patient has a **plan** for his/her suicide.

DRUGS for DEPRESSION:

Almost all antidepressants carry the **black box warning for increased suicidal thinking in the first few weeks of treatment in young people under 24 years old** as a precaution**.**

MonoAmine Oxidase Inhibitors (MAOIs):

Older, ***irreversible*** MAO inhibitors**: phenelzine** *(Nardil),* tranylcypromine *(Parnate)*

See the autonomic handout to review:
MAO breaks down NE (In particular, MAO **type A**), as well as 5HT
So, if you inhibit MAO, you increase NE (and 5HT)

These work well but are not used as first line treatment due to **dietary restriction of tyramine**.
Tyramine causes release of NE from vesicles
Tyramine + MAO Inhibitor = huge (synergistic) outflow of NE
-> huge jump in your blood pressure -> stroke.
Some foods that have tyramine: chocolate, red wine, cheese, ~anything with preservative
Many many severe drug interactions (remember alpha-1 agonists?)
MAOIs also cause low BP, constipation, and impotence in men. *oh yay*.

10 day to TWO WEEK window around <u>MAOIs</u> for many drugs
(Since the half-life for Nardil and Parnate are only 3-11 hours, why do you think it takes two weeks to clear these MAOIs' effects? -hint: think mechanism of action of MAOI...)

Tricyclic (Cyclic) Antidepressants (TCAs)

Block re-uptake of the neurotransmitters (usually NE and 5HT)
    Could be considered first-generation, kinda crappy SNRIs
    effective for about 60% of patients with MDD
Also block histamine, alpha-adrenergic and muscarinic receptors-> many side effects
Side effects: ***anticholinergic*****:** dry mouth, blurred vision, etc.
    alpha-blockade causes orthostatic hypotension and *reflex* _____*?*
    sedation (due to H1 and M blockade)
    can cause arrhythmias in overdose

Toxicity to heart and liver so **levels have to be checked (low TI!)**
    dispense to suicidal patients *with caution*.

TCAs have **many off-label indications**: **enuresis, chronic pain, neuralgia, migraine**
    low-dose doxepin (*Sinequan*) used for insomnia
Examples: nortriptyline *(Pamelor),* **amitriptyline** *(Elavil)*, protriptyline *(Vivactil)*,
    desimpramine *(Nopramin)*, clomipramine *(Anafranil)*, imipramine *(Tofranil)*,
    trimipramine *(Surmontil)*, doxepin *(Sinequan)*
Multiple drug interactions: alcohol, anticonvulsants, barbiturates, amphetamines, MAOIs…
Related drugs called "tetracyclic antidepressants" like mirtazapine *(Remeron)*, maprotiline,
    amoxapinework similarly.

Selective Serotonin Reuptake Inhibitors (SSRIs)

These only affect 5HT levels, so you don't get all the side effects of TCAs.
Prodrugs -> Liver metabolizes into an active metabolite which increases half-life
Have made a huge difference in treatment of depression… (remember some also used for anxiety)
increased suicidal ideation **black box warning** for adolescents, usually at 7-10 days

Examples:
    paroxetine *(Paxil),* sertraline *(Zoloft):* also used for OCD, PTSD, panic attacks…
    fluoxetine *(Prozac*): can be activating
    escitalopram *(Lexapro),* **citalopram** *(Celexa)*
most SSRIs reduce libido and are not "activating"
most require tapered dose when stopping; odd withdrawal syndromes (GI upset, ringing in ears)

overdose: "**serotonin syndrome**": confusion ⇒fever, tremor, hyperreflexia⇒ seizure ⇒coma
    ⇒death, usually evolves fairly rapidly

    can look a lot like malignant hyperthermia/neuroleptic malignant syndrome, but one clue
        is that **dantrolene** or dopamine agonist doesn't help

    Can also be brought on weirdly by combination of **SSRIs** with **fentanyl** or meperidine
    if supportive measures fail, use the **histamine** & **serotonin antagonist: cyproheptadine**

"Atypical antidepressants":

Are variably sedating or activating

buproprion *(Wellbutrin):* also used for quitting smoking (trade name Zyban),
seizure risk
increases libido, good for the depression part of some bipolars

SSNRIs: inhibits reuptake of serotonin and norepinephrine
must taper dose due to GI effects
duloxetine *(Cymbalta)*
venlafaxine *(Effexor),* desvenlafaxine *(Pristiq)*
SSNRIs are famous for their miserable **antidepressant withdrawal** symptoms

SARIs: Serotonin $5HT_2R$ blockers and Reuptake Inhibitors
NOTE: These are both direct AND indirect-acting drugs!
nefazondone *(Serzone),* trazodone (*Desyrel*):
can cause hypotension, drowsiness, are mild antipsychotics
vortioxetine *(Trintellix)* – mechanism not clear, also something to do with serotonin

Atypical "antipsychotics"
Supplementation with **low doses** of atypical antipsychotics like aprepitant *(Abilify*) due to 5HT (and possibly DA) activity

DRUGS for MANIA:

First of all, unless you have a lot of experience, and know what you are doing, **do not give antidepressants to a manic or bipolar disorder patient** because you might drive them into their manic phase.

Newer drugs for mania

Includes the"atypical antipsychotic drugs" (see next section)
aripiprazole *(Abilify)* Seems to work for both psychosis and depression, also autism.
olanzapine (*Zyprexa*): Can be used for mania.
Does not affect the pharmacokinetics of lithium, so don't have to adjust dose
Do not use *Zyprexa* in diabetics as it can increase blood glucose levels,
remember not to use in the elderly (see next section)
ziprasidone *(Geodon)*

Lithium

Lithium is the oldest and was the most commonly used drug in treatment of bipolar disease before the above drugs were invented because it reduces the highs of mania and improves the lows of depression. You will still see a lot of patients on lithium.
Lithium is an ion like sodium and interferes with sodium transmission; the mechanism of its affect on affective disorders is not well understood
Lithium has a **LOW Therapeutic Index (TI): toxic to heart and kidneys**
Lithium is cleared by the kidneys along with salt and water, so patients have to be cautioned **to keep themselves hydrated**. If they don't get enough salt, they can't excrete the lithium and they can get toxic, and more nauseated, more vomiting, more dehydrated, and so on...
Note: any drug that causes dehydration will make lithium toxic.
Toxicity symptoms: **nausea,** diarrhea, dizziness, tinnitus, frequent urination, blurred vision

Clear excess lithium by giving IV saline or increasing PO sodium and **hydration**.

"Mood stabilizers":

Anti-seizure drugs commonly used as mood stabilizers:

valproic acid (*Depakene/Depakote*)
carbamazepine (*Tegretol*)
lamotrigine *(Lamictal)*

ANTI-PSYCHOTICS: Anti-Dopamine Drugs, mostly

Psychosis is a medical disorder which causes a gross distortion or disorganization of a person's mental capacity, affective response, ability to recognize reality, communicate with others, and cope with demands of everyday life. Can be genetic (some forms of schizophrenia) or organic (related to toxicity). When controlled with drugs a patient can lead a functional life. Psychosis is related to Dopamine, Serotonin and Histamine. There are at least 5 receptors for dopamine and 13 for serotonin alone, but **it is easiest to think of all these drugs as anti-dopamine** when you are first learning them

There are a number of antipsychotic ("**neuroleptic**") classes available.

The oldest ones are the phenothiazines and haloperidol:
They have a **higher rate of EPS** than the newer "atypical" antipsychotics.
Many of the "atypical" antipsychotics antagonize serotonin to a greater extent than dopamine. To make things even a bit more confusing, although they all *mostly* act on the dopamine receptor (and serotonin receptor), many drugs also crossreact with the histamine, cholinergic and alpha-sympathetic receptors in the brain.

However, to understand the main side effects and the main actions of these drugs for a beginning pharm student, **it is truly easiest to think of all of these drugs as anti-dopamine** drugs first and foremost.

SIDE EFFECTS: Most commonly include: dry mouth, sedation & **basal ganglia**-related movement disturbances called extrapyramidal reactions.

Extrapyramidal Symptoms (EPS):

Dystonic reactions: muscle twitches and spasms caused by abnormal muscle tension.
Akathisia: constant pacing and restlessness
Parkinsonism: muscle rigidity, shuffling gait, masklike face
Tardive Dyskinesia: unwanted movements
a constant writhing of mouth, jaw, arms (pill rolling, cogwheel rigidity)
risk for this goes up 4% per year of use of the drug
Sometimes doesn't go away (or worsens!) after stopping the drug.
Anticholinergics are sometimes used to reduce severity of side effects (see p. 15)

***Neuroleptic Malignant Syndrome (NMS)**: Confusion/catatonia, hyperthermia (fever, sweating), muscle rigidity, tachycardia (autonomic BP instability)
treat with supportive care, **dantrolene** (and **stopping the drug**!)
AND a dopamine agonist like **bromocriptine** or **amantadine**

Classic "Antipsychotic" (neuroleptic) drugs:

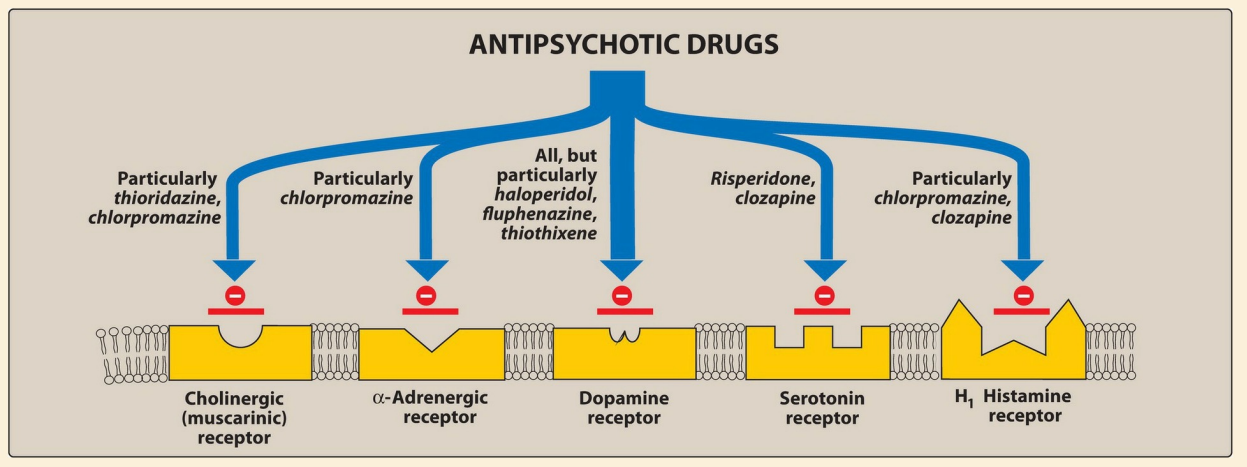
Phenothiazines: ex: **chlorpromazine** *(Thorazine):* Used most as **antipsychotic**
thioridazine (*Mellaril*), fluphenazine *(Prolixin),* perphenazine, trifluoperazine

Some are used more as **anti-emetics**:
- **prochlorperazine** *(Compazine)*
- promethazine *(Phenergan):* -antinausea effect due to cross-rxn with histamine receptors

Butyophenones**: Haloperidol** *(Haldol)*, droperidol
Very potent; has the basal ganglia side effects like phenothiazines
Used IM when a patient goes completely bananas because controls an acute psychotic episode in 30 minutes (usually given with a fast-acting sedative like lorazepam)
Other first gen antipsychotics: loxapine, molidone, pimozide, thiothixine,

"Atypical" (newer) "Anti-psychotics":

Atypical "anti-psychotics" turn out to be good for other problems, including depression and mania. They block **dopamine receptors**, but also affect **serotonin**, **histamine** (and even adrenergic and cholinergic receptors Gah!).



Since the atypicals work less through dopamine and more through other neurotransmitters, they have **<u>less</u> EPS effects than standard antipsychotics, but they still have EPS effects**

Many atypicals weirdly **increase mortality in the demented elderly** for *no apparent reason*

Although this mortality increase was originally noted with atypical antipsychotics, ALL antipsychotics carry a black box warning against use of antipsychotics in the demented elderly. But the FDA doesn't consider it a contraindication, because otherwise there are no drugs you can use. Yay for lawsuits!

aripiprazole (*Abilify*): also used as adjunct for Major Depression, mania, Tourette's
olanzapine (*Zyprexa*): orthostatic hypotension due to action on histamine-1 receptors.
-**raises glucose levels in diabetics**, used also for mania

respiridone (*Risperdal*): causes weight gain, orthostatic hypotension
ziprasidone *(Geodon)*: also used for mania
clozapine (*Clozaril*): has more serotonin than anti dopamine effects
also anticholinergic effects (helpful in PD)
causes aplastic anemia or seizures (less helpful)
quetiapine *(Seroquel):* like clozapine without the aplastic anemia

Clinical critical thinking questions:
If these drugs affect ADRenergic and CHOlinergic receptors, what is the likelihood they affect sexual function?
What do you do if you have a Parkinson's Disease (PD) patient (who needs a dopamine agonist drug) who has psychosis? Parkinson's patients NEED dopamine to move!

pimavanserin *(Nuplazid)* approved 2016 specifically for psychosis in Parkinson's
Blocks $5HT_{2A}$ receptor without affecting DA receptors.
April 2018 a report came out by CNN with deaths reported which is now causing pressure on the company that makes it so...
How might the deaths in Parkinson's patients be explained?
(Yay lawsuits?)

2. Anticholinergics: In practice, anticholinergics are a secondary treatment used for treatment of the side effects of the antipsychotics (and as we'll see in a few pages, the normal symptoms of Parkinson's Disease). So they're good at reversing some of the **movement** problems caused by dopamine blockade disease (movement regulation is complicated, yo!).
Some examples are:
benztropine (*Cogentin*), that we've already learned, or
trihexphenidyl (*Artane*).

*Remember that video of "Gerald" the schizophrenic? Anti-psychotics like Haldol mimic the chemical situation in Parkinson's disease, so the **benztropine** Gerald was receiving was meant to reduce the severity of his side effects!*

Drugs for Parkinson's Disease ("dopamine agonist drugs")

Control of movement and Parkinson's Disease

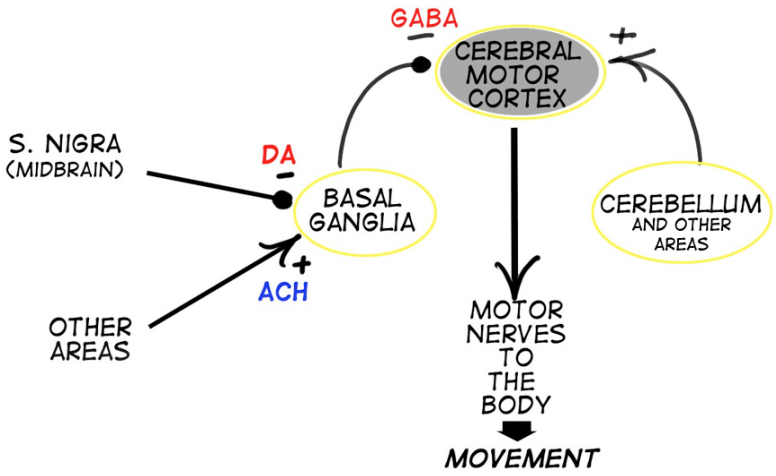
Parkinson's Brain Movement diagram

Many brain centers are involved with various types of movement. To *grossly* oversimplify:

Dopamine is *generally* inhibitory when we talk about movement with regards to Parkinson's.

If there is a deficiency of dopamine activity, the basal ganglia are not inhibited and are therefore overactive ("dis-inhibited"). In turn the over-active basal ganglia *over-inhibit* the motor cortex. The net result is inhibition of aspects of normal movement.

Another Diagram



Parkinson's disease is a progressive neurologic disease that strikes 1/100 Americans, usually after age 60. It is not genetic. In this disease the *substantia nigra* slowly dies off. So the basal ganglia are dis-inhibited, leading to "frozen" rigid muscles, odd tremors, changes in posture and balance, and other uncontrolled movements. So, to treat the disease, we use drugs to increase the amount of dopamine.

You can't just administer pure **dopamine** because it **is degraded too fast in the bloodstream** and it **doesn't easily cross the Blood-Brain Barrier (BBB)**… so we need an indirect way to increase dopamine activity. Most commonly you can use:

L-DOPA aka levadopa: this is just the dopamine precursor "DOPA"
(review the NE production nerve diagram in the ANS handout)

L-DOPA is quickly degraded in the bloodstream before even getting to the brain, so it is usually given in combination with **Carbidopa** (*Lodosyn*).

Carbidopa inhibits the dopa-decarboxylase enzyme in the bloodstream and thereby reduces the total dose of DOPA you need to give! This reduces side effects. Carbidopa does not cross the BBB

L-DOPA/carbidopa available as a single combination pill ***Sinemet***®.

Even with the carbidopa combination, the L-DOPA doesn't last very long in the bloodstream so patients end up taking the **drug 8-12 times a day.**

Side effects include nausea, blood pressure and movement problems as the drug levels rise and fall and the relative amounts of dopamine and ACh change.

Drug interactions: DOPA interacts with most antipsychotics *(Why?)*
Vitamin B_6 increases metabolism of levo-dopa

Suddenly stopping Sinemet can cause Neuroleptic Malignant Syndrome*!*
*(How? Hint: think dopamine **activity**!)*

On-Off Phenomenon: Certain fluctuations in clinical response to levodopa occur more and more as treatment progresses. Usually this is initially related to the timing of doses and are called "**wearing off"** or "end of dose" reactions.
Off-period of akinesia (little movement)
On-period of improved mobility but dyskinesia (too much movement)
In some patients the relationship to timing of the dose is lost!

Since L-Dopa is increasing dopamine levels, you get **side effects** from dopamine action, most notably nausea, rapid heart beat, psychiatric issues and OTHER movement issues.
Brown pigment in saliva and urine due to melanin made by catecholamine oxidation

<u>Other drugs used to treat Parkinson's Disease:</u>

1. Dopamine agonists:

A. Indirect Dopamine Agonists

Amantadine (*Symmetrel*) – this antiviral drug stimulates the release of Dopamine from vesicles in nerve endings (an indirect effect).

Enzyme Inhibitors (and therefore increase levels) of dopamine

MAO-B Inhibitors: MAO-B form of Mono Amine Oxidase is specific for Dopamine (MAO-A breaks down NE and 5HT). Inhibiting MAO-B results in higher levels of dopamine. Side effects are like those above, some reports of manic/psychotic behavior.

- reduces amount of levo-dopa needed
- these appear to slow progression of the disease
- if taken at higher doses, will inhibit MAO-A as well (dietary restrictions)

-examples: selegiline (*Eldepryl*), **rasagiline** (*Azilect*)
selegiline has an amphetamine-like metabolite - insomnia

COMT Inhibitors: Catechol-O-Methyl Transferase: another enzyme that breaks down DA
tolcapone (*Tasmar*): used with levo-dopa to reduce the wearing off effect
must monitor LFTs; causes **severe liver necrosis**
entacapone (*Comtan*)

B. Direct Dopamine Agonists

bromocriptine (*Parlodel*) –also used for prolactin-secreting tumors
apomorphine – used acutely for a hypomobility "off" episode
pergolide (*Permax*)
ropinirole (*Requip*)
pramipexole *(Mirapex)*- depends on healthy kidney

excreted by renal tubular secretion of bases; ex. cimetidine ⇑ $t_{1/2}$ by 40%

2. Anticholinergics: For Parkinson's patients, anticholinergics are a secondary treatment. They're good for early symptoms like **tremor** or **drooling**, as well as reversing some of the **movement** problems caused by Parkinson's disease (movement regulation is complicated, yo!). Some examples are:

benztropine (*Cogentin*), that we've already learned, or
trihexphenidyl (*Artane*).

OTC DRUGS FOR PAIN

Pain consists of the sensation of pain (nociception) and the emotion of perceiving pain (suffering). **To stop pain** you can either (broadly speaking): blunt or **reduce the cause of the pain (anti-inflammatories), reduce the transmission of pain (local anesthetics) or reduce the perception of pain (opiates & Tylenol)**. Numerous neurotransmitters and signaling molecules are involved in the response, transmission and perception of pain.

Analgesia = reduction of pain **Anesthesia** = loss of sensation

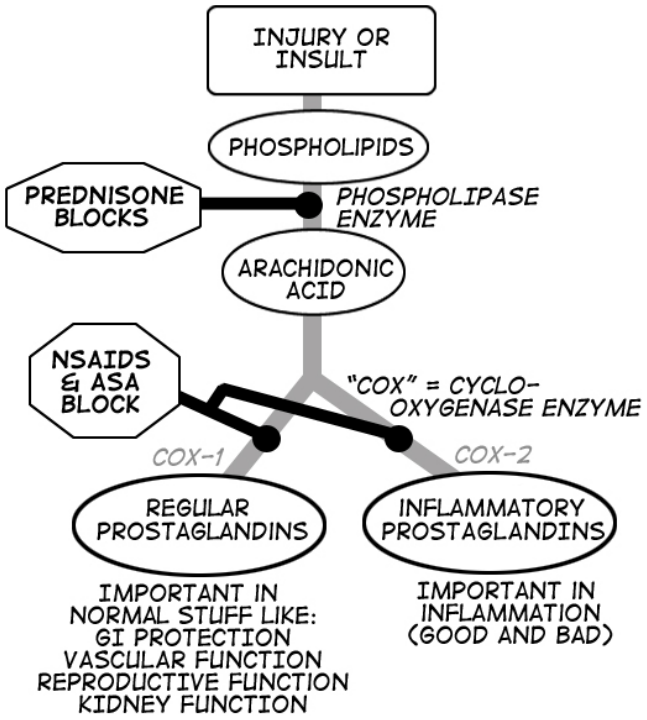
NON-OPIOID ANALGESICS

ASA and NSAIDs

How do anti-inflammatory drugs work? Let's look at aspirin (ASA). **Aspirin can reduce inflammation, but it also reduces fever, relieves mild pain and prevents clotting**. How can one drug do so many things?

Whether we talk about the allergic response, or the more generalized inflammatory reaction of cells due to insult or injury (or infection), there are some common events that take place: redness, swelling, heat production and pain. *(In Latin:"rubor, tumor, calor, dolor")* This is regulated via immune cells, enzymes and other chemical mediators produced via multiple pathways.

One such pathway is the arachidonic acid pathway, which, through the action of the enzyme cycloxygenase (**COX-1, COX-2**), produces **prostaglandins** as well as other inflammatory factors. There are a wide variety of prostaglandins, and they are very useful in normal tissues in processes having nothing to do with pain or inflammation (such as protective mucus production in the stomach). In theory, the "normal" "good" prostaglandins are made by the COX-1 enzyme. The inflammatory pain-inducing prostaglandins are made mostly by COX-2.



The drug **aspirin (ASA) inhibits *both* the COX-1 and COX-2 enzymes**.
(They are "COX Blockers", although no one calls them that)

We usually use aspirin (and NSAIDS) to treat unwanted symptoms like pain and inflammation due to actions of COX-2.

Side effects of (like reduction of stomach mucus production) are usually due to the drug also blocking the actions of COX-1.

Additionally, it is critical that you understand that the **normal actions of the prostaglandins** (and related molecules like thromboxanes and

leukotrienes) **have many actions** in the body, **some of which oppose each other,** which explains why **aspirin** vs **other NSAIDs** do not have the same effects.

For example: **aspirin reduces** the chance of heart attack, **but naproxen increases** the chance of heart attack. **Aspirin** and the **other NSAIDS** are **not interchangeable**.

By the way: **NSAID stands for *Non Steroidal* Anti-Inflammatory Drug.** .
Technically, Aspirin is considered an NSAID since it isn't a steroid, but because it is SO different in its effects on cardiovascular health and clotting, as well as its indications, you should think of it as a different drug.

Aspirin's effects are ***irreversible***. NSAIDS like ibuprofen ***reversibly*** inhibit COX synthesis.

A *steroidal* anti-inflammatory drug refers to cortisol agonists like **prednisone**. Glucocorticoids reduce inflammation by inhibiting phospholipase production as shown in the figure on page 1. A topical steroid you may be familiar with is **hydrocortisone**.

Also note: Unlike some opioids, pain relievers like aspirin, NSAIDS and acetaminophen have a ceiling to the pain relief they can provide, **so more is NOT better**.

ASPIRIN (ASA)

stands for Acetyl Salicylic Acid)

chemical class is "**salicylates**"

DO NOT confuse aspirin with other salicylates like:
methyl salicylate (*BenGay, Oil of Wintergreen*) – poisonous PO, used topically only
trolamine salicylate *(Aspercreme)*
para-amino-salicylic acid : bacteriostatic against tuberculosis
salicylic acid: topical acne drug that burns off top layers of skin
bismuth subsalicylate (*Pepto Bismol):* prevents bacterial adherence to GI mucosa

Indications: **pain:** at usual 325mg dose
fever: at usual 325mg dose
inflammation: usually requires *very high* doses
stable **angina** *(see unit 3)*
some types of acute MI
a history of MI, angina, CVA, TIA
-ASA is an "antiplatelet" drug
-for anticoagulation, a **low dose 81mg/day** is as effective as the higher doses but does **NOT** increase risk of GI ulcer.
low dose ASA may also reduce risk of colon and prostate cancer!

NOTE: concomitant chronic use of other NSAIDS will negate the beneficial effect of low-dose aspirin therapy to prevent <u>recurrent</u> MI and stroke

Contraindications for Aspirin:
Stomach Ulcers
Children under 18, esp. those with **flu/fever** symptoms: **Reye's Syndrome!**
Pregnant women (esp. third trimester) Pregnancy Category D
concern is premature closure of **ductus arteriosis** (see below)
Bleeding or bleeding disorders
One low dose ASA can prolong bleeding time for up to two weeks!
Be especially careful about possible bleeding into the brain or spinal cord
"**Samter's Triad**": 1. **nasal polyps**
2. **asthma**
3. **allergy-*like* reactions to ASA/NSAIDS**
Note: Patients can also be truly allergic to ASA & NSAIDs

Side Effects: Bleeding, GI disturbances (**GI bleeding**, stomach upset, diarrhea, nausea etc)
Only at higher doses!
ASA Toxicity aka **"Salicylism"**: **tinnitus**, **tingling in fingers**
High levels of ASA in bloodstream lowers pH (this is called metabolic acidosis)
In response, rapid breathing/panting increases the blood pH!
(that effect called respiratory alkalosis it's so cool!)
Severe poisoning: seizures, coma

Beware aspirin disguised in other OTC and prescription products such as
Anacin, Excedrin, percodan, Alka-Seltzer, Pamprin, OTC migraine drugs

NSAIDS like ibuprofen

ibuprofen (*Advil*, *Motrin*)

Indications: **pain**
fever
inflammation (can take 3-10 days to get maximum effect)
very high dose NSAIDs are used for some types of arthritis
patent ductus arteriosus in babies born premature (used in IV form)

Contraindications:
Cardiovascular or cerebrovascular disease
BLACK BOX WARNING 1: increased risk of MI or CVA with increased dose and duration of use.
BLACK BOX WARNING 2: causes GI disease (ulcer, etc)
Bleeding: ibuprofen prolongs bleeding time mildly, but not in a useful way.
Kidney disease, heart failure,
Pregnant women (esp. third trimester) Pregnancy Category D
Ibuprofen can close the ductus arteriosus, right? You don't want that to happen until after the baby is born and can breathe air!
Allergy and/or **Samter's Triad**

Side effects: **GI ulcers, GI bleeding**

Toxicity: (GI injury can be prevented with the **prostaglandin agonist misoprostol**)
Blurred vision, tinnitus similar to salicylism
Kidney failure :-(

Also, different NSAIDs seem to act preferentially on different areas of the body.
Ex. **ibuprofen** is particularly good for **menstrual cramps** as compared to some other NSAIDS.

NSAIDs like ibuprofen negate the beneficial actions of antiplatelet drugs like ASA or *Plavix*
Drug interactions: anticoagulants, lithium, SSRIs, loop diuretics, beta-blockers, ACE inhibitors, (high protein binding)

Other NSAIDS that are like ibuprofen: All carry the same black box warnings

1. naproxen (*Aleve*): PO
Naproxen also comes in combination with a proton pump inhibitor lansoprazole in OTC formulation called *Prevacid*.
Note: Some recent correlative studies suggest that naproxen may not be as likely to cause MI or stroke as ibuprofen.

2. ketorolac (*Toradol*): Used PO, **IV, IM** and as eye drops for post-surgical pain
(Eye drops don't carry a black box warning)

3. celecoxib (*Celebrex*): A COX-2- specific NSAID
Indications: severe **arthritis** (various forms)
juvenile arthritis
ankylosing spondylitis (severe back arthritis seen usu. in young men)
familial adenomatous polyposis (FAP) colon polyps -*weird!)*

Celecoxib *theoretically* was not going to cause the COX-1 side effects of other NSAIDS. It *does* reduce GI side effects but reduction of GI toxicity is lost if *any* other NSAID is added, including low-dose aspirin. Also, it still **increases risk of MI** (by four-fold!!)

Tylenol®

acetaminophen (*Tylenol*) is chemically a para-aminophenol derivative:
Mechanism of action: Acts **centrally** in the brain to reduce pain and fever.

Lab evidence shows that acetaminophen also acts on prostaglandin synthesis, but only centrally (in the brain). Perhaps there is a brain-specific COX-3 enzyme? Still not clear.

Indications: **pain, fever** (no action on inflammation)
Contraindications: **liver disease**, **alcoholism**, some anemias

Pharmacodynamics: **Metabolized in the liver to a very toxic metabolite that is normally immediately neutralized by glutathione**. In liver disease or overdose, this toxic metabolite kills liver cells.
The metabolite is neutralized also by **N-acetylcysteine.** ⇐ the antidote for poisoning

Side effects/toxicity: Acutely: **hepatotoxicity**
Increased lifetime dose increases chance of kidney failure later in life

VERY LOW TI
Acetaminophen poisoning: Single dose: **>7.5-10g** (liver changes seen as low as **4g** if fasting)
toxicity with chronic use is ~ 4-6g/day
(kids 0-5y: 200 mg/kg over 8 hours, over 6y 200 mg/kg over 24 hours)

Toxic **chronic** dose: 4 g/d in adults, 75 - 150mg/kg in children)

Horribly, **it takes up to two weeks to die from a toxic dose.**

Toxicity timeline: Stage 1: GI symptoms (nausea), may not start for 12 hours after dose
Stage 2 (24-72 h): increased LFTs (liver function enzymes)
Stage 3 (72-96 h): liver failure
Stage 4 (**up to 14 days later**): death or recovery with liver transplant

N-acetylcysteine (the "antidote" to acetaminophen) **must be administered in the first 24 hours**

Beware acetaminophen in other OTC and prescription drugs: Tylenol with codeine, Nyquil, Percocet, Vicodin,Alka-Seltzer Aspirin-free, Benedryl Allergy Sinus, Dimetapp, Theraflu

Several drug interactions: **alcohol**, warfarin, carbamazepine, phenytoin, others

New labeling intended to make dosing easier to understand and reduce risk of overdose

Example: Extra-strength 500mg Tylenol (and generic clones)
Take 2 caplets (1,000 mg) every 6 hours while symptoms last (revised from 2 caplets every 4 to 6 hours).
Do not take more than 6 caplets (3,000 mg) in 24 hours (revised from 8 caplets in 24 hours).
"Severe liver damage may occur if more than 4,000 mg of acetaminophen is taken"

Fun Fact! In Europe acetaminophen has the generic name "paracetamol" or "APAP"
(APAP because the chemical name N-Acetyl-P-AminoPhenol)

Headache and Migraine Drugs

There are over 150 classifications of headache. Major classes used to treat "migraine" are:
OTC Pain relievers
Triptans (constrict blood vessels and block pain awareness in the brain)
- These drug names end in **-triptan**
- ex. sumatriptan

Ergots
- Used at the onset of a migraine
- Can make vomiting worse
- Drug names end in **-ergot**

Opioids
Glucocorticoids
Anti-nausea drugs (see GI Lecture)
Preventative drugs:
- **Beta-blockers** like **propranolol**
- Calcium channel blockers
- ACE Inhibitors

Antidepressants: TCAs, SSRIs, venlafaxine *(Effexor)*
Antiepileptic drugs: valproic acid, topiramate *(Topamax)*
Botox injected into muscles of neck and head every 3 months

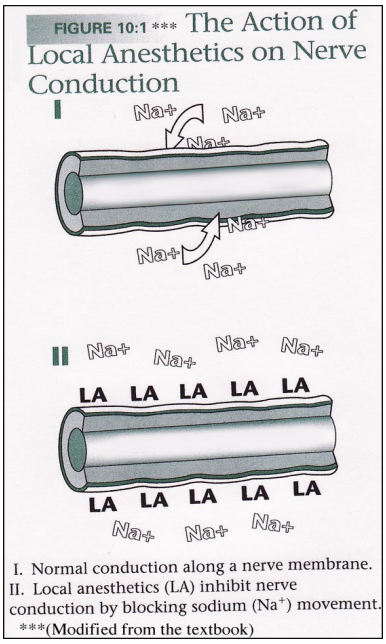
LOCAL ANESTHETICS

(Chapter 10)

Used **locally**:

Topically (creams/ gels) or Injected (infiltrative, intradermal, nerve block, epidural, etc.)

Many available OTC (over the counter): potential for overdose



Mechanism of action: affects permeability of voltage-gated sodium **(Na+) channels** by binding receptors on the channels themselves

LAs first block small fibers with smaller myelin sheaths, so:

Order of loss of nerve function: Pain ⇒Temperature ⇒Touch

They recover from LAs in reverse order.

Why does your dentist tell you not to eat for an hour after dental work?

Adjuncts:

Bicarbonate: LAs are weak bases, so bicarbonate is added to solution to allow the drug to penetrate myelin and get to nerves.

Epinephrine: Local vasoconstriction of blood vessels (⇓blood flow)
Increases duration of action (slows loss of the LA)
Usually ***very*** diluted (i.e. 1:200,000)

Overdose: **First complains of weird taste in mouth.**
Then, hypotension (↓BP) , ↓heart rate and arrhythmias
CNS effects direct neural toxicity at very high doses
(dizziness ⇒agitation ⇒ tremor⇒ seizure ⇒coma ⇒ death)

Black box warning for some drugs for heart patients, pregnancy

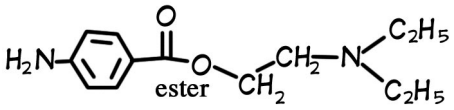
<u>TWO MAIN CLASSES of Local Anesthetics</u>

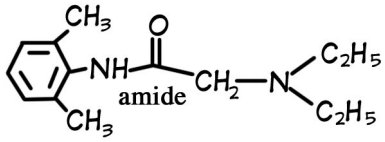
ESTERS

Metabolized by plasma cholinesterases

allergy more common than for amides
-patients are allergic to a metabolite of the drug

Examples: **procaine** *(Novocain),* benzocaine *(Solarcaine)*
because of **allergy issues**, rarely used by dentists





lipophilic region *hydrophilic region*

AMIDES

Longer acting
Metabolized by liver with some active metabolites
Excreted by kidney in urine

Examples: **lidocaine** *(Xylocaine, Soalarcaine, Lidoderm)*: indicated for local anesthesia and heart arrhythmias, contraindicated in patients with sulfite allergies
other amides: bupivacaine (*Marcaine*), prilocaine (*Citanest*), articaine *(Septocaine)*

Popular OTC TOPICAL Pain Killers:

Many of these compounds have been used for hundreds of years, but even now their mechanisms of action are poorly understood or attributed to placebo effect

menthol (various throat lozenges, *Icy Hot*® cream)
- inhibits pain nerves by interfering with calcium movement
  - lozenges inhibit cough only if it is caused by irritation of the throat
- "cooling effect" is due to action on cold and heat receptors (also via calcium channels)
- also shown to bind kappa opioid receptors in the lab (see opioids on next page!)
- extracted from mint plants (peppermint odor)
  - Sept 2012 FDA warning of cases of burns after topical use

methyl salicylate (*BenGay*, Oil of Wintergreen) – poisonous PO, used topically only
- inhibits prostaglandins similar to aspirin
- absorption through skin adds to this action (but **do NOT EVER take internally**!!!!)

trolamine salicylate (*Aspercreme)*- no convincing proof OTC is better than placebo

capsacin - the hot molecule that makes chili peppers hot
- low doses found in over-the-counter medications are only modestly better than placebo
- high doses given in clinic setting (can cause burns) helpful in some pain types
- binds its own receptor (TRPV1) and changes pain receptors and nerves in several ways
  - including changes in calcium movement
- may have role in coughing
- does increase blood flow in area applied

camphor - also binds a variety of receptors involved in pain and cough
- binds TRPV1, TRPV3 and TRPA1

Counter-irritants: Menthol, camphor, capsacin, and methyl salicylate are often cited by all-natural enthusiasts as example of "counter-irritants", compounds that cause superficial pain to relieve deeper pain
- There is very little evidence that these are better than placebo to relieve pain
- Previous theories about substance P depletion as a basis for the idea disproved
- Other promoted counter irritants include: turpentine, iodine, mustard

Consider the placebo effects of rubbing, moisturizing, odors or the sensation of hot or cold when evaluating the actions of many OTC and all-natural topicals.

CNS Study Tip:

This is how I personally categorize CNS Drugs in my head: This is an introductory pharm class, so I divide up these drugs in the **simplest way** I know, and that is by major neurotransmitters

Neurotransmitter	**GABA**	**Norepinephrine (NE)**	**Serotonin (5HT)**	**Dopamine (DA)**	**Endorphins (Opiates)**
Actions of the Neurotransmitter	Reduces brain activity, Makes you sleep, Makes you calm	Wakes you up, Activates you, Helps you to focus, Activates fight or flight, Reduces appetite	Makes you happy Makes you content	Makes you lusty or furious Helps you move smoothly	Make you high, Reduce coughing, Make you constipated, kill pain
Diseases/conditions that are related in some way	Insomnia Agitation Seizures Anxiety Need for Anesthesia	Narcolepsy ADHD Obesity	Depression Anxiety	Parkinson's Disease Psychosis Vomiting Galactorrhea (probably also depression and ADHD)	Pain, Cough, Diarrhea, Euphoria
Some Example Drug Classes	Benzodiazepines Barbiturates New GABA-agonists	Amphetamines	SSRIs SSNRIs MAOI-A TCAs	L-DOPA MAOI-B	Opiates

...and then there are only a few weird things left to remember, like:
melatonin for insomnia
buspirone for anxiety
some seizure drugs (phenytoin, carbamazepine, valproic acid)
buproprion for depression
lithium, seizure drugs or antipsychotics for mania
amantadine, COMTIs for Parkinson's

Too much dopamine: you get psychosis and vomiting
(the side effects of anti-Parkinson drugs)

Too little dopamine: you get Parkinson's and movement disorders
(the side effects of anti-psychotics)

Pain:
ASA: pain fever inflammation MI/Stroke; Reyes, Salicylism, minidose, GI effects
Ibuprofen: pain fever inflammation: GI effects, Increases MI/CVA
Tylenol: pain fever: liver toxicity, N-acetylcysteine
Local Anesthetics: Block Sodium (Na^+) channels