Autonomic System

The nervous system of the body is divided into 2 major divisions, one of which has several other divisions. The primary divisions are the Central Nervous System or CNS and the Autonomic Nervous System or the ANS. You should be familiar with both to understand how pharmaceutical agents affect the body. The one we are primarily going to study is the Autonomic Nervous System, but read about the CNS anyway because it’s still pertinent to the discussion.

1. CNS – Central Nervous System
That’s the brain and the spinal cord. The system receives sensory input from the body from the afferent nerves, decides what to do about them, and then sends the decision and appropriate motor responses via the peripheral efferent nerves.

The Reticular Activating System, part of the CNS, is situated at the core of the brain stem between the medulla oblongata and the midbrain. It is responsible for maintenance of consciousness, wakefulness and alertness. It also regulates the cardiovascular and respiratory systems as well as sexual patterns. When this system is disturbed the sleep cycle can also be disturbed. This system is affected by psychotropic drugs, general anesthetics and melatonin.

The Limbic System, also part of the CNS is a set of brain components including the hippocampus, amygdala, anterior thalamic nuclei, and limbic cortex. It supports functions such as emotion, behavior, long term memory, and the sense of smell. One part is involved in reward, pleasure and addiction, another in decision making. If you want the whole list and what each component does, [check this link out](#).

2. PNS – Peripheral Nervous System
This includes the 12 cranial nerves which we’ve had to relearn about 4 times now and 31 pairs of spinal nerves which is what you’re affecting when you needle Jiaji points. The PNS is further divided into 2 subdivisions:

### Terminology

- **Acetylcholine (ACh)** – neurotransmitter of parasympathetic (aka cholinergic) nerves. Stimulates the cholinergic receptors.
- **Adrenergic receptors** – receptor located on internal organs, response to norepinephrine.
- **Afferent nerve** - sends sensory info from body to CNS.
- **Autonomic nervous system (ANS)** - innervates involuntary muscles (smooth and cardiac muscle of internal organs).
- **Cholinergic receptor** - located on internal organs, responds to ACh. Part of parasympathetic system.
- **Efferent nerve** – carries motor response from CNS to appropriate motor area of body.
- **Epinephrine** – hormone from adrenal medulla. Stimulates adrenergic/sympathetic receptors, esp during stress.
- **Fight or flight** – body response to stress, occurs when sympathetic nervous system (part of ANS) fires up.
- **Homeostasis** – normal state of balance in
a. **Somatic/Motor**
   This is the part that activates the voluntary muscles – your biceps, triceps, thighs, calves, and some components of your naughty bits. (There’s also an EPS or Extra Pyramidal System which controls fine motor movements.) The somatic system is under your conscious control.

b. **Autonomic**
   This is the part that runs your involuntary muscles – cardiac and smooth muscle in your internal organs…and some other parts of your naughty bits. This is the stuff that is *not* under your conscious control (unless you’re a meditating monkish sort), but is instead regulated by the hypothalamus and medulla oblongata, the more primitive parts of your brain.

   This is the subsystem we’re really going to hammer on in this unit of pharmacology because you need to understand how drugs affect the two divisions of the autonomic nervous system, the sympathetic and parasympathetic nervous systems.

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**The Physiology of the Autonomic Nervous System (ANS)**

The ANS regulates homeostasis, the balance among the body’s internal organs by regulating the smooth and cardiac muscle found in the internal organs. The *parasympathetic* division of the ANS is also known as the *cranio-sacral* division. It originates from the brain at cranial nerves 3, 7, 9, and 10 and from the spinal cord’s sacral nerves S2-S4. The *sympathetic* division, also referred to as the *thoracolumbar* division. The sympathetic/thoracolumbar division originates from the thoracic and lumbar spinal nerves, T1 to L3.

The sympathetic system increases the activity of certain organs and depresses others during times of stress or duress in order to generate the “fight or flight” reaction to make more energy available for physical and mental action. While you don’t often have a T-Rex chasing you these days you probably have daily stress and anxiety (and the occasional illness) which produce similar reactions. When the sympathetic nervous system is stimulated it’s all or nothing and all sympathetic nerves are activated at once. The parasympathetic system is more active during periods of “rest and digest,” regulating bodily functions such as digestion and elimination of waste. Unlike the sympathetic division, when the parasympathetic nervous system is stimulated only select nerves are active.

So how does this happen? First, neurons emerge from the spinal cord. These are called *preganglionic* nerves. The ones in the sympathetic nervous system happen to be shorter than those in the parasympathetic system. The preganglionic nerves exit the spinal column and meet at *ganglions* (bundles of nerve synapses in the peripheral nervous system) where they connect with *postganglionic* nerves. These nerve endings aren’t physically joined. There is a small gap between them so they
communicate through chemical compounds called neurotransmitters. The postganglionic fibers travel to the target tissues where more neurotransmitters stimulate the internal organs and target tissues.

The primary neurotransmitter in the parasympathetic system is ACH or acetylcholine. Nerves that release ACH are called cholinergic. The sympathetic system uses the neurotransmitter ACH too, but also employs adrenaline or epinephrine, norepinephrine/noradrenaline, dopamine, and serotonin or 5-HT. Nerves that release adrenaline or noradrenaline are called adrenergic nerves. When there is a releaser there is always a receptor for the neurotransmitter. Receptors that receive ACH/acetylcholine are called cholinergic receptors while the ones receiving adrenaline and norepinephrine are called adrenergic receptors.

**Drugs Affecting the Sympathetic Nervous System**

**Adrenergic Nerve Endings and Receptors**

It’s the nerve endings that store the adrenergic neurotransmitters. Mostly they are referred to as NE (for norepinephrine) and EPI (for epinephrine). When the nerve is stimulated a neurotransmitter is released. In the case of NE, it travels to smooth or cardiac muscle and attaches to the receptor producing the sympathetic response. It is then reabsorbed (called “reuptake) back into the nerve endings. Sometimes it is reused, sometimes it’s destroyed. When EPI is released it either inhibits or relaxes smooth muscle in certain organs. In the case of the lungs, it causes bronchodilation by relaxing the respiratory passageways allowing the body to take in more oxygen. That’s important because if you’re in fight or flight mode, you need oxygen for both!

There are two kinds of adrenergic receptors: alpha and beta. The alphas are mostly in smooth muscle and contract when stimulated by NE or EPI.

**Alpha Adrenergic Receptors**

Found mostly in smooth muscle. Stimulated by NE or EPI. Produce contraction.

**Beta Adrenergic Receptors**

Found on cardiac and some smooth muscle membranes.

- **Cardiac**
  - Mostly Beta 1 receptors.
  - Can be stimulated by NE or EPI. Results in increase in heart rate/force of contraction

- **Smooth muscle**
  - Mostly Beta 2 receptors.
  - Can only be stimulated by EPI (not NE). Results in:
    - Vasodilation in skeletal muscle/ blood vessels/ coronary arteries
    - Bronchodilation (relaxation)

**What this means in terms of drugs**

Two main classes of drugs affecting the sympathetic nervous system: sympathomimetics and sympatholytics. More detail on these in the next section, but here’s your 101.
**Sympathomimetics**
Basically, these mimic the *stimulation* of the sympathetic nervous system. They produce an increase in BP, heart rate and dilate the bronchioles. They are used for shock, cardiac arrest and respiratory distress for this reason.

Alpha Adrenergic Drugs
If it stimulates the alpha receptors you call it an “alpha-adrenergic” drug. This includes both NE and EPI which cause contraction of smooth muscle.

Beta Adrenergic Drugs
If an adrenergic drug stimulates the beta receptors they are called “beta-adrenergic drugs.” They affect both Beta 1 and Beta 2 receptors.

- **EPI** can also stimulate the heart’s beta 1 receptors as well as cause relaxation of smooth muscle by stimulating beta 2 receptors. EPI is weird this way – it’s one of the few that does both alpha and beta.

- **Selective Beta 2 Adrenergic Drugs** are special in that they only stimulate beta 2 receptors at therapeutic doses, dilating the bronchioles.

**Sympatholytics**
Anything ending in –lytic block the activity of a system, *inhibiting* the sympathetic system. In this case it refers to blocking and thus decreasing sympathetic activity, especially in the cardiovascular system. How? Glad you asked. They compete with NE and EPI for receptor sites – basically they lose at musical chairs. If they can’t get their butts in the seats (receptor sites) then there’s no message for the sympathetic system to fire up.

They decrease BP and heart rate. They are used for hypertension, angina pectoris and some types of cardiac arrhythmias. There are a couple of flavors of these:

- **Alpha Adrenergic Blockers**
  Block alpha effects of NE and EPI

- **Non-selective Beta-Adrenergic Blockers**
  Block beta1 and beta2 effects of EPI

- **Selective Beta-1 Adrenergic Blockers**
  Block only Beta 1 receptor sites.

**Adrenergic Neuronal Blockers**
OK, there is actually one other way to inhibit the sympathetic nervous system. You can simply decrease the formation of or the release of NE. Drugs that do this are called adrenergic neuronal blockers.
Alpha Adrenergic Class of Drugs

Again, these are sympathomimetics, *stimulating* the sympathetic nervous system. NE is the parent/prototype for this class and alpha drugs produce very similar effects, namely contraction of smooth muscle, including vasoconstriction in blood vessels, gastrointestinal sphincters, and muscle in urinary passage. It also dilates the pupil of the eye (mydriasis).

Clinical Indications

Used intravenously usually for hypotensive states. Examples:
- Post-surgical - increase BP and keep circulation working
- Decongestant effect – vasoconstriction in nasal passages. That’s why OTC cold and allergy meds have some of this in them.
- Ophthalmology – dilates pupils (also called a “mydriatic drug” since mydriasis means to dilate the pupils). Also used as an “ocular decongestant.”
- Appetite suppressant – the ones that pass the blood brain barrier can do this. Amphetamines for instance. Dexadrine was popular in my youth for this…and that dates me big time because you can’t just walk into HEB and pick that stuff up anymore!

Endings are –ine and –ol.

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main Use</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>Nasal decongestant</td>
<td>Capsule, parenteral inject</td>
<td></td>
</tr>
<tr>
<td>Metaraminol</td>
<td>Aramine</td>
<td>Increase BP</td>
<td>Parenteral injection</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>Vasoxyl</td>
<td>Increase BP</td>
<td>Parenteral injection</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Levophed</td>
<td>Increase BP</td>
<td>Parenteral injection</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Lots of names</td>
<td>Nasal decongestant</td>
<td>Spray, drops, tabs, inject</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Many of °em</td>
<td>Nasal decongestant</td>
<td>Tabs, caps, oral liquids</td>
</tr>
<tr>
<td>Tetrahydrozoline</td>
<td>Visine</td>
<td>Ophthalmic decongestant</td>
<td>Ocular/eye drops</td>
</tr>
<tr>
<td>Tetrahydrozoline</td>
<td>Tyzine</td>
<td>Nasal decongestant</td>
<td>Nasal drops</td>
</tr>
</tbody>
</table>

And yes, that last one is the same generic name twice in 2 different forms.

Adverse Effects

The unwanted effects have to do with excessive vasoconstriction of vessels resulting in:
- Cardiac side effects such as hypertension, hypertensive crisis, heart palpitations, cardiac arrhythmias
- Cerebral hemorrhage

This is why you have to be very careful using it with patients who have hypertension or history of cardiac problems. Check their BP at frequent intervals.

Another common, though non-dramatic side effect when using it as a decongestant is irritation of nasal tissues or eyes. The vasoconstriction and reduced blood flow causes dryness here.

Caution: if administered in IV form, needle should be checked to make sure it isn’t emptying into the skin surface. This can cause enough constriction to kill off the tissue and cause gangrene.
Beta Adrenergic Class of Drugs

These are sympathomimetics, *stimulating* the sympathetic nervous system. Their specific action is to link to beta receptors. Most produce few alpha effects, except for EPI. Beta-1’s stimulate the heart and beta-2’s stimulate and dilate the bronchioles. If you don’t use a specific beta adrenergic but instead use something like EPI or isoproterenol you will open the bronchioles, but possibly over stimulate the heart. While there are no beta-1 specific drugs, there are a number of beta-2 specifics to use for bronchodilation only.

**Clinical indications for EPI**

EPI is primarily used for acute allergic reactions like anaphylaxis. Anaphylaxis can occur when an individual has been sensitized to something such as insect stings, drugs or other allergens (though Dr. Mandyam said in class it was stings only…) Signs of anaphylaxis are:
- Dyspnea
- Decreased blood pressure
- Signs of **shock**

EPI is administered subcutaneously, stimulating both alpha and beta receptors. Alpha actions are also used during surgery or combined with local anesthetics to constrict the vessels, decreasing blood flow and bleeding. It also makes the local work longer for the same reason. Beta effects are used for cardiac stimulation and bronchodilation in emergency situations. Both EPI and isoproterenol are available OTC for asthma type rescue inhalers.

All end in *–ine* or *–ol*.

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Class</th>
<th>Main use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Adrenaline</td>
<td>Alpha, beta-1, beta-2</td>
<td>Vasopressor, cardiac stim, bronchodilator</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Isuprel</td>
<td>Beta-1 and beta-2</td>
<td>Cardiac stim, bronchodilator</td>
</tr>
<tr>
<td>Isoetharine</td>
<td>Bronkometer</td>
<td>Beta-2</td>
<td>Bronchodilator</td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>Alupent</td>
<td>Beta-2</td>
<td>Bronchodilator</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Brethine</td>
<td>Beta-2</td>
<td>Bronchodilator</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Proventil and ventolin</td>
<td>Beta-2</td>
<td>Bronchodilator</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>Berotec</td>
<td>Beta-2</td>
<td>Bronchodilator</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent</td>
<td>Beta-2</td>
<td>Bronchodilator</td>
</tr>
</tbody>
</table>

**Adverse Effects**

- Betas can produce overstimulation of the CNS thus tremors, restlessness, anxiety.
- Overstimulation of the heart/cardiac arrhythmias – bigger danger with older beta drugs such as EPI and isoproterenol. Use extreme caution if patient has existing heart disease.
- Hypotension – beta-2 effects dilate the blood vessels of skeletal muscles.
- Higher than therapeutic doses of beta-2 specific drugs can stimulate the beta-1 receptors in the cardiac muscle.
- Cardio-vascular effects in pre-term pregnant patients – can arrest preterm labor, but also can have cardiovascular effects/complications. Fetal heart rate is also affected.
Dopamine

Not a class, but gets special mention because it is an NT in the brain and is formed in the body’s production of NE in the peripheral adrenergic/sympathetic nerve endings. If you create it in a lab (like the drug Intropin) and pump it into an IV you can treat cardio effects in circulatory shock.

The low and moderate dose effects below are important in the treatment of shock. It is used in a drip IV. Effects cease shortly after the flow of the IV ceases.

**Low doses**
Stimulates dopaminergic receptors in renal, mesenteric blood vessels. Vasodilation and increased renal blood flow.

**Moderate doses**
Stimulates beta-1 receptors, increasing heart contractility and output.

**High doses**
Stimulates alpha receptors – vasoconstriction. Overdose results in excessive heart stimulation and increased blood pressure.

Dobutamine, marketed as Dobutrex, is a drug similar to dopamine. Greater beta-1 effects, mainly used for heart failure in and IV infusion.

**Alpha-Adrenergic Blocking Drugs**

Sympatholytics, *inhibiting* the sympathetic nervous system. These compete with NE for binding rights to the receptors. If they beat the NE to the receptor, NE doesn’t produce sympathetic responses, so organs with alpha receptors have decreased sympathetic response.

The primary alpha organ: the blood vessels.

The result: vasodilation and lower blood pressure.

**Clinical Indications**
- Hypertension
- Peripheral vascular problems with poor blood flow to skin/extremities like Reynaud’s disease.
- Diagnosis of pheochromocytoma (tumor on adrenal medulla → increased catecholamine and severe hypertension).
- Diagnosis and treatment of benign prostatic hyperplasia causing enlargement of prostate gland and difficult urinary flow

Note that all end in *–in* or *–ine*.

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main use</th>
<th>Common daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxazosin</td>
<td>Cardura</td>
<td>HTN, benign prostatic hyperplasia</td>
<td>1 – 16mg po, 1-8mg po</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Regitine</td>
<td>Pheochromocytoma – diagnosis</td>
<td>5mg IV</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Minipress</td>
<td>HTN</td>
<td>1 – 20 mg po</td>
</tr>
<tr>
<td>Tamulosin</td>
<td>Flomax</td>
<td>Benign prostatic hyperplasia</td>
<td>0.4 – 0.8mg po</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Hytrin</td>
<td>HTN, benign prostatic hyperplasia</td>
<td>1-5mg po, 1-10mg po</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Aphrodyne</td>
<td>Male impotence</td>
<td>5.4-16.2mg po</td>
</tr>
</tbody>
</table>

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**Adverse Effects**

If you block activity in 1 part of the ANS, activity in the other branch increases it seems.

Common things that happen:

- Constriction of the pupils (miosis)
- Nasal congestion
- Increased GI activity
- Compensatory reflex tachycardia occurs if you lower the blood pressure
- Blocking the alpha interferes with normal cardio reflexes, so some patients get orthostatic hypotension and fainting.

**Beta-Adrenergic Blocking Drugs**

Sympatholytics, *inhibiting* the sympathetic nervous system. These bind to beta adrenergic receptors which keeps EPI and NE from binding and producing sympathetic responses. Hypertension, angina, and arrhythmia patients often have high levels of EPI and NE. This class of drugs includes beta-1 blocking to decrease heart rate, force and impulse conduction. There’s not really any reason therapeutically to block beta-2.

**Types of Beta-Blockers**

There are selective beta blockers and non-selective beta blockers. Note that all but one ends in *-olol*.

Selective beta blockers will only block beta-1 when used at a therapeutic dose, but can affect beta-2 when used at higher doses.

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>Sectral</td>
<td>HTN, ventricular arrhythmias</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Tenormin</td>
<td>HTN, angina pectoris</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Zebeta</td>
<td>HTN</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Brevibloc</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Lopressor</td>
<td>HTN, angina pectoris</td>
</tr>
</tbody>
</table>

Non-selective types block both beta-1 and beta-2. Propranolol was the first used clinically, though there are others to choose from. The difference between them all is mostly about duration of action and extent of metabolism.

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>Coreg</td>
<td>HTN, CHF</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Normodyne</td>
<td>HTN</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Corgard</td>
<td>HTN, angina pectoris</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Visken</td>
<td>HTN</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Inderal</td>
<td>HTN, migraine, angina pectoris, arrhythmias, post-myocardial infarction</td>
</tr>
<tr>
<td>Timolol</td>
<td>Blocadren</td>
<td>HTN, post-myocardial infarction, glaucoma</td>
</tr>
</tbody>
</table>
Pharmacological Effects

Propranolol is the main topic covered in the book in regards to the pharmacological effects of beta blockers. Oral administration of propranolol results in a big first-pass effect, so less of the drug gets to the system.

The main effects of propranolol and the primary reason it is given to a patient are those effects on the cardiovascular system:
- Decrease in rate, contraction force, conduction velocity of the heart
- Lower blood pressure
This reduces the work load on the heart and decreases oxygen consumption, which helps w/ a variety of cardio conditions especially due to hyperactivity of the sympathetic nervous system.

Other possible effects of propranolol are more of a cautionary tale and should be taken into consideration when it is given:
- Carbohydrate and lipid metabolism
  Beta blockers affect this metabolism and while usually no big deal, it can cause hypoglycemia in diabetic patients. They may need to increase triglyceride levels when on these drugs continually.
- Crosses the blood-brain barrier
  This can result in CNS sedation, depression, decreased sympathetic activity. The good news is that it can lower blood pressure for people with HTN.

There are other lipid insoluble/water soluble beta blockers that don’t cross the blood brain barrier such as nadolol and atenolol. The downside is that they largely excreted unmetabolized through the urine.

Clinical Indications

- **Propranolol**
  Angina pectoris, HTN, various cardiac arrhythmias, glaucoma, migraines, post-myocardial infarction (long term therapy can decrease the incidence of additional heart attacks/sudden cardiac death).
- **Esmolol**
  Short duration, emergency use. Lowers ventricular heart rate in cases of supraventricular tachycardia.

Adverse Reactions

- **Non-selective beta blockers such as Propranolol:**
  N/V/D, bradycardia → CHF or cardiac arrest. Generally contraindicated for asthma and respiratory conditions since non-selectives can cause bronchoconstriction.
- **Selective beta-blockers**
  At higher than therapeutic doses beta-1 blockers will affect beta-2 receptors as well. Selective beta blockers can also gain access to the brain causing drowsiness, depression and CNS disturbances.

Drug Interactions

Beta-blockers plus other drugs deceasing cardio function are the ones to watch out for. These include cardiac glycosides, anti-arrhythmic drugs, and calcium blockers. The combinations can
cause low heart rate and cardiac output leading to hypotension and drug-induced congestive heart failure.

### Adrenergic Neuronal Blocking Drugs

These drugs inhibit the sympathetic nervous system by decreasing the formation/storage of the release of NE inside the adrenergic nerve endings at the ends of the postganglionic nerve fibers. NE is created from the amino acids phenylalanine and/or tyrosine. When less NE is released, the sympathetic system activity is decreased.

#### Methyldopa

Methyldopa is marketed as Aldomet. When administered the adrenergic nerve endings convert it into alphamethylnorepinephrine. This is then stored and released like NE in the adrenergic nerve endings. Drugs like methyldopa are called *false transmitters* because they release something neurotransmitter-like, yet reduce neuronal activity.

Methyldopa’s primary use is for HTN. It reduces BP in the vasomotor center of the medulla oblongata, producing a central effect. The formulation/release of alpha-methylnorepinephrine at this site causes a decrease in sympathetic activity in the smooth vascular muscle tissue which translates to vasodilation and lowered blood pressure. You give 250-2000 mg total per day orally for this.

Transient side effects include drowsiness/sedation but these go away. Other effects: N/V/D, nasal congestion, bradycardia. Even worse side effects: drug fever, liver dysfunction, hemolytic anemia, lupus-looking skin eruptions and even arthritis.

#### Reserpine

This drug comes from an ancient plant used for Ayurveda, the *Rauwolfia serpentina*. It works at the nerve endings too, preventing NE from being stored so that there isn’t sufficient supply to power the sympathetic activity.

Reserpine is used in HTN, dilating the vessels and lowering blood pressure. It is usually combined with a diuretic.

It can produce CNS sedation/tranquilization so it was once used as an antipsychotic. Now it is the last drug used for psychotic patients when nothing else works.

Side effects:
- Decreased sympathetic activity
  - Increased salivation
  - Diarrhea
  - Nasal congestion
  - Bradycardia
  - Excessive hypotension
- Excessive sedation
- Psychic disturbances
  - Confusion
- Hallucination
- Mental depression
  - Suicide attempts
- At high doses can produce what looks like Parkinson’s – tremors and muscular rigidity.

**Guanethidine**
This is marketed as Ismelin. Guanethidine is a potent adrenergic neuronal blocker with 2 main actions on nerve endings:
- Prevents release of NE from nerve endings
- Depletes NE storage (similar to reserpine)
It is used mainly to treat severe HTN and it has a long half life. Effects can continue for up to 10 days after usage is stopped.

Adverse reactions (mostly due to decreased sympathetic activity):
- Diarrhea
- Nasal congestion
- Bradycardia
- Orthostatic hypotension
- Impotency (males)

**Guanadrel**
This drug is marketed as Hylorel. Works a lot like Guanethidine and is used for hypertension. It has a lower incidence of adverse effects than Guanethidine.

**Drugs Affecting the Parasympathetic Nervous System**
The parasympathetic system regulates body functions during rest, digestion and elimination of waste. It increases GI and genitourinary activity and decreases cardiovascular activity. It’s primary neurotransmitter is ACH or acetylcholine. Nerves that release this neurotransmitter are cholinergic nerves and the receptors that love them are cholinergic receptors. It stands to reason that cholinergic drugs are the ones that bind to the cholinergic receptors and produce effects like ACH. Those that bind to the receptors but don’t produce (or block) cholinergic activity are then cholinergic blocking drugs since they keep ACH from acting on it’s receptors.

ACH is produced and stored inside the cholinergic nerve endings. When stimulated these nerves release ACH from it’s little storage pods. It then travels to smooth or cardiac muscles and binds with the cholinergic receptors, causing the parasympathetic response. Since you don’t want it to do this forever, the body also produces acetylcholinesterase, an enzyme that inactivates ACH while it is outside of the nerve ending and not on a receptor. The effects are visible within seconds.

There are 3 types of cholinergic receptors and each uses ACH as the neurotransmitter, though each type of receptor requires a different cholinergic blocking drug. Here are the three types and the drugs who love them:
Muscarinic Receptors
These receptors live at the postganglionic nerve endings. There are muscarinic receptors located at smooth and cardiac muscle tissue sites. Drugs that block ACH at these receptors are called anticholinergic or antimuscarinic drugs.

Nicotinic-neural (Nn) Receptors
These are located at the ganglionic sites of both parasympathetic and sympathetic nerves. The neurotransmitter is again, ACH. Once upon a time someone noticed that nicotine stimulates ganglia in low doses, but blocks the ganglia in high doses. As a result, drugs that act like a low dose of nicotine are called ganglionic stimulants. Drugs that act like a high dose of nicotine and block ACH at the receptor sites are called ganglionic blockers.

Nicotinic-muscle (Nm) Receptors
These receptors live at the neuromuscular junctions of the skeletal muscle. ACH is the neurotransmitter here too. If you block the effects of ACH at the skeletal muscles you are using neuromuscular blockers or skeletal muscle relaxants.

Cholinergic Drugs
These mimic the actions of ACH at the muscarinic receptors. These are parasympathomimetic. They are divided into direct and indirect acting drugs.

Direct-acting Cholinergic Drugs
Bind to the muscarinic receptors. Because ACH is so short in duration you use derivatives of ACH which are inactivated more slowly by acetylcholinesterase.

Pharmacological effects include an increase in GI secretions and motility, increases in genitourinary activity, bronchoconstriction, miosis (pupil constriction), decreased blood pressure due to vasodilation, and decrease in heart rate.

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Miochol-E</td>
<td>Miotic in cataract surgery</td>
</tr>
<tr>
<td>Bethanechol</td>
<td>Urecholine</td>
<td>Nonobstructive urinary retention</td>
</tr>
<tr>
<td>Carbachol</td>
<td>Miostat</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Pilocar and Ocusert-Pilo</td>
<td>Glaucoma</td>
</tr>
</tbody>
</table>

Clinical indications:
Except for bethanechol, these drugs aren’t used systemically very often. Bethanechol is given orally to stimulate the urinary and intestinal tracts. This is useful for drug induced urinary retention and intestinal stasis, especially in the elderly. Adverse effects can include overstimulation and therefore diarrhea/urinary frequency.

Cholinergics are also used during ophthalmic examinations as a miotic to contract the pupils. This is of use in glaucoma because it promotes better drainage of intraocular fluids which build and cause increased pressure in glaucoma, eventually destroying the retina. It is used in drops for glaucoma.
Indirect-acting Cholergic Drugs

These are anticholinesterases, inhibiting the enzyme acetylcholinesterase. This allows the accumulation of ACH at the cholinergic receptor sites. There are two flavors: reversible and irreversible inhibitors. Both produce effects similar to ACH and parasympathetic stimulation (*parasympathomimetics*).

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambenomium</td>
<td>Mytelase</td>
<td>Myasthenia Gravis</td>
</tr>
<tr>
<td>Demacarium</td>
<td>Humorsol</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Endrophium</td>
<td>Tensilon</td>
<td>Dx of myasthenia gravis/antidote for curare type drugs</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Reminyl</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Prostigmin</td>
<td>Myasthenia gravis/antidote for curare type drugs</td>
</tr>
<tr>
<td>Physostimine</td>
<td>Antilirium, eserine</td>
<td>Antidote to anticholinertics and treatment of glaucoma</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Mestinon</td>
<td>Myasthenia gravis/antidote for curare type drugs</td>
</tr>
<tr>
<td>Tacrine</td>
<td>Cognex</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
<td>Alzheimer’s</td>
</tr>
</tbody>
</table>

Reversible Inhibitors

Used in the treatment of myasthenia gravis and as antidotes to reverse the effects of drugs that block cholinergic/nicotinic receptors.

Myasthenia gravis has insufficient ACH activity. The reversible inhibitor Edrophonium has a 30 minute duration and is given by IV to diagnose myasthenia gravis. Once diagnosed drugs like neostigmine, pyridostigmine and/or ambenonium are given, all of which have longer duration, are given orally for treatment.

These same drugs can be used with an IV to reverse the effects of excessive cholinergic blocking. None of these drugs will cross the blood-brain barrier, so they only function at the peripheral receptor sites.

These drugs are also used as eye drops for glaucoma.

Irreversible Inhibitors

These have a very long duration and form an irreversible bond with the acetylcholinesterase enzyme. These are derivatives of organophosphate compounds and are primarily used for rather awful things such as pesticides, insecticides, and in chemical warfare.

A couple of these derivatives are used in tiny amounts in eye drops for treating glaucoma (phospholine for example). In larger doses they cause cholinergic crisis – respiratory paralysis and death.

Adverse and Toxic Effects of Cholinergic Drugs

Most common effects (from over stimulation of the parasympathetic nervous system):

- ☯ NVD (nausea/vomiting/diarrhea)
- ☯ Blurred vision
- ☯ Excessive sweating
- ☯ Muscle tremors
Bronchoconstriction
Bradycardia
Hypotension

Toxic overdose symptoms:
Muscular paralysis
Respiratory depression

Enough of this and death occurs.

**Cholinergic Crisis**
This is the term used for excessive cholinergic drug dosage and the above symptoms. The people that suffer from it the most are those taking cholinergic drugs for myasthenia gravis. ACH causes overstimulus of the muscarinic receptors and blockage of the nicotinic receptors causing paralysis of the voluntary muscles needed for breathing.

If this occurs anticholinesterase drugs are stopped and atropine is administered, blocking the excess muscarinic stimulation.

Farmers spraying organophosphates/anticholinesterases can also experience this. Since these are irreversible inhibitors, you use pralidoxime (marketed as Protopam) to reactivate the acetylcholinesterase enzyme. This, incidentally, is also the antidote to organophosphate chemical warfare. I hope we never really need to know that!

**Clinical Indications for Anticholinesterase Drugs**
These are indirect acting cholinergics, called *anticholinesterase* drugs. They are more often used than the direct acting variety. They are used for:

- **Treatment of glaucoma**
  Used topically to lower intraocular pressure. Use of these drugs increases ACH levels in the eye, producing miosis (pupil constriction) and improving drainage of intraocular fluids to lower intraocular pressure.

- **Treatment of and diagnosis of myasthenia gravis**
  Myasthenia gravis is probably an autoimmune disease in which the body produces antibodies that attack the Nm receptors in the skeletal muscle endplates. Skeletal muscle loses strength and tone. Eventually the eyelids droop, movement becomes difficult, and patients become bedridden and have difficulty breathing. Long-duration reversible anticholinesterases are used, especially pyridostigmine and ambenonium, taken orally.

- **Treatment of urinary retention, intestinal stasis/paralysis**
  Treated with neostigmine, increasing the levels of ACH to stimulate bladder contraction and intestinal peristalsis.

- **Treatment of Alzheimer’s**
  Alzheimer’s is associated with lowered levels of ACH in the brain causing memory loss, dementia, and lowered mental function. Two reversible anticholinesterase drugs, tacrine (marketed as Cognex) and donepezil (Aricept) increase ACH levels in the brain. These work better in early stages, not so good as it progresses. Lecithin (marketed as Phoschol)
is a building block for ACH and is often administered with anticholinesterases.

Antidotes to curare-type skeletal muscle blockers
These drugs are used in surgery to paralyze skeletal muscles (specifically the Nm receptors). Neostigmine is used to increase ACH and compete with the blockers in cases where the blockers cause respiratory paralysis.

Antidotes to anticholinergics
Anticholinergics such as atropine and scopolamine and the like block cholinergic muscarinic receptors causing urinary and intestinal inhibition, tachycardia, seizures, and coma. Physostigmine is the antidote since it crosses the blood brain barrier and increases the levels of ACH in the brain. This increase reverses the effects of the excessive anticholinergic blockade.

### Anticholinergic Drugs

These are *parasympatholytic* drugs and act by “competitive antagonism” of ACH. This means that two substances are competing for one receptor. Sufficient amounts of ACH can't bind to the receptors because of the parasympatholytic, so there is lowered parasympathetic activity.

Atropine and scopolamine are the oldest in use and are derived from alkaloids found in the belladonna plant. There are also newer synthetics and semisynthetics.

### Belladonna Derivatives

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>---</td>
<td>PO, IV, IM, SC: Increases heart rate, used for pre-op med, controls enuresis, for GI and biliary colic, and an antidote to cholinergic drugs. Topical eye drops: dilates pupils (mydriatic) and paralyzes the ciliary muscles of the eye (cycloplegic)</td>
</tr>
<tr>
<td>Hyoscyamine</td>
<td>Levsin</td>
<td>Same as atropine. Given PO and IV</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Transderm-Scop</td>
<td>Motion sickness, most often in patch form every 3 days</td>
</tr>
</tbody>
</table>

### Semisynthetic

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homatropine</td>
<td>---</td>
<td>Mydriatic in an ophthalmic solution</td>
</tr>
</tbody>
</table>

### Synthetic – given orally

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
<th>Main use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dicyclomine</td>
<td>Bentyl</td>
<td>Treats GI disorders like ulcers and colitis</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>Robinul and Robinul Forte</td>
<td>Ulcers</td>
</tr>
<tr>
<td>Methscopolamine</td>
<td>Pamine</td>
<td>Treats GI disorders like ulcers and colitis</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Ditropan and Ditropan XL</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td>Propantheline</td>
<td>Pro-Banthine</td>
<td>Treats GI disorders like ulcers and colitis</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Detrol and Detrol LA</td>
<td>Overactive bladder</td>
</tr>
</tbody>
</table>
Pharmacological Actions/Clinical Indications

**Cardiovascular**
Decreases activity of vagus/parasympathetic nerve by blocking ACH from the receptors. Heart rate increases which is great for those with bradycardia. Also speeds atrioventricular conduction in the heart.

**Respiratory**
Cause bronchodilation, treat asthma. Also used preoperatively to inhibit secretions in the respiratory tract which might interfere with administration of general anesthetics. (Remember ACH increases secretions and can cause bronchoconstriction.)

**GI System**
Reduce salivary and GI secretions, decrease motility in GI tract. Used as antispasmodics in GI tract for IBS. (Were once used to treat peptic ulcers by decreasing gastric acid secretions, but have been replaced by stuff that works better now.) Because they reduce movement in the GI tract you should use them when there is intestinal blockage.

**Genitourinary**
Treat urinary incontinence and overactive bladder in which there are spasms and urinary urgency (because anticholinergics inhibit urinary peristalsis and the voiding of the bladder). These drugs are contraindicated in cases of hypertrophy of the prostate gland since that causes difficult urination to begin with!

**Central Nervous System**
Sleep aid/sedative. Anticholinergics that cross the blood brain barrier produce a depressant effect causing drowsiness/sedation. Also used in Parkinson’s disease and as an antiemetic for motion sickness.

At higher doses there is a combination CNS stimulant and depressant effect. At toxic doses atropine and scopolamine can cause excitation, delirium, hallucinations and heavy duty CNS depression that can cause respiratory arrest and death.

**Ocular Effects**
Used in ophthalmology to help examine retina and lens of the eye because they cause miosis (pupil dilation) and loss of muscular accommodation (cycloplegia).

The caution here is that pupil dilation suddenly increase intraocular pressure and should therefore never be given to glaucoma patients.

**Adverse and Toxic Effects**
Symptoms stem from excessive blockage of the parasympathetic nervous system…because these are parasympatholytics!

- Dry mouth

- Visual disturbances
Urinary retention

Constipation

Flush redness of the skin
Anticholinergics inhibit sweating and vasodilate blood vessels on the surface.

Dryness of the skin

Fever (hyperpyrexia)
Can be severe in toxic doses. Can be accompanied by depression of visual centers of the brain.

Tachycardia
Symptoms of both CNS stimulation and depression
Can be severe in toxic doses. Can be accompanied by depression of visual centers of the brain. Can result in respiratory paralysis and death.

Children have mistakenly eaten non-edible berries which can contain belladonna alkaloids. Watch for the symptoms above plus pupil dilation. Treatment for overdose involves emesis or gastric lavage (stomach pumping) to limit absorption as well as administration of activated charcoal, saline cathartics which inactivate the compounds and accelerate elimination. Physostigmine may need to be given in IV if there is delirium or coma.