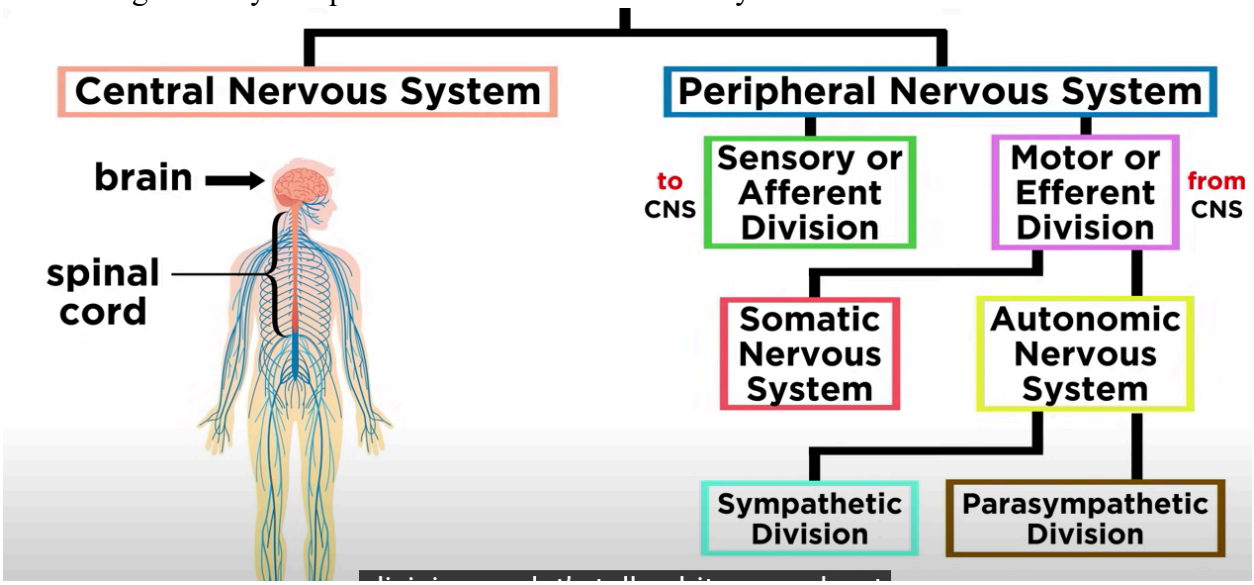
Autonomic Nervous System, Neurological Illness, and Anticholinergics

Selective Serotonin reuptake inhibitors

- Goal: treat depression by increasing serotonin levels
- Mechanism of action: uses reuptake where a transporter protein, transports excess transmitter molecules out of the synaptic cleft and into the neuron that released them. Inhibit the reuptake of serotonin
- Causes: levels of serotonin the synaptic cleft to rise.
- More to it! Symptoms improve after four weeks even though serotonin levels rise within an hour of taking medications. Therefor it is not just the increased in serotonin levels but actually other mechanisms are happening.

Autonomic Nervous System

- Automatic processes such as heart beat
- Regulated by components of the central nervous system



- Innervates smooth and cardiac muscle
- Neurons are lightly myelinated or nonmyelinated and a two-neuron chain
    - 1. Preganglionic neuron
    - 2. Post ganglion neuron
        - Release acetylcholine or epinephrine.

Sympathetic Division

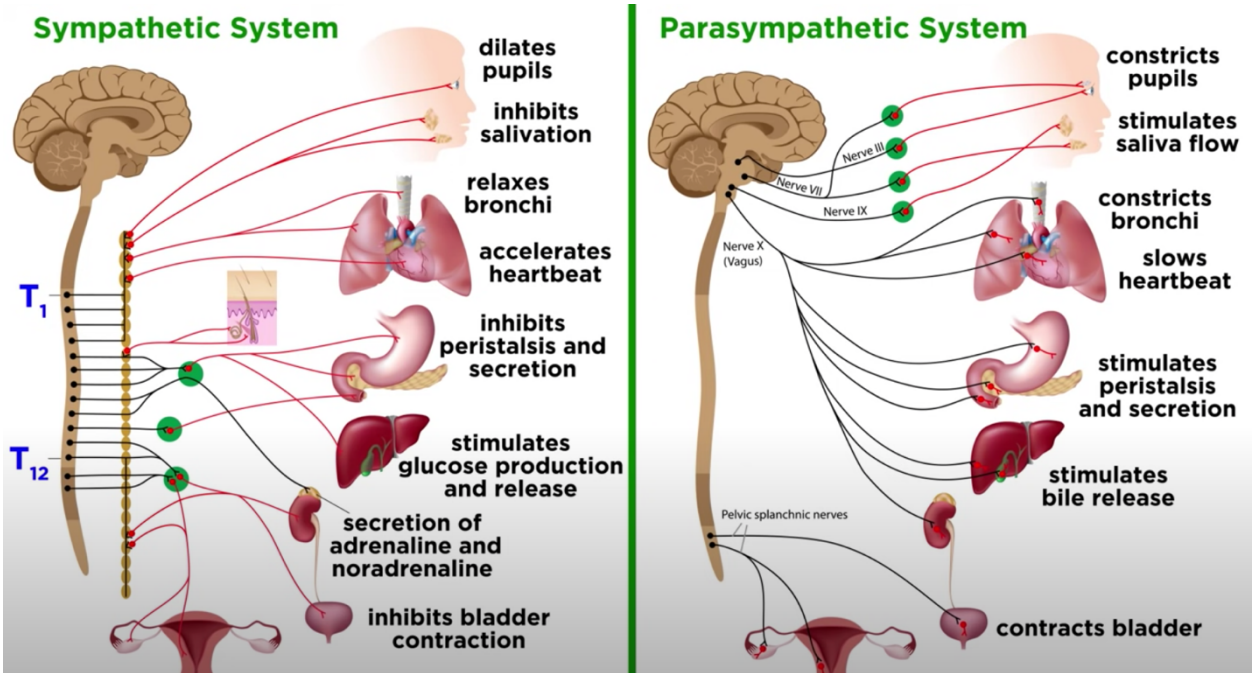
- Fight or flight
- Raising HR
- Blood vessels constrict
- Glucose release
- Fibers originate in the Thoracic and lumbar regions of the spinal cord
- short preganglionic and long postganglionic fibers
- ganglia near the spinal cord
- Regulates sweating (controls body temperature)

- Influences metabolism
- Influences kidney activity

Parasympathetic Division

- Rest and digest
- General maintenance that occur in a state of relaxation
- Fibers originate in the brain and sacral region of the spinal cord (opposite ends of the central nervous system)
- Long preganglionic and short postganglionic fibers

They work together in dual innervation
One may dominate due to immediate need of the organism

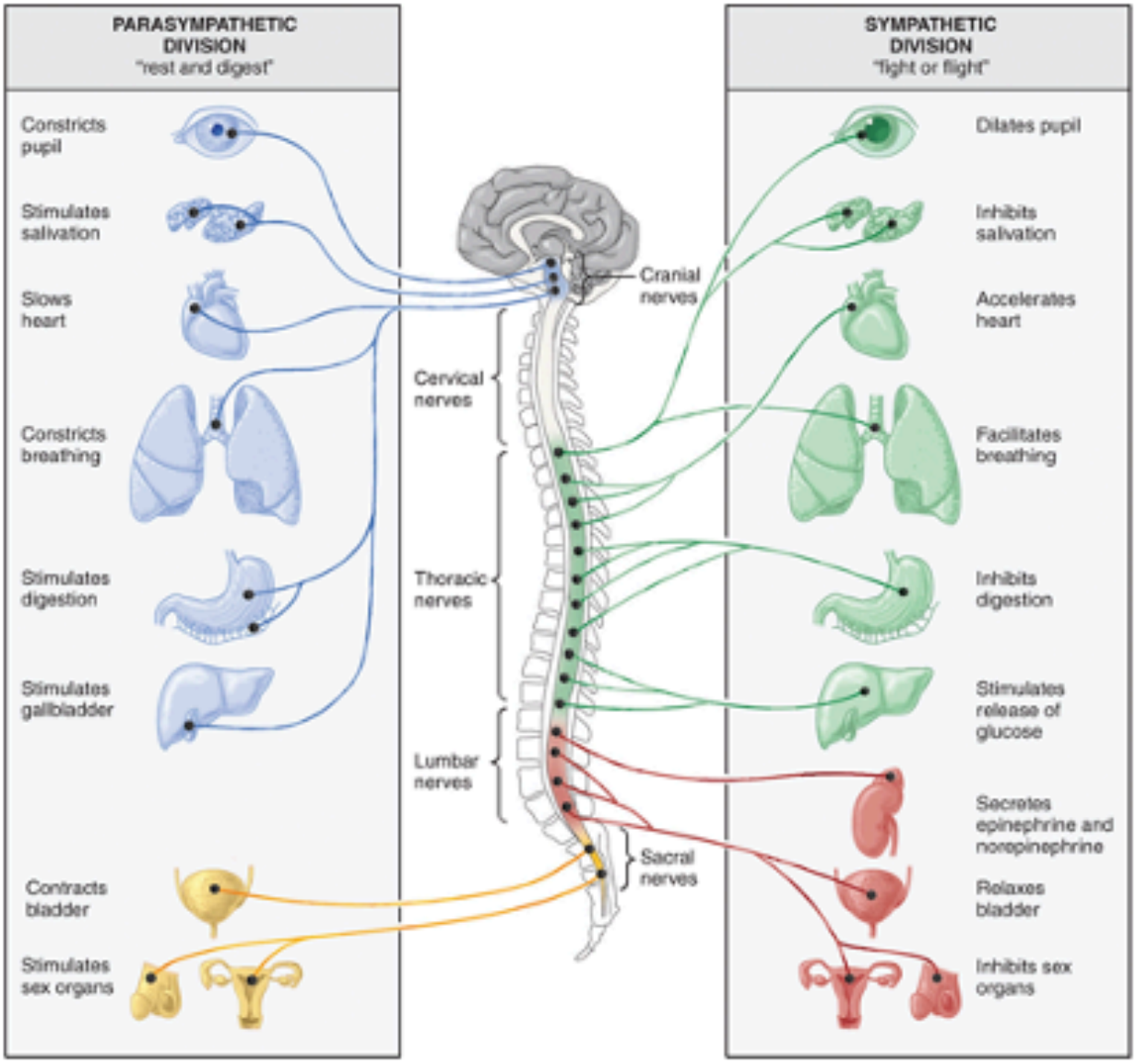


Chapter 12 Autonomic Nervous System

- Review of Neurotransmitters and the Autonomic Nervous System
- Two major divisions
  - Central nervous system (CNS)
    - Brain
    - Spinal cord
  - Peripheral nervous system (PNS)
    - Nerves that carry messages to and from the CNS
  - Overview of the Nervous System
- Peripheral nervous system
  - Neurons
    - Sensory
      - Specialized nerves
        - Light
        - Specific chemicals in body fluids
    - Motor
      - *Respond* to changes by moving muscles or secreting chemicals

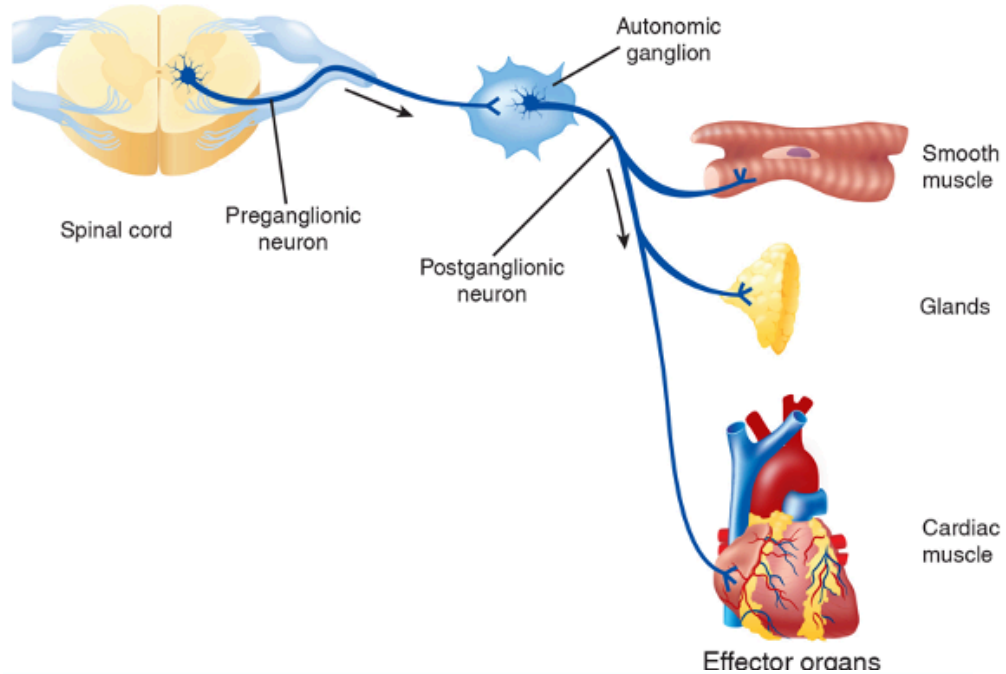
- Peripheral nervous system
  - Neurons
    - Motor
      - Somatic nervous system
        - Voluntary control over skeletal muscles
      - Autonomic nervous system (ANS)
        - Involuntary control over vital functions of the cardiovascular, digestive, respiratory, and genitourinary systems

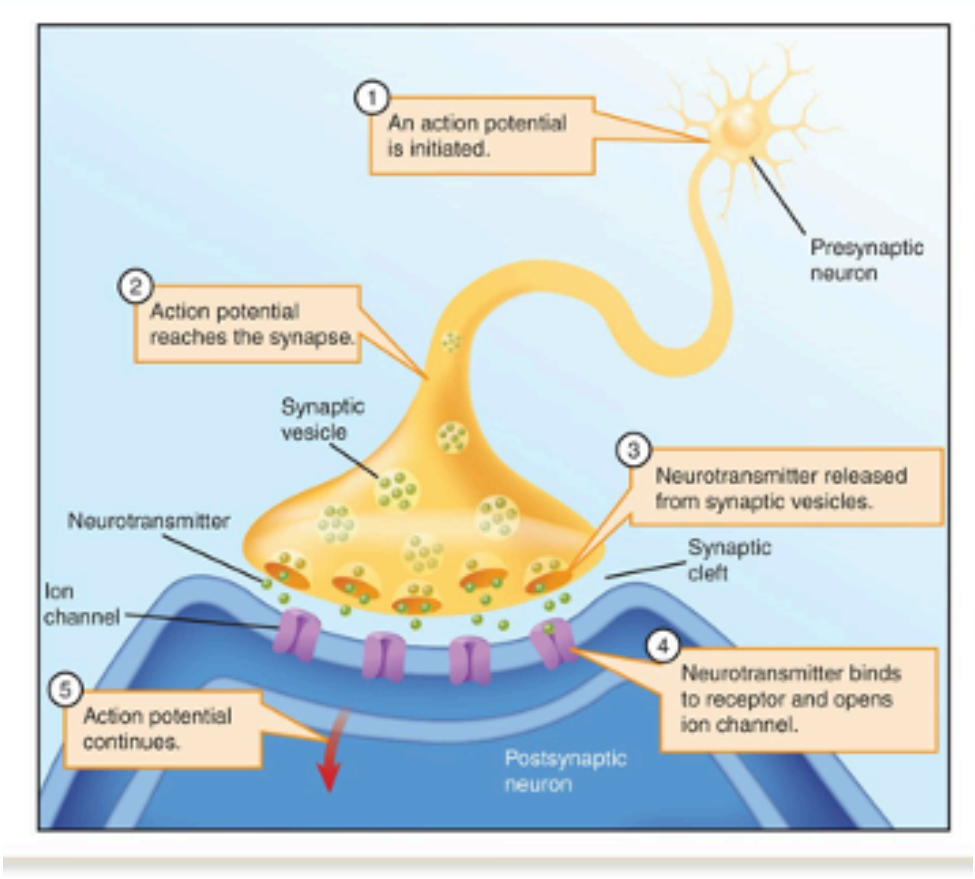
- Autonomic Nervous System three main activities
  1. Contraction of smooth muscle of the bronchi, blood vessels, gastrointestinal tract, eye, and genitourinary tract
  2. Contraction of cardiac muscle
  3. Secretion of salivary, sweat, and gastric glands
- Structure and Function of the Autonomic Nervous System
- Two divisions
  1. Sympathetic
  2. Parasympathetic
- Organs and glands
  - Receive nerves from both branches
  - Opposing actions



- Diagram shows parasympathetic nervous system vs sympathetic nervous system
- Homeostasis
  - Achieved by changing one or both branches
    - Increasing firing of sympathetic nerves
    - Decreasing firing of parasympathetic nerves
- Synaptic Transmission
- Synaptic transmission allows information to be communicated between two nerves or from nerves to muscles or glands.

- Autonomic Nerve Pathway



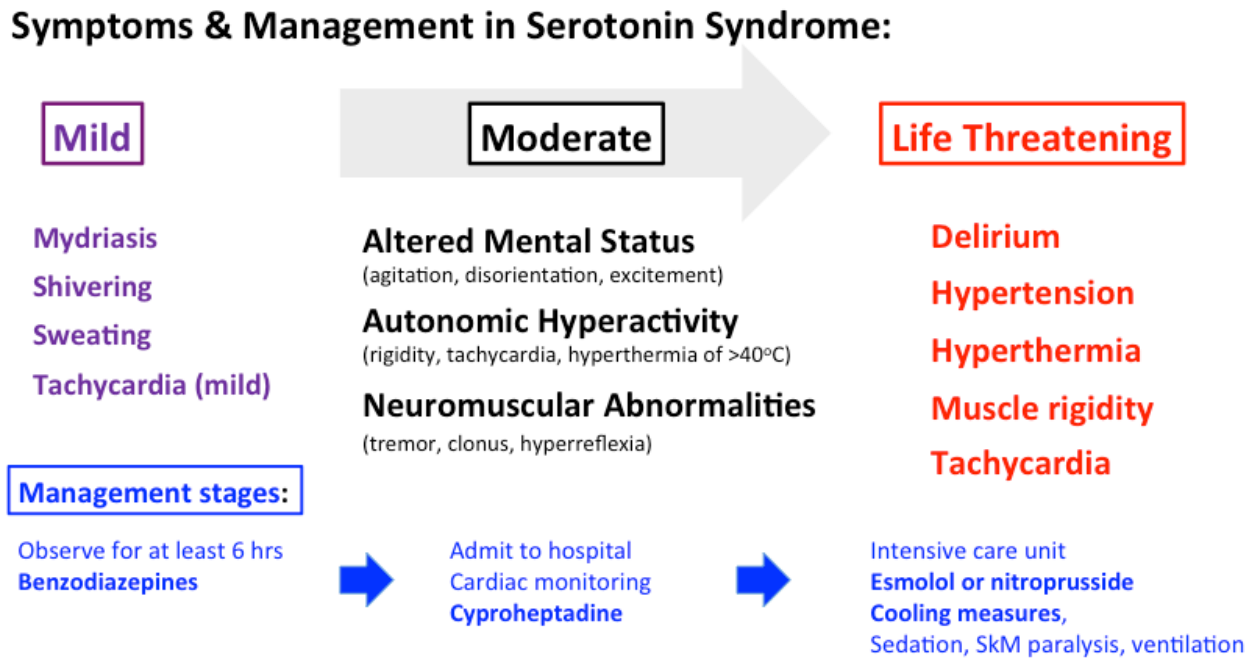


Synaptic Transmission

- Autonomic drugs exert their effects by acting at synapses.
- Two-neuron chain of ANS allows multiple locations drugs can act
  - CNS
  - Ganglia
  - End of the chain
- General mechanisms of ANS drugs
  - Synthesis of neurotransmitter in preganglionic nerve
  - Prevent storage of neurotransmitter in vesicles within preganglionic nerve
  - Influence release of neurotransmitter from preganglionic nerve
  - Bind to neurotransmitter receptor site on postganglionic nerve
  - Prevent normal destruction or reuptake of neurotransmitter
  - May be preventing reuptake or stimulating the release

Serotonin Syndrome

- Too much serotonin due to too much of an SSRI is prescribed, or synergistic affect with other drugs, herbs.
- Increased blood pressure
- Drugs that affect ANS must be carefully monitored.



Adrenergic Transmission

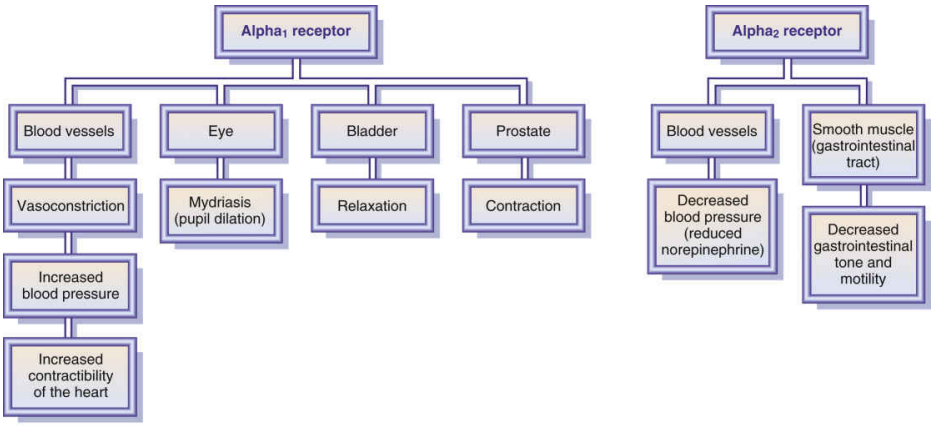
Neurotransmitter	Primary Location	Clinical Application (Chapter Number)
Acetylcholine	Synapses throughout the CNS; preganglionic neurons ending in the ganglia in both the sympathetic and parasympathetic nervous systems (nicotinic); postganglionic neurons ending in neuroeffector target tissues in the parasympathetic nervous system (muscarinic)	Alzheimer's disease (21); Myasthenia gravis (13)
Dopamine	Limbic system and hypothalamus; some sympathetic ganglia	Attention deficit/hyperactivity disorder (24); Parkinson's disease (21); psychoses (20)

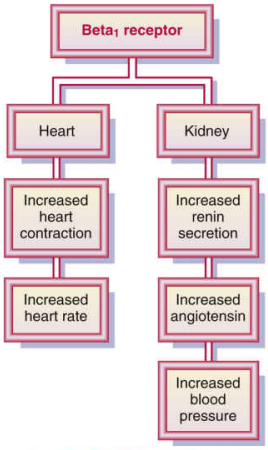
Neurotransmitter	Primary Location	Clinical Application (Chapter Number)
Gamma aminobutyric acid (GABA)	Cerebellum, cerebral cortex; interneurons throughout the CNS	Anxiety (18); seizures (22)
Glutamate	Throughout the CNS	Seizures (22)
Nitrous oxide	CNS, adrenal gland, and nerves to the penis	Impotence (71)
Norepinephrine	Throughout the CNS; most neuroeffector target junctions in the sympathetic nervous system	Attention deficit/hyperactivity disorder (24); cocaine and amphetamine abuse (27); depression (19)
Serotonin (5-HT)	Limbic system and hypothalamus; primary neurotransmitter in the extrapyramidal system; GI tract	Anxiety (18); depression (19); nausea and vomiting (60); psychoses (20)

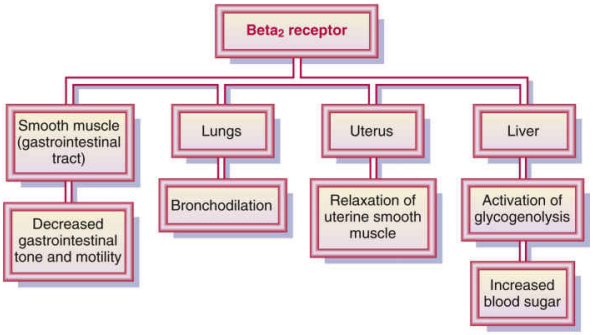
Neurotransmitter	Primary Location	Clinical Application (Chapter Number)
Substance P	Pain pathways in the spinal cord; brain and sensory neurons	Analgesia (25)

- Norepinephrine is the primary neurotransmitter released at adrenergic receptors, which may be alpha or beta.
- Adrenergic receptors
  - Receptors at ends of postganglionic sympathetic neurons
- Norepinephrine (NE)
  - Catecholamine
- Alpha-adrenergic receptors
  - $Alpha_1$ receptors
  - $Alpha_2$ receptors
  - $Beta_1$ receptors

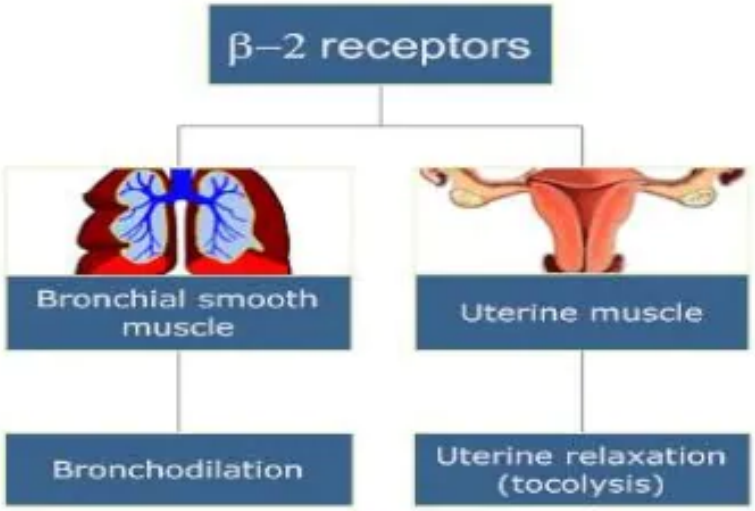
- $Beta_2$ receptors
- Other
    - Dopaminergic receptors
- Cholinergic Transmission

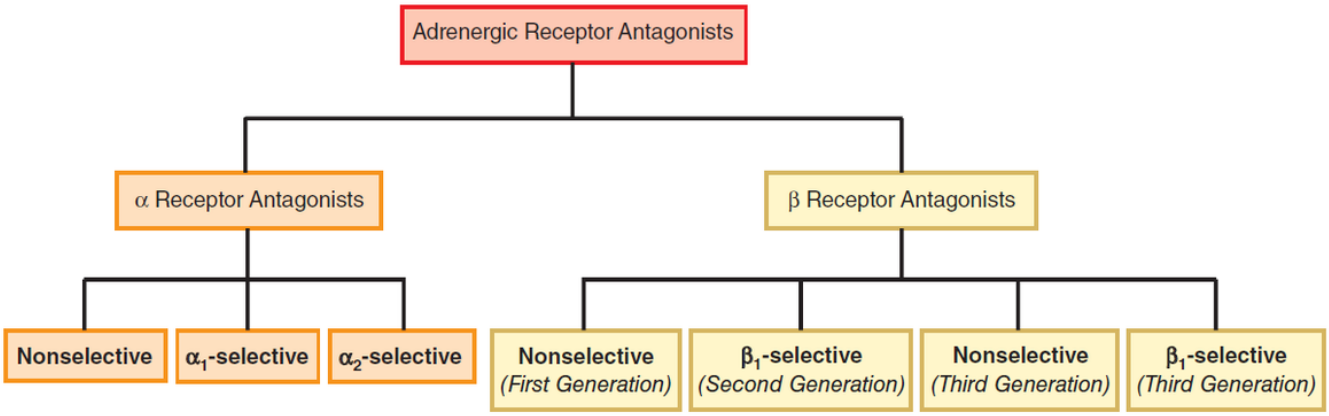






1. Terbutaline
2. Clenbuterol
3. Salbutamol
4. Salmeterol
5. Pirbuterol
6. Isoetarine
7. Orciprinaline





Classification of adrenergic receptor antagonists. Drugs marked by an asterisk (*) also block α_1 receptors.

Source : Goodman Gilman PHARMACOLOGICAL BASIS 13th edi

Neurotransmitter	Receptor	Primary Locations	Selected Responses
Acetylcholine (cholinergic)	Muscarinic	Parasympathetic target (other than the heart) Heart	Stimulation of smooth muscle and exocrine gland secretions Decreased heart rate and force of contraction
Nicotinic	Postganglionic neurons and neuromuscular junctions of skeletal muscle	Stimulation of smooth muscle and gland secretions	
Norepinephrine (adrenergic)	$Alpha_1$	All sympathetic target organs except the heart	Constriction of blood vessels; dilation of pupils
	$Alpha_2$	Presynaptic adrenergic nerve terminals	Inhibition of norepinephrine release
	$Beta_1$	Heart and kidneys	Increased heart rate and force of contraction; release of renin
$Beta_2$	All sympathetic target organs except the heart	Inhibition of smooth muscle contraction	

Cholinergic Transmission

- Acetylcholine (ACh) is the neurotransmitter released at cholinergic receptors, which may be nicotinic or muscarinic
    - Nicotinic
    - Muscarinic

Table 12.2 Types of Autonomic Receptors

Neurotransmitter	Receptor	Primary Locations	Selected Responses
Acetylcholine (cholinergic)	Muscarinic	Parasympathetic target organs (other than the heart) Heart	Stimulation of smooth muscle and exocrine gland secretions Decreased heart rate and force of contraction
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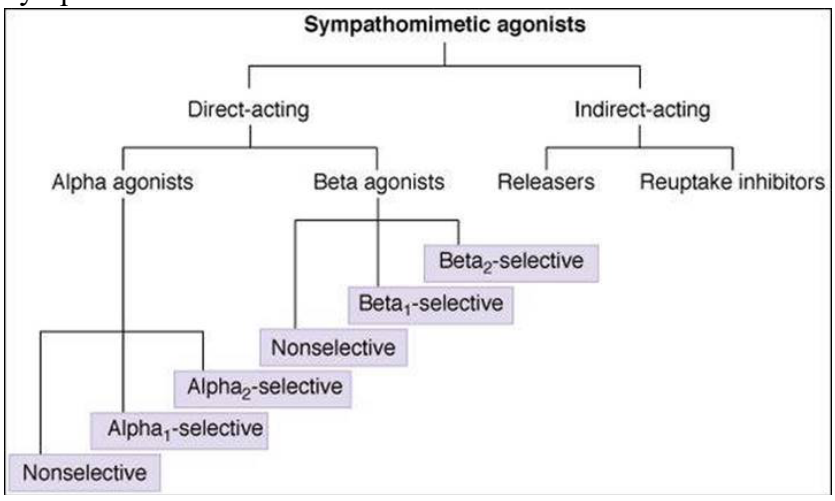
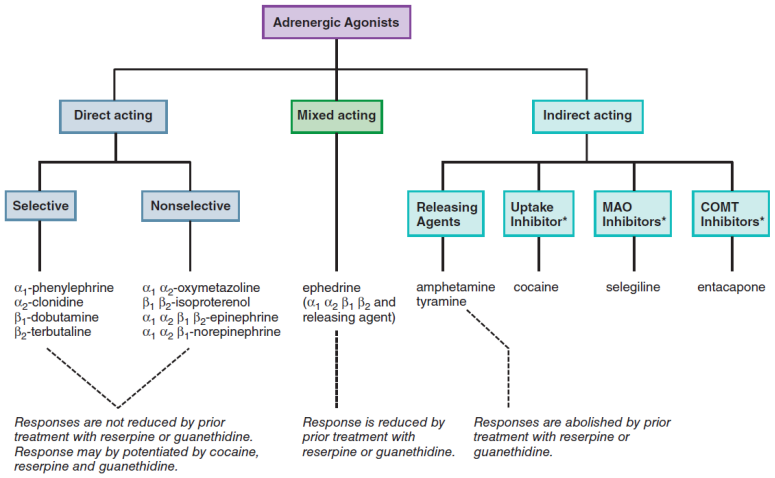
	$Beta_2$	All sympathetic target organs except the heart	Inhibition of smooth muscle contraction

- Autonomic drugs are classified by which receptors they stimulate or block.
- Four possible actions
    1. Stimulation of sympathetic nervous system
        - Sympathomimetics

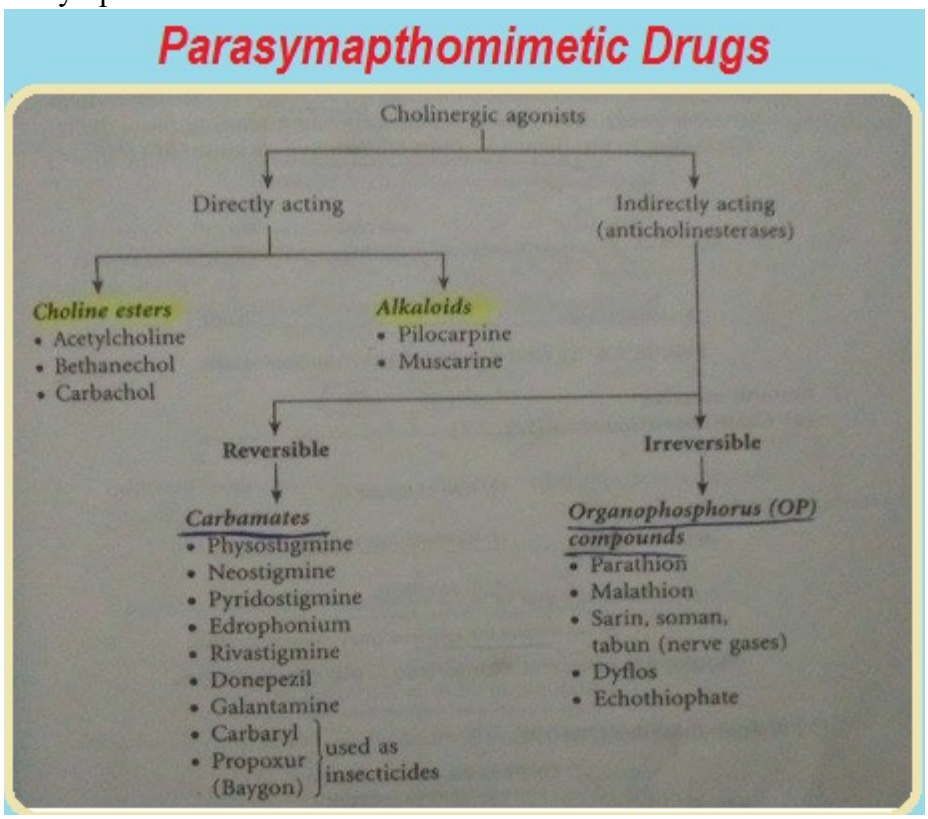


- Adrenergic agonists



Classification of adrenergic receptor agonists (sympathomimetic amines) or drugs that produce sympathomimetic-like effects. For each category, a prototypical drug is shown. (*Not actually sympathetic drugs but produce sympathomimetic-like effects.)
Source : Goodman Gilman PHARMACOLOGICAL BASIS 13th edi

2. Stimulation of parasympathetic nervous system
   - Paraympathomimetics



- Muscarinic agonists

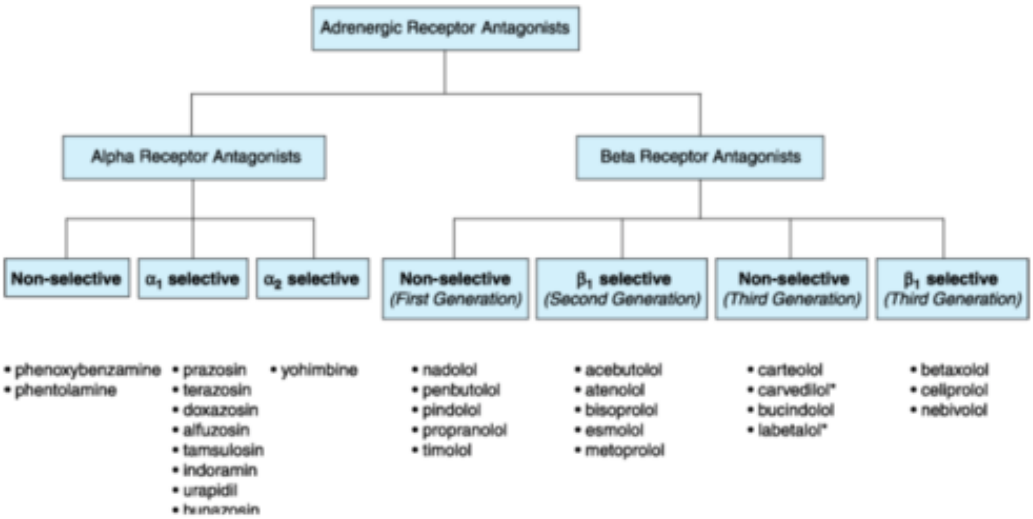
Drug Facts for Your Personal Formulary: *Muscarinic Receptor Agonists and Antagonists*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Muscarinic Receptor Agonists		
Methacholine	• Diagnosis of bronchial airway hyperreactivity	• Muscarinic effects: GI cramps, diarrhea, nausea, vomiting; lacrimation, salivation, sweating; urinary urgency; vision problems; bronchospasm • Do not use in patients with GI obstruction, urinary retention, asthma/COPD
Carbachol	• Glaucoma (topical administration)	• Systemic muscarinic effects minimal with proper topical application, otherwise similar to methacholine
Bethanechol	• Ileus (postoperative, neurogenic) • Urinary retention	• Similar to methacholine • Take on empty stomach to minimize nausea/vomiting

Pilocarpine	• Glaucoma (topical administration)
	• Xerostomia due to
	  • Sjögren syndrome
	  • Head and neck irradiation
		• Systemic muscarinic effects minimal with proper topical application, otherwise similar to methacholine

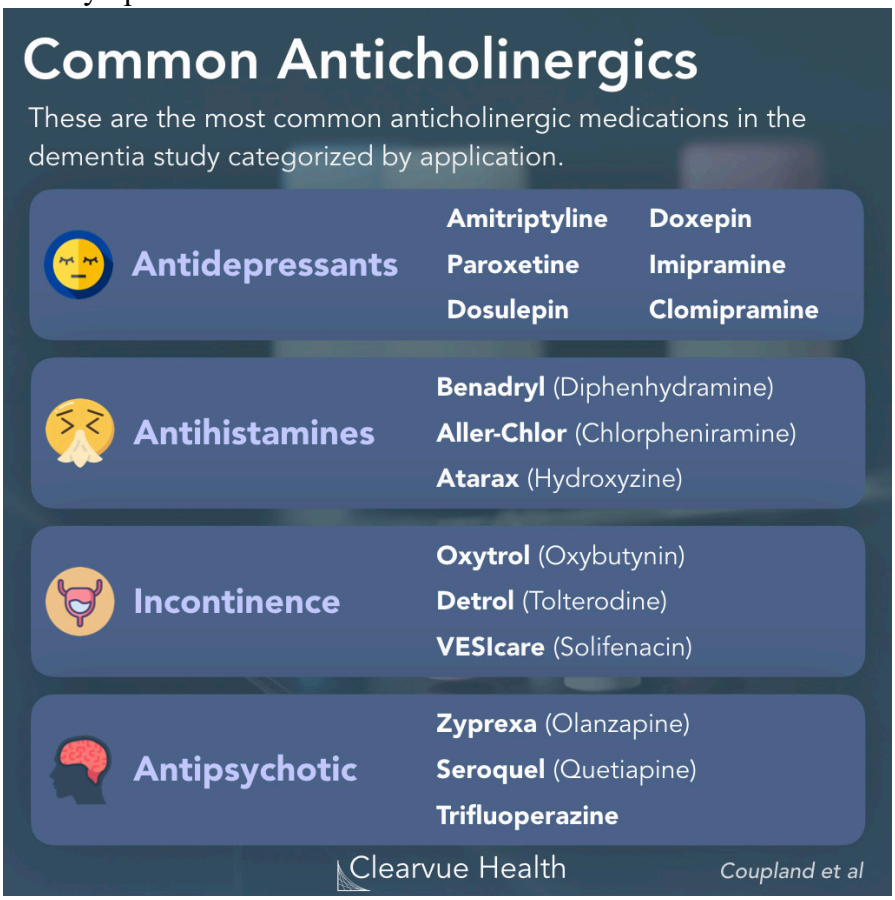
Cevimeline	• Xerostomia due to • Sjögren syndrome	• Similar to methacholine

3. Inhibition of sympathetic nervous system
    - Adrenergic antagonists or blockers

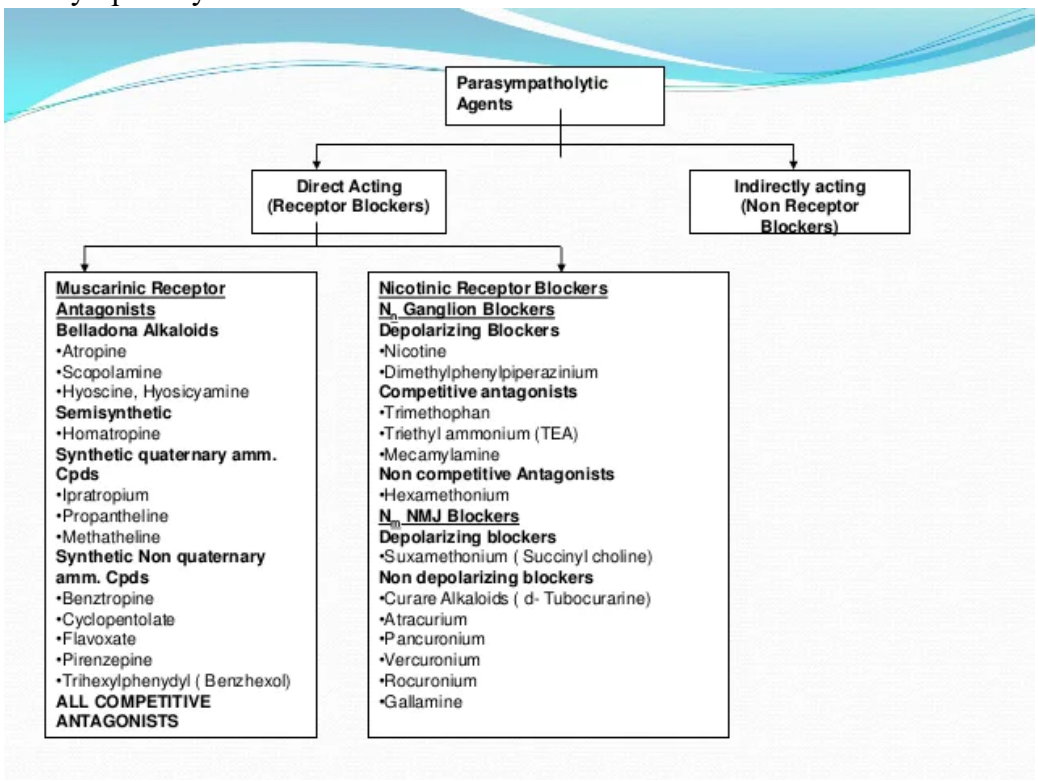


4. Inhibition of parasympathetic nervous system
    - Anticholinergics

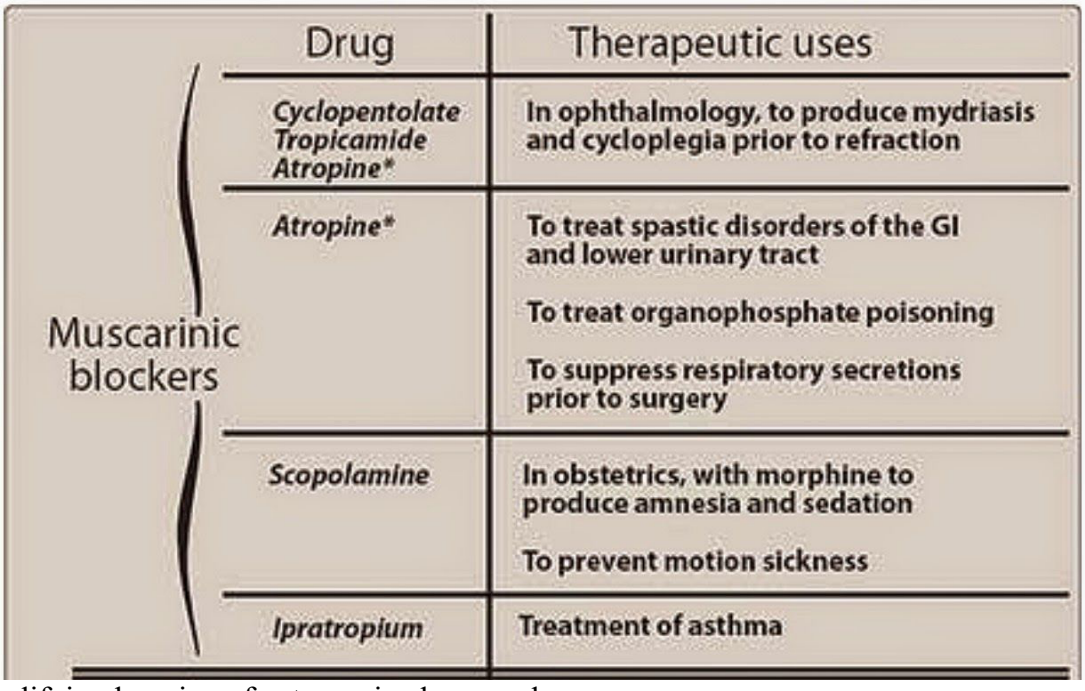
i. Treats symptoms of parkinsonism but can lead to dry mouth and CNS symptoms



- Parasympatholytics



- Muscarinic blockers



- Method for simplifying learning of autonomic pharmacology
  - Only one group of previous four drug classes need to be learned because the others are logical extensions of the first.
    - Other three groups' effects either same or opposite
- Classifying Autonomic Drugs

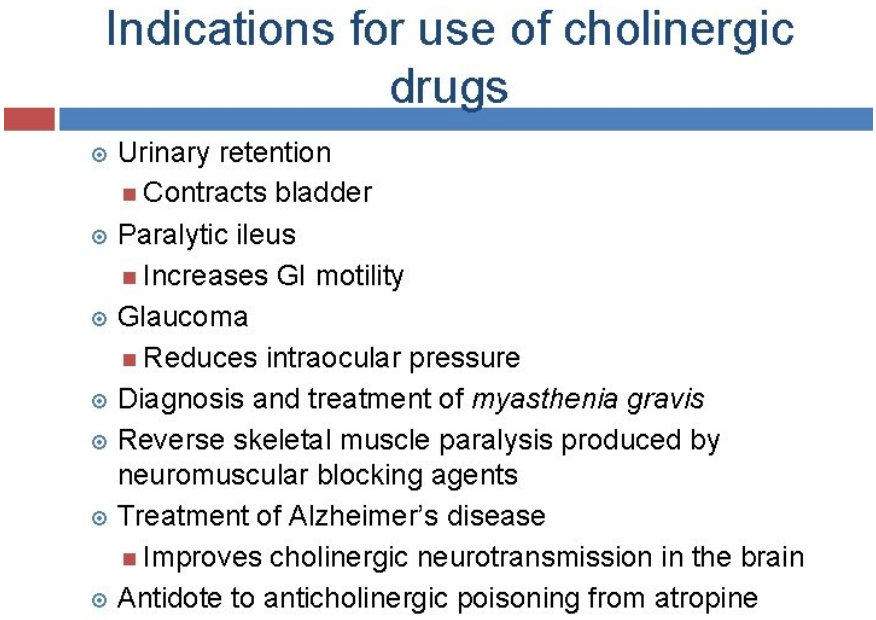
- Method for simplifying learning of autonomic pharmacology
  - Exceptions do exist; however, this is a time-saving means of learning basic actions.

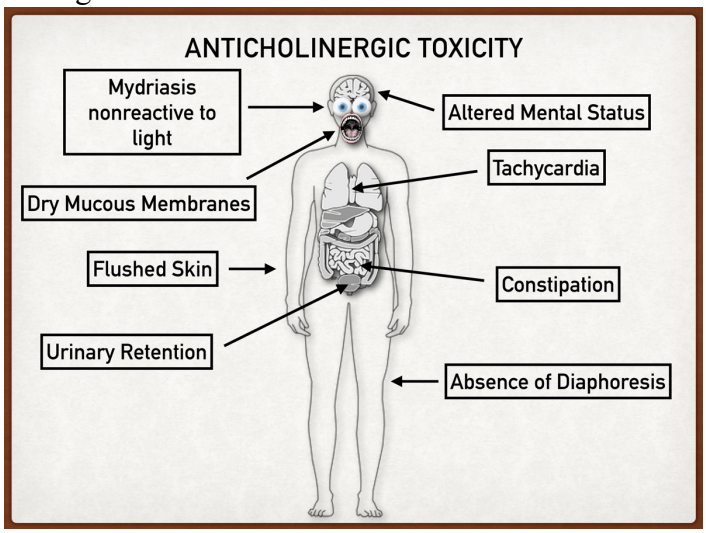
Need to know information

- The actions of the parasympathetic system
  - The parasympathetic nervous system is activated under nonstressful conditions and produces a set of symptoms known as the rest-and-digest response . These nerves promote relaxation and body maintenance activities. Digestive secretions increase, peristalsis propels substances along the alimentary canal, and defecation is promoted. Heart rate and blood pressure decline. Because less air is needed, the bronchi constrict and respiration slows. The student should notice that the actions of the parasympathetic division are opposite to those of the sympathetic division.
- Autonomic drugs and how the effect synaptic transmission
  - Drugs act by altering neurotransmitter activity in the ANS.
  - Some drugs are identifcal or have a similar chemical structure and are able to directly activate the gland or muscle.
  - Drugs can act on the outflow of nervous impulses at the source (CNS) or a second site is the at the ganglia, the synapse where the preganglionic and postganglionic neurons meet.
  - 5 ways drugs affect synaptic transmission in the ANS
    1. Medications may affect the ***synthesis*** of the neurotransmitter in the preganglionic nerve. Drugs that decrease neurotransmitter synthesis inhibit autonomic responses. Those that increase neurotransmitter synthesis have the opposite effect.
    2. Medications can prevent the ***storage*** of the neurotransmitter in vesicles within the preganglionic nerve. Prevention of neurotransmitter storage inhibits autonomic action
    3. Meds can influence the ***release*** of the neurotransmitter from the preganglionic nerve. Promoting neurotransmitter release stimulates the autonomic nervous system responses, whereas preventing neurotransmitter release has the opposite effect
    4. Medications can ***Bind*** to the neurotransmitter receptors on the post ganglionic cell. Drugs that bind to receptors stimulate the cell will increase autonomic responses. Those that attach to the postganglionic cell and prevent the natural neurotransmitter from reaching its receptors will inhibit autonomic actions
    5. Medications can ***Prevent the destruction or reuptake*** of the neurotransmitter. These drugs can cause the neurotransmitter to remain in the synapse for a longer time and will stimulate autonomic action.
- Nicotinic receptors and their effect
  - Nicotinic receptors are also found in skeletal muscle, which is controlled by the somatic nervous system, and in the adrenal medulla. Because nicotinic receptors are present in so many locations, drugs affecting these receptors produce profound effects on both the ANS and somatic nervous system. Activation of Ach nicotinic receptors always produces stimulatory actions. Nicotinic actions include increased

sweat production, increased release of adrenal medullary hormones, and enhanced nerve conduction in the ganglia; and tachycardia, hypertension, and increased tone and motility in the digestive tract. Although nicotinic receptor blockers were some of the first drugs used to treat hypertension, they are rarely used for this purpose today due to the discovery of safer drugs. The primary current therapeutic application of these drugs is to produce skeletal muscle relaxation (a somatic effect) during surgical procedures

- The use of cholinergic medications
  - A few have applications in the treatment of glaucoma, myasthenia gravis, and early Alzheimer's disease.



- Anti cholinergic side effects
  - 

- Parkinsons pt on anticholinergic and side effects

Signs of the Anticholinergic Toxidrome

Peripheral	Central
Dry warm skin	Altered mental status
Dry mucous membranes	Incoherent speech
Flushing	Carphologia*
Hyperthermia	Agitation
Mydriasis	Delirium
Decreased visual acuity	Hallucinations (auditory, visual, or tactile)
Photophobia	Seizures
Tachycardia	Coma

*Involuntary picking at imaginary objects, bedding, and clothing.

Adapted from Boroughf WJ. Anticholinergic Syndrome. In *Critical Care Toxicology* (2nd Edition) Springer 2017.

Class-subclass	Prototype/ Generic	Administration Considerations	Therapeutic Effects	Adverse/Side Effects
Antiparkinson agent	carbidopa/ levodopa	Avoid high-protein diets due to decreased absorption Monitor for sudden somnolence and increased depression Contraindicated with MAOIs Periodically monitor hepatic, renal, and hematopoietic functions	Slow progression of symptoms of Parkinson's disease (tremors, rigidity, and mobility issues)	Depression, suicidal ideation, hallucinations, and intense urges with inability to control them Somnolence and fatigue NMS symptoms with dose reductions or when discontinued Dyskinesia Discolored body fluids Hypomobility with long-term use

- Be able to describe the fight or flight reaction
  - Fight-or-flight response characteristic set of actions produced when the sympathetic nervous system is activated that prepares the body for heightened activity and for an immediate response to a threat
  - produce the fight-or-flight response, the hypothalamus activates two systems: the sympathetic nervous system and the adrenal-cortical system. The sympathetic nervous system uses nerve pathways to initiate reactions in the body, and the adrenal-cortical system uses the bloodstream. The combined effects of these two systems are the fight-or-flight response.

- When the hypothalamus tells the sympathetic nervous system to kick into gear, the overall effect is that the body speeds up, tenses up and becomes generally very alert. If there's a burglar at the door, you're going to have to take action -- and fast. The sympathetic nervous system sends out impulses to glands and smooth muscles and tells the adrenal medulla to release epinephrine (adrenaline) and norepinephrine (noradrenaline) into the bloodstream. These "stress hormones" cause several changes in the body, including an increase in heart rate and blood pressure.
- At the same time, the hypothalamus releases corticotropin-releasing factor (CRF) into the pituitary gland, activating the adrenal-cortical system. The pituitary gland (a major endocrine gland) secretes the hormone ACTH (adrenocorticotropic hormone). ACTH moves through the bloodstream and ultimately arrives at the adrenal cortex, where it activates the release of approximately 30 different hormones that get the body prepared to deal with a threat.
- The sudden flood of epinephrine, norepinephrine and dozens of other hormones causes changes in the body that include:
- heart rate and blood pressure increase
- pupils dilate to take in as much light as possible
- veins in skin constrict to send more blood to major muscle groups (responsible for the "chill" sometimes associated with fear -- less blood in the skin to keep it warm)
- blood-glucose level increases
- muscles tense up, energized by adrenaline and glucose (responsible for goose bumps -- when tiny muscles attached to each hair on surface of skin tense up, the hairs are forced upright, pulling skin with them)
- smooth muscle relaxes in order to allow more oxygen into the lungs
- nonessential systems (like digestion and immune system) shut down to allow more energy for emergency functions
- trouble focusing on small tasks (brain is directed to focus only on big picture in order to determine where threat is coming from)
- ¬¨All of these physical responses are intended to help you survive a dangerous situation by preparing you to either run for your life or fight for your life (thus the term "fight or flight"). Fear -- and the fight-or-flight response in particular -- is an instinct that every animal possesses.

- Describe dopamine’s effects on receptors and which receptors are effected
  - Five dopamine receptors D1-D5
  - The function of each dopamine receptor:
    - D1: memory, attention, impulse control, regulation of renal function, locomotion
    - D2: locomotion, attention, sleep, memory, learning
    - D3: cognition, impulse control, attention, sleep
    - D4: cognition, impulse control, attention, sleep
    - D5: decision making, cognition, attention, renin secretion
    - Clinical significant Parkinsons disease
      - Bromocriptine is a D2 receptor agonist; other dopamine agonists include pramipexole and ropinirole

    - Amantadine increases dopamine availability by increasing the release of dopamine and decreasing reuptake
    - Carbidopa and levodopa are commonly used together; in the CNS levodopa is converted into dopamine to increase the amount of dopamine in the CNS and carbidopa inhibits DOPA decarboxylase, which blocks the peripheral conversion of levodopa to dopamine - this decreases the peripheral side effects of dopamine
    - Other medications, such as selegiline and tolcapone inhibit the breakdown of dopamine, which increases the availability at the synapse
- Schizophrenia
    - Associated with an increase in dopaminergic activity
    - Genetic and environmental risk factors affect the dopamine function
    - Diagnosis includes greater than 6 months of at least 2 of the following: delusions, disorganized speech, hallucinations, disorganized behavior, and negative symptoms (anhedonia, flat affect, etc.), and at least one of the symptoms needs to be hallucinations, delusions, or disorganized speech
    - Treatment for schizophrenia includes medications that target to decrease dopamine availability, which includes atypical and typical antipsychotics
        - Typical antipsychotics are also known as first-generation antipsychotics - these drugs block the D2 receptor
            - High potency typical antipsychotics include haloperidol, trifluoperazine, and fluphenazine
            - Low potency typical antipsychotics include chlorpromazine and thioridazine.
    - The atypical antipsychotics have unique characteristics
        - Most are D2 antagonists and also affect other receptors, such as the serotonin and histamine receptors; aripiprazole is D2 partial agonist
        - Atypical antipsychotics bind more loosely to the dopamine D2 receptor than the typical antipsychotics
- At intermediate doses, dopamine also stimulates β_1-receptors on the heart. At high doses, dopamine stimulates **α-adrenergic receptors** in the vasculature, which exacerbates HF by increasing afterload. (However, this may be a desired effect in patients who are in hemorrhagic shock.)

-

- Flomax for benign prostate hypertrophy.
    - **Tamsulosin** is used by men to treat the symptoms of an enlarged prostate (benign prostatic hyperplasia-BPH). It does not shrink the prostate, but it works by relaxing the muscles in the prostate and the bladder.

Selected adverse effects of antipsychotic medications for schizophrenia

	Weight gain/diabetes mellitus	Hyper-cholesterolemia	EPS/TD	Prolactin elevation	Sedation	Anticholinergic side effects	Orthostatic hypotension	QTc prolongation
First generation agents								
Chlorpromazine	+++	+++	+	++	+++	+++	+++	+++
Fluphenazine	+	+	+++	+++	+	−/+	−	−/+*
Haloperidol	+	+	+++	+++	++	−/+	−	Oral: ++ IV: +++
Loxapine	++	ND	++	++	++	+	+	−/+*
Perphenazine	++	ND	++	++	++	+	−	−/+*
Pimozide	+	ND	+++	++	+	+	+	++¶
Thioridazine[Δ]	++	ND	+	+++	+++	++++	++++	++
Thiothixene	++	ND	+++	++	+	+	+	ND
Trifluoperazine	++	ND	+++	++	+	+	+	ND
Second generation agents								
Aripiprazole	+	−	+	−	+	−	−	−/+*
Asenapine	++	−	++	++	++	−	+	+
Brexpiprazole[◇]	+	+	+	−/+	+	−/+	−/+	−/+*
Cariprazine[◇]	+	−/+	++	−/+	+	−/+	−/+	−/+*
Clozapine[§]	++++	++++	−/+	−/+	+++	+++	+++	++
Iloperidone	++	++	−/+	−/+	+	+	+++	+
Lurasidone	−/+	−/+	++	−/+	++	−	+	−/+*
Olanzapine	++++	++++	+	+	++	++	+	++
Paliperidone	+++	+	+++	+++	+	−	++	+
Pimavanserin	+	−	−/+	−	+	+	++	+
Quetiapine	+++	+++	−/+	−/+	++	++	++	++
Risperidone	+++	+	+++	+++	+	+	+	++
Ziprasidone	−/+	−/+	+	+	+	−	+	+++

Adverse effects may be dose dependent. The QTc classifications are consistent with US Food & Drug Administration (US FDA) guidance.[1] Other sources may use a different classification system resulting in some agents being classified differently.

EPS: extrapyramidal symptoms; TD: tardive dyskinesia; IV: intravenous; ND: insufficient data.
* Clinically relevant QTc prolongation was not detected in preliminary studies or reported in the manufacturer's labeling.
¶ Although the available evidence concerning the average QTc prolonging effect of pimozide is consistent with a classification of moderate significance (ie, ++), label warnings have characterized the QTc effect and cardiovascular risks as severe and sudden deaths in patients on pimozide have been reported.
Δ Thioridazine is also associated with dose-dependent retinitis pigmentosa. Refer to UpToDate text.
◇ Based upon limited experience.
§ Clozapine also causes granulocytopenia or agranulocytosis in approximately 1% of patients requiring regular blood cell count monitoring. Clozapine has been associated with excess risk of myocarditis and venous thromboembolic events including fatal pulmonary embolism. These issues are addressed in the UpToDate topic review of guidelines for prescribing clozapine section on adverse effects.

Neurological Illness

Dizziness

- Variety of causes from vestibular, neurological or cardiovascular.
- 40% have peripheral vestibular dysfunction (usually seen in elderly, can happen before a stroke)
- 10% central brainstem lesion
- 15% psychiatric disorder (usually in younger patients)
- 25% syncope/pre-syncope or disequilibrium
- 10% uncertain cause
- Elderly more likely due to vestibular causes or pre-stroke, younger patients account for more of the psychiatric diagnoses and pre-syncope.

Vertigo

- Illusion of movement-spinning, tilting, moving back and forth – never continuous.
- Made worse by moving the head
- Patients become petrified to move
- Question patient on what provokes it
- Brain stem involvement-ataxic gait, vision changes, slurred speech, numbness of face or body, weakness or incoordination.

Syncope/Pre-syncope

- Sense of wooziness or impending faint
- May be lightheaded, warm, nauseous, have visual disturbances
- Cardiac history - Palpitations or chest pain
- Recent illness – Influenza, herpes zoster, measles, mumps, viral illness
- Meds- opiates, neuroleptics, ASA, ETOH, sedatives, diazepine, streptomycin/gentamycin

Differential/Work up

- Otitis (ear infection), Labyrinthitis, Meniere's disease, Acoustic neuroma, benign postural vertigo, CVA, TIA, Multiple Sclerosis, Meningitis, Migraine.
- CBC w diff to rule out anemia/infection
- Electrolyte imbalances
- TSH, T4, Hgb A1C, audiogram, MRI, x-ray of cervical spine, carotid ultrasound

Treatments

- Vertigo -Meclizine (antivert) 12.5-25mg q6hours prn or Compazine 5-10mg q6hours BID prn
- Meniere's Disease (a disorder of the inner ear that can lead to dizzy spells (vertigo) and hearing loss) – restrict salt & caffeine
- Acute Labrynthitis – rehydration, Prednisone taper for three weeks
- Benign Positional Vertigo – vestibular conditioning exercises, some may eventually need surgery

Tremors

- Usually due to a cerebellar or extra pyramidal disorder. May also be a side effect of medications
- Resting tremor – occurs at rest
- Intentional tremor- brought on when the patient moves.
- 10 million in the United States have essential tremor.

Parkinson's Disease

- 40,000 new cases per year in US
- Symptom's can begin as early as 40 but with peak onset at 65
- Not hereditary, but increased risk in first degree relative- various possible causes – vascular, viral or metabolic.
- Related to dopamine depletion in basal ganglia- degeneration of dopamine pathway
- Diagnosis based on symptoms
- Tremor at rest, rigidity, bradykinesia(freezing) and postural instability

Parkinson Symptoms

- Tremors- in most cases in distal parts of body- hand tremor-"*pill rolling*", lips, chin and legs
- Rigidity- "*cogwheel phenomenon*" is a circular jerking of flexion and extension in background of tremor
- Bradykinesia – slowness of movement usually in the legs. Difficulty planning, initiating and executing movements. Also affects fine motor co-ordination. Loss of facial expressions, drooling and reduced arm swing.
- Postural Instability- Flexed forward posture, more of a latent affect. Increases risk of hip fractures.

Differential Diagnosis Parkinsonism

- Difficult at early stages
- Mainly based on symptoms- Lewy bodies found on autopsy
- r/o depression, hydrocephalus, essential tremor, cortical-basilar degeneration, medication side effects. Certain drugs can cause parkinson-like symptoms-
    - Neuroleptics such as Haldol and Risperdal,
    - Antidepressants can cause bradykinesia and tremor
    - Calcium channel blockers

Treatment

- Manages symptoms but does not stop degenerative process.
- Goal is to prolong independence
- Levodopa- antidyskinetic, improves muscle coordination and movement. Does not help with freezing. Many side effects-N&V, HA, numbness and weakness, confusion & teeth grinding.
- Dopamine agonists – Parlodel, Requip and Mirapex may be used with Levodopa. Also can have side effects of drowsiness and confusion.

Huntington's Disease

- Genetic illness occurring in ap.15,000 Americans
- Genetic testing
- Severe degeneration of the Basal Ganglia
- Symptoms progress slowly- hypotonia, hyperkinesia and fragmentary movements(chorea)
- Neuro exam – mental status changes, loss of muscle tone, writhing movements, c/o feeling clumsy.
- Supportive care= xenazine may reduce chorea
- Antidepressants may help

- Antipsychotics can make the condition worse by increasing dystonia (involuntary muscle contractions that cause slow repetitive movements or abnormal postures)

Neuroleptic Malignant Syndrome

- Life threatening side effect of dopamine-blocking medications (can occur with all antipsychotics)
- Fever, muscle rigidity, autonomic dysfunction and altered mental state and tremor
- Medical emergency- take off medication and give supportive care (ABCs, cooling blankets, benzodiazepines for severe agitation)
- Mortality rate 10-20%
- Risks- high dose antipsychotics, withdrawal of medication for parkinsonism, dehydration and increased ambient temperature

Headaches

- Four types of headaches
    1. Muscular contraction – 50% of headaches in primary care, also called "tension headaches"
        - 20-25% from trauma, infection or arthritis
    2. Vascular – migraine or cluster headaches
    3. Mixed – muscular contraction and vascular
    4. Traction or inflammatory headaches
- Patients c/o worse HA of their life- abrupt explosive pain may have an intracranial hemorrhage
- Question HA patients about onset, frequency, severity and character- throbbing vs. constant

Migraines

- Complex neurological events
- Symptoms may vary from HA to HA

1. Premonitory phase-disruption of CNS equilibrium
2. Aura-spreading cortical excitation/depression
3. Mild HA- trigeminal neurons fire
4. Moderate to severe HA- activation of trigeminovascular system
5. Central sensitization

- Process can be terminated at any phase

<u>Dementia</u>

- Loss or decline in memory and other cognitive abilities – caused by conditions that damage brain cells. Decline in abilities must be severe enough to interfere with daily life.
- Alzheimer's- 57% of cases – mainly > age 85
- Multi-Infarct Dementia- 13% of cases -males 60-75
- Dementia with Lewy Bodies & Parkinson's- may include early onset
- Also Depression (4.5%), Alcohol (4.2%) Drugs(1.5%)
- Mild cognitive impairment is a normal part of aging

Alzheimer's Disease-Pathophysiology

- Beta-amyloid accumulates between brain cells and forms neurotic plaques that kill brain cells
- Tau protein forms tangles inside brain cells and disrupt cell function
- Deficiency in Acetylcholine causes impaired neuronal communication

Lewy Body Dementia

- Similar to Alzheimer's disease with daily fluctuations of alertness and severity of cognitive symptoms
- Tend to have visual hallucinations and delusions early in course of illness
- Muscle rigidity and tremors are common.

Differential work-up for Dementia

- Brian tumor
- Depression
- Delirium
- Traumatic Brain Injury
- Vitamin B12 deficiency
- Hypothyroidism
- Neurosyphilis
- Lyme Disease
- Parkinson's or Huntington's Disease
- Toxins, medications

Screening for Dementia

- Mini Mental Exam-
    - severe < 9 points, Moderate 10-20, mild 21-24
- Clock Drawing Test – 1 point for all correct components-circle, two hands, numbers in right order, correct time
- Labs –
    - CBC, LFTs, Toxin screen, B12 and Folate, RPR, UA, C&S
- Head CT or MRI

Treatment for Dementia

- No Disease Modifying treatment available
- Focus on Quality of Life for patient & Caregiver
- May need antidepressant/antipsychotic
- Neuropeptide-Modifying Agent
    - Memantine
- Cholinesterase Inhibitors
    - Donepezil
    - Galantamine
    - Rivastigmine
    - Side effects- N/V/D, anorexia, dizziness, agitation, bradycardia
    - Combination therapy Donepizine & Memantine most common

Delirium

- An abnormal mental state – if identified correctly can be corrected and reversed.
- Use mini mental exam to assess confusion
- Acute onset, fluctuating course, difficulty focusing, disorganized thinking – incoherent, rambling, irrelevant conversation, unclear flow of ideas, unpredictable switching.
- Hyperactive, hypoactive or mixed-up to 60% elderly develop some symptoms during hospitalization – diagnosis is missed in many of them.
- Risks>age, sleep deprivation, polypharmacy, dementia, infection, surgery, multiple changes.

Differential and treatment Delirium

- Similar to Dementia- infection, Lyme, CVA, Neurosyphyllis, B12, hypothyroid, traumatic brain injury.
- Treatment- correct underlying metabolic or infectious process, manage pain, frequent orientation, hydrate, remove invasive lines.
- Meds- Haldol, Risperidol, Trazadone
- May also try benzodiazepines and pain relievers such as acetaminophen and tramadol

Seizures

- Two main types- generalized and partial seizures
- Generalized-
    - Primary generalized tonic-clonic seizures or "Grand Mal seizures" loss of consciousness occurs precedic by myoclonic jerks
    - Absence seizures - very brief(10 sec.)periods of nondistractible staring- prim in children.
    - Atypical Absence seizure- mild clonic movements also know as "Petite Mal" seizures
    - Partial seizures
- Simple Partial Seizures
    - Motor- may start in one part of body –move to whole side, parasthesia, flashing lights, tachycardia, loss of bowel or bladder function, hallucinations, no LOC
    - Complex Partial Seizures
        - Impairment of consciousness occurs. No warning, confusion, also known as temporal lobe or psychomotor seizures
- Secondary generalized partial seizures
    - Impairment of consciousness occurs. Increased muscle tone, clonic movements, lasts over a minute, comatose than slowly recovers, tongue biting and incontinence occur

Treatment of seizures- First Line Therapy

- Partial Seizures
    - Mysoline
    - Trileptal
- Partial or generalized seizures
    - Dilantin, Topamax, Tegretol, Valproic Acid, Phenobarbital
- Petite Mal/Myoclonic Seizures

- Valproic acid, Depakote, Klonopin
- Each drug has it's own precautions- need t maintain optional level, may cause headaches, CNS depression with alcohol, ataxia, peripheral neuropathy