Chapter 13: Principles of Neuropharmacology

- Study of drugs that alter processes controlled by the nervous system
  - Peripheral nervous system drugs
  - Central nervous system drugs
    - *Drugs used to treat:*
      - Depression
      - Epilepsy
      - Hypertension
      - Asthma
  - These types of drugs help the body to help itself

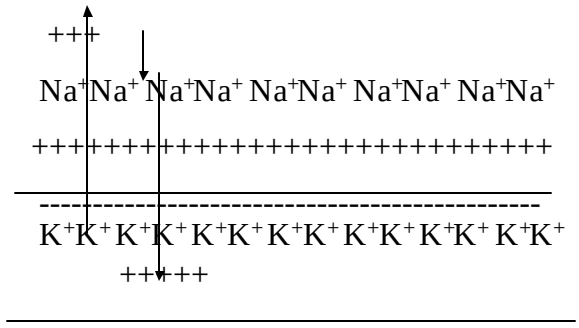
- Neuropharmacologic drugs can:
  - **Mimic normal actions of body neurotransmitters**
  - **Block normal actions of body chemicals**
  - **Modify actions of all body systems**
    - ***Skeletal muscles***
    - ***Cardiac muscle and output of blood***
    - ***Vascular tone***
    - ***Respiration***
    - ***Gastric function***
    - ***Uterine motility***
    - ***Glandular secretion***
    - ***CNS functions (heat, pain, mood, etc…)***

- **Neuron Function:**
  - *Neuron, synapse, response organ*
- **Reflex arc:**
  - *Sensory neuron, synapse, CNS, synapse, motor neuron*
- **Response through brain:**
  - *Sensory neuron, synapse, CNS spinal ganglia, brain, spinal ganglia, motor neuron*
- **3 major steps in neuron action:**
  - *Conduction of action potential*
  - *Release of neurotransmitter from axon*
  - *Binding of transmitter molecules to receptors on post-synaptic cell*

- **Action at synapse level**
  - **Most neuropharmacologic agents act at synapse transmission level**
    - *Axonal conduction NOT a common site of action*
      - **(local anesthetics decrease axonal conduction)**
    - *Synaptic transmission site more selective*
  - **Nerve action**
    - *Stimulus*
    - *Change in polarity (de-polarization)*
    - *Dendritic receptor → cell body → axon transmission → synapse → response*
      - **Synapse response different at different sites**
        - » **Different transmitters**
        - » **More than one type of receptor**

■ Resting Potential

- **Resting nerve cell more positive on outside than inside**
  - ***Semi-permeable membrane***
    - **Keeps Na^+ out and K^+ in until stimulus**
  - ***Stimulus causes Na^+ to diffuse in***
    - **This changes polarity to more positive inside than outside membrane**
    - **Stimulus then continues down dendrite/axon**
  - ***Repolarization***
    - **To re-polarize, membrane becomes impermeable to Na^+ and permeable to K^+ and K^+ moves out from nerve to create + charge outside and more negative inside**
    - **If this continues without the nerve allowed time to PUMP K^+ back in and Na^+ out, then nerve stimulation will ultimately stop due to inability to de-polarize**



Semi-permeable membrane

De-polarization= movement of Na^+ into cell

Re-polarization= movement of K^+ out of cell

Receptors

- Nerve synaptic transmitter diffuses across synaptic space and binds to receptors on target cell
  - *Number of receptors on target cell will determine the level of response to transmitter*
- Steps in synaptic transmission
  - *Synthesis of transmitter molecules*
  - *Storage of transmitter molecules in vesicles*
  - *Release of transmitter molecules by action potential into synaptic gap*
  - *Receptor binding (reversible)*
  - *Termination by release of transmitter from receptor (uptake, enzymatic degradation, and diffusion)*

Drug action on receptors

- Enhance receptor activation
  - *May increase effect by increasing release*
  - *May activate receptor BUT decrease activity*
    - Actylcholine decreases heart rate when receptors are activated
  - *Increase number of receptor molecules*
- Reduce receptor receptor activation
  - *Decrease response by decreasing release*
  - *Down-regulating receptor number*
- Transmitter synthesis
  - *Increase*
  - *Decrease*
  - *Cause synthesis of transmitter type that is more effective than natural transmitter (higher affinity for receptor)*

- **Interference with transmitter storage**
  - ***Can increase storage or decrease storage in vesicles***
- **Transmitter release**
  - ***Promote or inhibit release***
    - **Amphetamines (CNS stimulant) increase transmitter release**
    - **Botulism toxin inhibits transmitter release**
- **Receptor binding**
  - ***Enhancement of binding (agonists)- synergism of action- both bind to receptor***
  - ***Blocking binding (antagonists)- blockage of receptor or lowering of affinity of receptor for transmitter***

- **<u>Drugs that that act at receptor level</u>**
  - **Activation**
    - ***Morphine (effect on CNS)***
    - ***Epinephrine (effect on cardiovascular system)***
    - ***Insulin (effect on diabetes)***
    - ***Benzodiazepines (Valium)- treats anxiety, seizure disorders and muscle spasm***
  - **Inhibition**
    - ***Naloxone (treats overdose of morphine-like drugs)***
    - ***Antihistamines (treat allergic disorders)***
    - ***Propranolol (treats hypertension, angina pectoris, and dysrhythmias)***

- **Termination of transmitter action**
  - Blockade of transmitter reuptake
    - *increase concentration of transmitter*
  - Inhibition of transmitter degradation
    - *Increase concentration of transmitter*
- **Multiple receptor types & Selectivity**
  - The greater the number of receptors, the greater the chances of obtaining selective drug effects
- **Drug action on receptors** ***
  - Type of receptor drug works on
  - Normal response to activation of "R"
  - What does the drug do to "R" function

- **Isoproterenol**
  - Reacts with β and β_2 receptor
    - *Reaction with beta causes*
      - Increased heart rate and increased force of cardiac contraction
    - *Reaction with beta 2 receptors causes*
      - Bronchial dilation
      - Elevation of glucose levels in blood
  - Isoproterenol causes activation of both types of receptors and elicits 3 types of responses
    - *Increased cardiac output (increase rate and force of contraction)*
    - *Dilation of bronchi*
    - *Elevation of blood glucose*

Chapter 14: Physiology of PNS

- **CNS- brain and spinal cord**
- **Peripheral Nervous System**
  - **Somatic motor system**
  - **Autonomic nervous system**
    - **Sympathetic nervous system**
    - **Parasympathetic nervous system**
    - ***3 functions***
      - **Regulation of heart**
      - **Regulation of secretory glands (salivary, gastric, sweat and bronchial glands)**
      - **Regulation of smooth muscles (bronchi, blood vessels, urogenital and gastrointestinal systems)**

- **Parasympathetic System**
  - **Increases responses that are involved in "recovery" phases**
    - ***Increase digestion***
    - ***Decrease heart rate***
    - ***Bladder and bowel emptying***
    - ***Focusing eye for near vision***
    - ***Contraction of bronchiolar smooth muscle***
- **Sympathetic System**
  - **"Fight or Flight" responses**
    - ***Increase pupil dilation***
    - ***Increase heart rate***
    - ***Move blood from periphery to inner body***
    - ***Dilation of bronchi***

- Most organs innervated by both para- and sympathetic systems
  - *Balance by opposition-*
    - heart rate
  - *Complementary control- increase overall response or complement each other*
    - Erection is mediated by parasympathetic response while ejaculation controlled by sympathetic nerves
  - *Innervation and regulation by only one of the two branches*
    - Blood vessels innervated only by sympathetic nerves

Regulation

- Feedback reflex
  - *Baroreceptor reflex- blood pressure (receptors in carotid sinus and aortic arch)*

- Autonomic tone
  - *Steady state, basal, level of tone*
    - Muscle- neither fully relaxed or contracted
    - Parasynpathetic nerves in most organs provide basal level of control (predominant tone)

Site of Drug Action

- Parasympathetic
  - *Synapses between pre-ganglionic and post-ganglionic neurons*
  - *Junctions between post-ganglionic neurons and effector organs*
- Sympathetic
  - *Synapses between pre-ganglionic and post-ganglionic neurons*
  - *Junctions between post-ganglionic neurons and effector organs*

- **Somatic Motor System**
  - ***Only one neuron and site of drug action is the neuromuscular junction***

- **Transmitters of PNS** (~40 or more)
  - **Acetylcholine- released by**
    - ***all pre-ganglionic neurons of para-sympathetic nerves:***
    - ***by all pre-ganglionic neurons of the sympathetic system:***
    - ***all post-ganglionic neurons of parasympathetic system***
    - ***All motor neurons to skeletal muscles***
    - ***Most post-ganglionic neurons of the sympatheitic system that go to sweat glands***

- **Norepinephrine:** *released by*
  - ***All post-ganglionic neurons of sympathetic system***
  - ***Exception→Sweat gland nerves release acetylcholine at junction***
- **Epinephrine:**
  - ***Major transmitter released by adrenal medulla***
- **Dopamine:** not known conclusively– **located in vasculature of kidney and activation of receptors dilates renal blood vessels**

- Receptors- **distinct types and subtypes: allow for selectivity of drug action**
  - **Cholinergic**- ***response to acetylcholine***
  - ***Adrenergic- response to epinephrine (adrenaline) and nor-epinephrine***

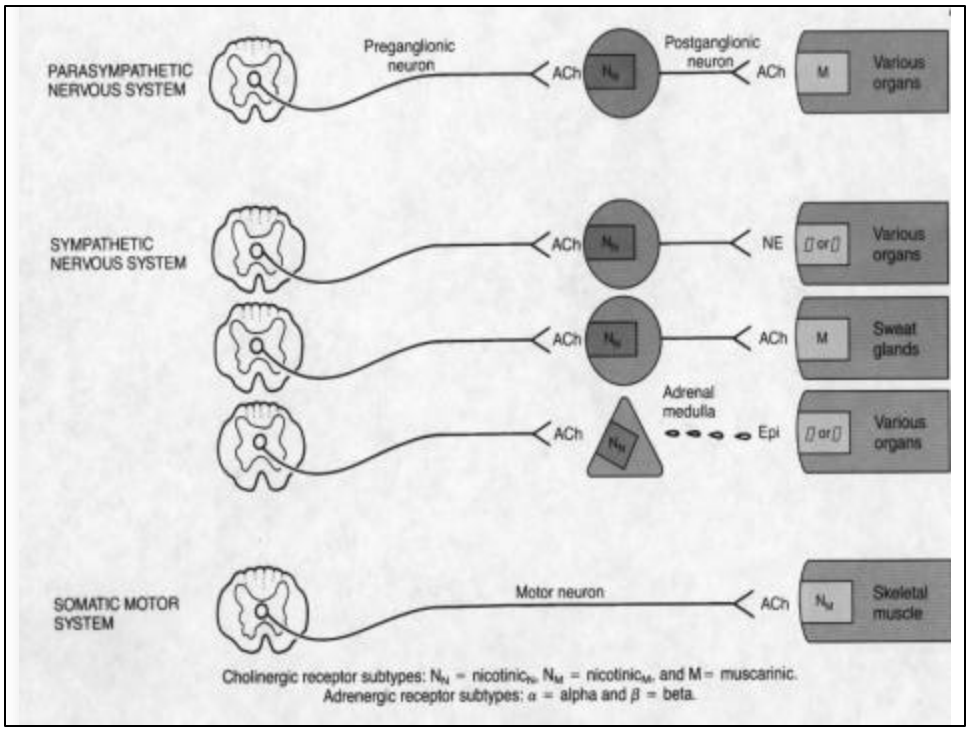
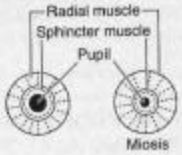


Table 14–4 RECEPTOR SPECIFICITY OF ADRENERGIC TRANSMITTERS

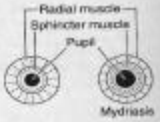
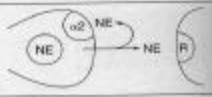
	Adrenergic Receptor Subtype				
Transmitter	*Alpha$_1$*	*Alpha$_2$*	*Beta$_1$*	*Beta$_2$*	*Dopamine*
Epinephrine	←		←	→	
Norepinephrine	←		←		
Dopamine	←		←		←

Table 14–2 FUNCTIONS OF PERIPHERAL CHOLINERGIC RECEPTOR SUBTYPES

Receptor Subtype	Location	Response to Receptor Activation
$Nicotinic_N$	All autonomic nervous system ganglia and the adrenal medulla	Stimulation of parasympathetic and sympathetic postganglionic nerves and release of epinephrine from the adrenal medulla
$Nicotinic_M$	Neuromuscular junction	Contraction of skeletal muscle
Muscarinic	All parasympathetic target organs:	
	Eye	Contraction of the ciliary muscle focuses the lens for near vision Contraction of the iris sphincter muscle causes miosis (decreased pupil diameter)
		
	Heart	Decreased rate
	Lung	Constriction of bronchi Promotion of secretions
	Bladder	Voiding
	GI tract	Salivation Increased gastric secretions Increased intestinal tone and motility Defecation
	Sweat glands*	Generalized sweating
	Sex organs	Erection
	Blood vessels†	Vasodilation

*Although sweating is due primarily to stimulation of muscarinic receptors by acetylcholine, the nerves that supply acetylcholine to sweat glands belong to the sympathetic nervous system rather than the parasympathetic nervous system.
†Cholinergic receptors on blood vessels are not associated with the nervous system.

Table 14–3 FUNCTIONS OF PERIPHERAL ADRENERGIC RECEPTOR SUBTYPES

Receptor Subtype	Location	Response to Receptor Activation
$Alpha_1$	Eye	Contraction of the radial muscle of the iris causes mydriasis (increased pupil size)
		
	Arterioles Skin Viscera Mucous membranes	Constriction
	Veins	Constriction
	Sex organs, male	Ejaculation
	Bladder neck and prostatic capsule	Contraction
$Alpha_2$	Presynaptic nerve terminals*	Inhibition of transmitter release
		
$Beta_1$	Heart	Increased rate Increased force of contraction Increased AV conduction velocity
	Kidney	Renin release
$Beta_2$	Arterioles Heart Lung Skeletal muscle	Dilation
	Bronchi	Dilation
	Uterus	Relaxation
	Liver	Glycogenolysis
	Skeletal muscle	Enhanced contraction, glycogenolysis
Dopamine	Kidney	Dilation of kidney vasculature

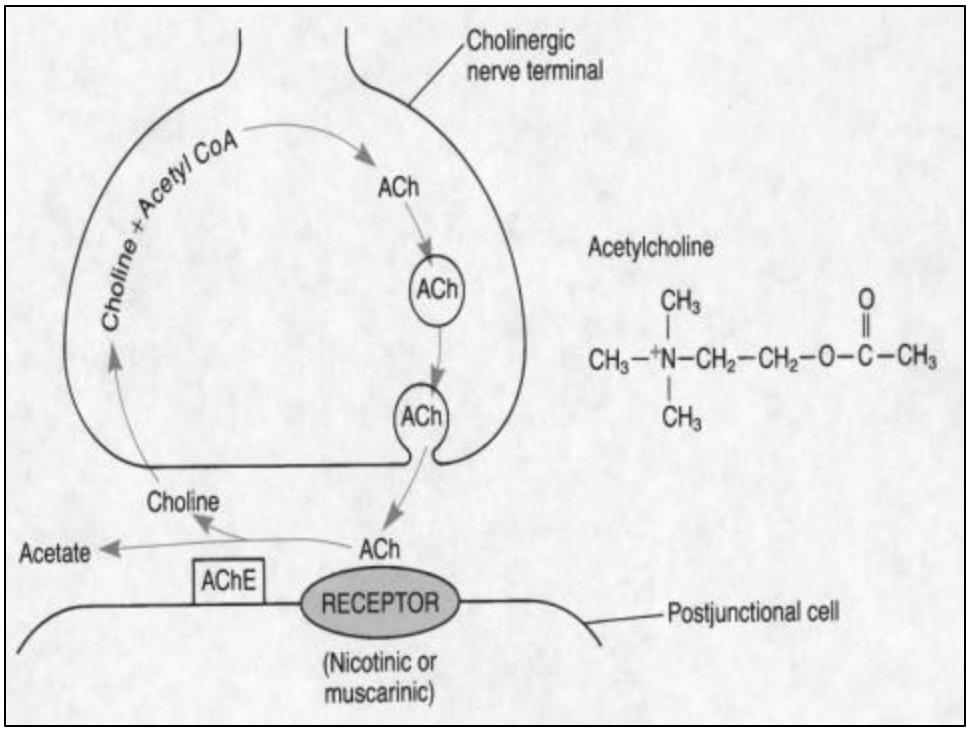
AV = atrioventricular, NE = norepinephrine, R = receptor.
*Alpha$_2$ receptors in the central nervous system are postsynaptic.

■ Life Cycle of Acetylcholine

- ***Synthesis of Ach from choline + acetylcoenzyme A (Krebs cycle?)***
- ***Stored in vesicles***
- ***Released***
- ***Binds to receptors***
- ***Destroyed almost instantaneously by acetylcholinesterase (AChE)***
- ***Choline released as end product and recycled back into nerves for synthesis (not acetyl co-A)***

– **Drugs act at:**

- ***Botulism blocks Ach release***
- ***Action at receptor level to block or mimic Ach***
- ***Inhibition of AChE (Ach accumulates in junction!!)***



■ Life Cycle of Epinephrine

– **Synthesis of epinephrine within chromaffin cells of adrenal medulla**

- ***Norepinephrine produced and then converted to epinephrine (NOT PRODUCED IN NERVES)***
- ***Epinephrine stored in vesicles in adrenal medulla***
- ***Released from adrenal gland***
- ***Travels in blood throughout body***
- ***Hepatic metabolism destroys action of epinephrine, not re-uptake by nerves***
- ***MAO produces inactive product (what would MAO inhibitors do?)***

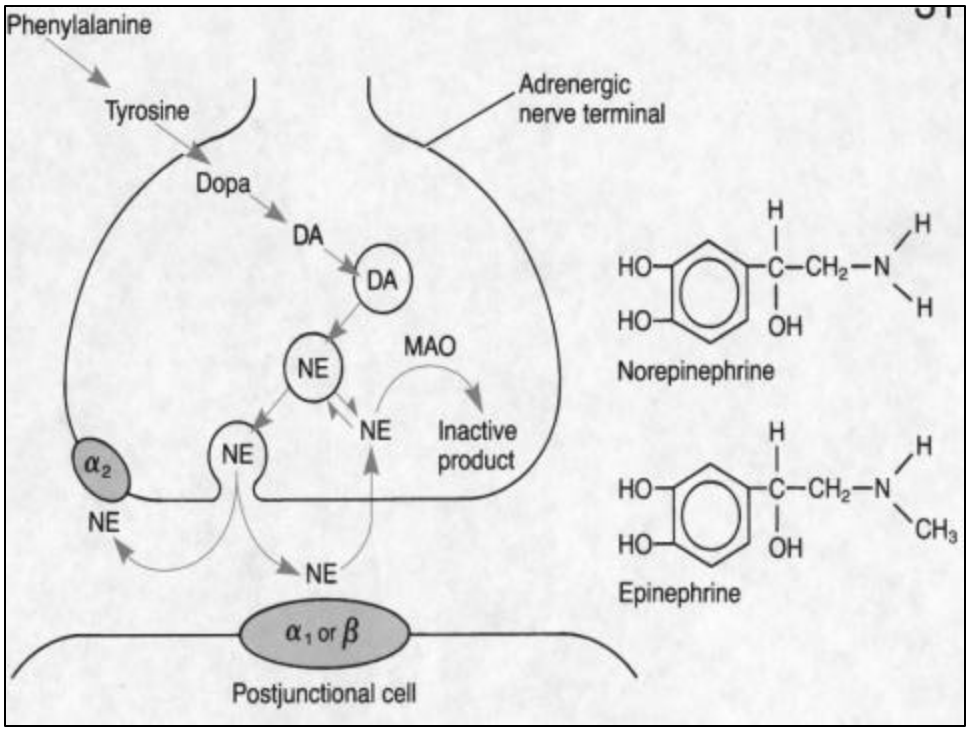


Table 2 SUMMARY OF CHOLINERGIC DRUGS AND THEIR RECEPTORS

	Receptor Subtype		
	Muscarinic	*Nicotinic$_N$*	*Nicotinic$_M$*
Receptor Location	Sweat glands Blood vessels All organs regulated by the parasympathetic nervous system	All ganglia of the autonomic nervous system	Neuromuscular junctions (NMJ)
Effects of Receptor Activation	Many, including: ↓ Heart rate ↑ Gland secretion Smooth muscle contraction	Promotes ganglionic transmission	Skeletal muscle contraction
Receptor Agonists	Bethanechol	Nicotine	(Nicotine*)
	Cholinesterase inhibitors: physostigmine, neostigmine (these drugs indirectly stimulate all cholinergic receptors)		
Receptor Antagonists	Atropine	Mecamylamine	*d*-Tubocurarine, succinylcholine

*The doses of nicotine needed to stimulate nicotinic$_M$ receptors of the NMJ are much higher than the doses needed to stimulate nicotinic$_N$ receptors in autonomic ganglia.

Chapter 15: Muscarinic Agonists and Antagonists

- **Agonists-**
  - **Drugs that bind to muscarinic receptors and cause receptor activation**
    - ***(associated with parasympathetic system, and effects mimic those produced by parasympathetic stimulation)***

Bethanechol

- Reversible binding to muscarinic cholinergic receptors and causes activation (Table 14-2 for effects)
  - *Causes*
    - Bradycardia (decreased heart rate)
    - Increased sweating
    - Increased salivation
    - Increased bronchiolar secretions
    - Increased secretion of gastric acid
    - Contraction of smooth muscles
    - Increased motility of peristalsis
    - Contraction of bladder
    - Relaxation of vascular smooth muscle (hypotension)
    - Near vision accomodation (near vision)
    - Pupillary constriction

Administered

- *Orally*
  - Effects begin 30-60 minutes and last 1 hour
  - To produce equivalent effect the oral dose must be 40X that of s.c. dose
- *Injection s.c.*
  - Effects in 5-15 minutes and last 1 hour
- *Has + charge and cannot get across membranes of GI tract well (small amount absorbed)*

Therapeutic uses

- *Relieves urinary retention*

- **Adverse Effects**
  - *Hypotension & bradycardia*
  - *Abdominal cramps & diarrhea*
  - *Contraindicated for patients with asthma (because of bronchiolar constriction*
  - *Contraindicated for patients with hyperthyroid conditions (dysrhythmias)*
- **Dosage & administration**
  - *Adult dosage: ORAL→10-50 mg 3 to 4 times/day*
    - **1 hour prior to meals or 2 hours after meals**
  - *SC injection- 5 mg up to 4 times/day*
- **Toxicity if injected i.m. or i.v.**

- **Other muscarinic Agonists**
  - **Pilocarpin- used for glaucoma**
  - **Acetylcholine- dilation of pupil (lacks selectivity and degraded quickly)**
  - **Muscarine- mushrooms; not used clinically**
- **Toxicology**
  - **Mushrooms:: *Inocybe* and *Clitocybe* species**
  - **Treatment:: atropine (selective muscarinic blocking agent**

Muscarinic Antagonists

- **Atropine**
  - **Found in variety of plants**
    - **Atropa belladonna and Datura stramonium**
    - ***Acts as competitive inhibitor of muscarinic receptors (blocks ACh)***
    - ***High and low affinity receptors in different organs***
      - **Doses needed to block stomach and bronchiolar smooth muscle higher than other organs**
      - **Has opposite effect of agonists on heart, exocrine glands and smooth muscles**
      - **CNS-- mild hallucinogen and causes delirium**
        - » **High doses cause coma, respiratory arrest and death**

- **Pharmacokinetics**
  - ***Administered orally, topically and by injection (im, iv, sc)***
  - ***Goes to all tissues, including CNS***
  - ***Elimination by urinary mechanisms and liver***
  - ***½ life of about 3 hours***
- **Therapeutic uses**
  - ***Pre-anesthetic medication-***
    - **slow heart rate due to stimulation of baroreceptors can be reversed by atropine**
  - ***Eye examinations***
  - ***Bradycardia***
  - ***Used with morphine for gallstones to relax biliary tract smooth muscle***
  - ***Peptic ulcer medication (reduces gastric acid)***
  - ***Asthma- blocks bronchiolar constriction***

- **Adverse Effects**
  - *Dry mouth (xerostomia)*
  - *Blurred vision and photophobia*
  - *Elevation of intraoccular pressure*
    - Do not use in patients with glaucoma
  - *Urinary retention*
    - Void bladder prior to medication
  - *Constipation*
    - Decreased motility of GI smooth muscle
  - Anhidrosis
    - *Decreased sweating (at risk for hyperthermia)*
- **Drug interactions**
  - *Avoid anti-histamines, phenothiazine antipsychotics and tricyclic antidepressants due to potential enhancement of atropine effects*

- **Dose and Administration**
  - *Oral tablets-- 0.4 to 0.6 mg*
  - *Systemic dose-- 0.5 mg if by injection*
- **Other antagonists**
  - *Scopolamine- sedation and suppression of emesis and motion sickness*
  - *Ipratropium- treat asthma and allergies*
  - *Tolterodine- used for incontinence treatment*
  - *Dicyclomine- used for irritable bowel syndrome*

Cholinesterase inhibitors and their use in Myasthenia Gravis

- **Drugs that prevent degradation of Ach by acetylcholinesterase (AChE)**
  - **Enhance action of Ach**
    - ***Cholinergic agonists by indirect action***
  - **Lack of specificity and therefore should not be used widely for therapies**
    - ***Reversible vs non-reversible inhibitors***

- **Reversible AChE inhibitors**
  - **Neostigmine**
    - ***Carries a + charge and cannot easily cross membranes (GI tract, Blood-brain barrier, or placenta)***
    - ***Splitting of neostigmine occurs more slowly than hydrolysis of ACh, and AChE cannot act on Ach until broken down***
    - ***Intensify transmission at all junctions where ACh is the transmitter***
    - ***Usually affects only muscarinic and nicotinic receptors of the neuromuscular junction***
      - **Increase glandular secretions, increase tone and motility of GI tract smooth muscle, urinary urgency, and bronchiolar constriction**
      - **Increase force of contraction of skeletal muscles (at toxic levels force of contraction is reduced**

- **Pharmacokinetics**
  - ***Oral or injection***
    - **Oral doses must be MUCH larger than parenteral to elicit same effects**
    - **Action lasts 2-4 hours**
    - **Eliminated by enzymatic degradation**
- **Treatment of Myasthenia Gravis**
  - ***Accumulation of ACh at neuromuscular junction, the ACh can reverse blockade due to tubocurarine***
    - **Good in post-operative patients**
    - **Good in treatment of overdose with nondepolarizing neuromuscular blockers**
- **Adverse effects - muscarinic stimulation & respiratory depression**
    - **Excessive salivation, inc gastric secretions, ….**
    - **Neuromuscular blockade by causing excessive depolarization**

■ Irreversible AChE Inhibitors

- **Highly lipid soluble**
    - **Get into CNS**
    - **Absorbed through skin**
    - **Structure of molecule similar for medication, insecticide and for nerve gas!**
  - ***Bind to active site in AChE and prevent enzyme from hydrolyzing ACh***
    - **Effects continue until new AChE are made**
      - » **Can be reversed by Pralidoxime**
- **Used only in treatment of glaucoma**

■ Myasthenia Gravis

- **Neuromuscular disorder**
  - ***Muscle weakness and rapid fatigue***
  - ***Ptosis= drooping eyelids***
  - ***Difficulty breathing (weakness of diaphragm)***
  - ***Autoimmune disorder due to Ab's formed against nicotinic$_m$ receptors on skeletal muscles: reduces number of receptors 70-90%***
- **Treatment with neostigmine**
  - ***Increase muscle strength***
  - ***Not cure→ symptomatic relief***
  - ***Use drug for rest of life***
    - **Access ability to swallow (few sips of water) prior to giving orally; if cannot swallow give parenterally**

- **Distinguish between**
  - ***Cholinergic crisis- overdose with AChE inhibitor***

  And
  - ***Myasthenic crisis- inadequate medication***
- **Patient should use identification bracelet (Medic Alert)**

Chapter 17: Neuromuscular and Ganglionic Blocking Agents

- **Neuromuscular blocking agents**
  - Block at nicotinic$_M$ receptors at neuro-muscular junction: cause muscle relaxation
- **Ganglionic blocking agents**
  - Block at nicotinic$_N$ receptors in autonomic ganglia-
    - *Once used for hypertension but now replaced by newer drugs*

- **Neuromuscular blocking agents**
  - Given to relax during surgery
    - *Endotracheal intubation*
    - *Mechanical ventilation*
  - Muscle contraction
    - *Polarization- + outside and - inside*
    - *Depolarization- Na^+ diffuses in to make inside +*
    - *Repolarization- K^+ diffuses out to make inside –*
      - Action potential by motor neuron and ACh stimulation of nicotinic$_M$ receptors on motor end plate → depolarization
      - Calcium released (SR) allow interaction of actin and myosin
      - ACh dissociated, is degraded by AChE, end plate repolarizes, Ca^{++} reabsorbed into SR and muscle relaxes

- **Blockers**
  - **Classified by mechanism of action (non-depolarizing and depolarizing) and time course of action (long, intermediate, short, and ultra-short)**
  - **Non-depolarizing**
    - ***Tubocurarine (curare)- paralysis & death due to respiratory paralysis***
      - **Cannot cross membranes easily (parenteral, IV)**
      - **Cannot cross blood-brain barrier- no effect on CNS**
      - **Cannot cross placenta – no effect on fetus**
    - ***Competes with ACh for binding to nicotinic$_M$ receptors on motor end plate (does NOT mimic but blocks ACh)***
      - **Muscle relaxation**
      - **Hypotension**

  - **Adverse effects**
    - ***Respiratory arrest***
    - ***Cardiovascular effects***
  - **Drug interactions**
    - ***General anesthetics can enhance action***
    - ***Antibiotics can intensify response (tetracycline and gentamicin)***
    - ***AChE can decrease effects of tubocurarine (increase amount of ACh to compete for receptor binding)***
  - **Toxicology- overdose**
    - ***Prolonged apnea***
    - ***Massive histamine release***
    - ***Cardiovascular collapse***

Table 17–1 NEUROMUSCULAR BLOCKERS: TIME COURSE OF ACTION*

Generic Name	Route	Time to Maximum Paralysis (min)	Duration of Effective Paralysis (min)	Time to Nearly Full Spontaneous Recovery†
Long Acting				
Doxacurium [Nuromax]	IV	4–10	100	Hours
Metocurine [Metubine]	IV	3–5	25–90	Hours
Pipercuronium [Arduan]	IV	3–5	90–120	Hours
Rocuronium [Zemuron]	IV	1–3	30–70	—
Tubocurarine	IV, IM‡	2–5	35–60	Hours
Intermediate Acting				
Atracurium [Tracrium]	IV	2–5	20–35	60–70 min
Cisatracurium [Nimbex]	IV	2–5	20–35	—
Pancuronium [Pavulon]	IV	3–4	35–45	60–70 min
Vecuronium [Norcuron]	IV	3–5	25–30	45–60 min
Short Acting				
Mivacurium [Mivacron]	IV	2–5	10–15	21–34 min
Ultrashort Acting				
Succinylcholine [Anectine, others]	IV, IM‡	1	4–6	—

*Time course of action can vary widely with dosage and route of administration. The values presented are for an average adult dose administered as a single IV injection.
†Because spontaneous recovery can take a long time, recovery from the *nondepolarizing* agents (all of the drugs listed except succinylcholine) is often accelerated by giving a cholinesterase inhibitor.
‡Intramuscular administration is rare.

- **Dosage and Administration**
  - **IV administration**
  - **Only by specially trained clinicians**
  - **20 units/ml in solution**
    - ***Adult initially gets 40-60 units at time of initial incision: followed by 20-30 units w/i a few minutes***
- **Other Nondepolarizing Blockers**
  - ***Long acting***
    - **Doxacurium**
    - **Metocurine**
  - ***Intermediate acting***
    - **Atracurium**
  - ***Short acting***
    - **Mivacurium- maximal 2-5 minutes after IV, lasts 10-17 minutes**

Depolarizing Blockers

- **Succinylcholine**
  - ***Only depolarizing neuromuscular blocker in clinical use***
  - ***Very short acting***
  - ***Binds to nicotinic$_M$ receptors on motor end plate and causes depolarization***
  - ***Remains bound to receptor and prevents repolarization (constant depolarization)***
  - ***Causes brief contraction then paralysis***
  - ***Paralysis is only short lived***
    - **Peaks at 1 minute after IV and fades w/i 4-10 min**
    - **Degraded by *pseudocholinesterase* (in plasma)**
  - ***Used during endotracheal intubation, endoscopy and other short procedures***

Therapeutic uses of neuromuscular blockers

- ***Muscle relaxation during surgery***
- ***Facilitation of mechanical ventilation***
- ***Electoconvulsive therapy (depression)***
- ***Endotracheal intubation***
- ***Diagnosis of myasthenia gravis***

Ganglionic Blocking Agents

- **Lack selectivity & limited applications**
  - ***Used to lower blood pressure (only in special circumstances)***

Table 17–2 PREDOMINANT AUTONOMIC TONE AND RESPONSES TO GANGLIONIC BLOCKADE

Location	Predominant Tone	Response to Ganglionic Blockade
Salivary glands	Parasympathetic	Dry mouth
Ciliary muscle	Parasympathetic	Blurred vision
Iris sphincter	Parasympathetic	Photophobia (from mydriasis)
Urinary bladder	Parasympathetic	Urinary retention
Gastrointestinal tract	Parasympathetic	Constipation
Heart	Parasympathetic	Tachycardia
Sweat glands	Sympathetic[a]	Anhidrosis
Arterioles	Sympathetic	Hypotension (from vasodilation)
Veins	Sympathetic	Orthostatic hypotension (from pooling of blood in veins secondary to venous dilation)

[a]Sympathetic nerves to sweat glands release acetylcholine as their transmitter, which acts at muscarinic receptors on the sweat glands.

– **Mecamylamine**
  - ***Interrupts impulse through ganglia of autonomic nervous system***
  - ***Competes with ACh for binding to nicotinic$_N$ receptors of sympathetic and parasympathetic systems***
  - ***Stops all autonomic control of organs (Table 17-2)***

- **Pharmacokinetics**
  - *Well absorbed following oral administration*
  - *Effect w/i 2 hours and last ~ 12 hours*
  - *Lipid soluble*
    - Crosses blood brain barrier and placenta
  - *Eliminated through urine*
- Therapeutic use
  - *Essential hypertension*
- Adverse reactions
  - *Antimuscarinic effects*
  - *Hypotension*
  - *CNS effects – tremor, convulsions and mental abberations*

Chapter 18: Adrenergic Agonists

- Work by activating adrenergic receptors
  - *Similar reactions to stimulation by sympathetic response (sympathomimetics)*
- **Mechanisms of action**
  - *Direct receptor binding*
  - *Promotion of norepinephrine release*
  - *Blockade of NE uptake- increase in synapse*
  - *Inhibition of NE inactivation- block action of MAO*
- All promote NE increase

■ Table 18-1

Table 18–1 MECHANISMS OF ADRENERGIC RECEPTOR ACTIVATION

Mechanism of Stimulation	Examples
Direct Mechanism	
Binding to receptor to cause activation	Epinephrine Isoproterenol Ephedrine*
Indirect Mechanisms	
Promotion of NE release	Ephedrine* Amphetamines
Inhibition of NE reuptake	Cocaine Tricyclic antidepressants
Inhibition of MAO	MAO inhibitors

MAO = monamine oxidase, NE = norepinephrine.
*Ephedrine is a mixed-acting drug that activates receptors directly and also promotes release of norepinephrine.

■ Adrenergic Agonists

- **Catecholamines**
  - ***Contain catechol (benzene ring with 2 –OH groups) and amine groups***
  - ***Cannot be used orally: administered IV, SM, SC***
  - ***Discard when solution becomes discolored***
- **Non-Catecholamines**
  - **Ephedrine**
  - **Phenylephrine**
  - **Terbutaline**
  - ***Degraded slowly by MAO***
  - ***Have longer ½ lives than catecholamines***
  - ***Can be given orally***
  - ***Less polar and can penetrate blood-brain barrier and effect CNS***

■ Table 18-2

Table 18–2 RECEPTOR SPECIFICITY OF REPRESENTATIVE ADRENERGIC AGONISTS

Catecholamines		Noncatecholamines	
Drug	*Receptors Activated*	*Drug*	*Receptors Activated*
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$	Ephedrine*	$\alpha_1, \alpha_2, \beta_1, \beta_2$
Norepinephrine	$\alpha_1, \alpha_2, \beta_1$	Phenylephrine	α_1
Isoproterenol	β_1, β_2	Terbutaline	β_2
Dobutamine	β_1		
Dopamine†	α_1, β_1, dopamine		

Receptors Activated‡				
Alpha$_1$	*Alpha*$_2$	*Beta*$_1$	*Beta*$_2$	*Dopamine*
← Epinephrine →				
← Ephedrine* →				
← Norepinephrine →				
← Phenylephrine →		← Isoproterenol →		
		← Dobutamine →	← Terbutaline →	
← Dopamine† →		← Dopamine† →		← Dopamine† →

α = Alpha, β = beta.
*Ephedrine is a mixed-acting agent that causes NE release and also activates alpha and beta receptors directly.
†Receptor activation by dopamine is dose dependent.
‡This chart represents in graphic form the same information on receptor specificity given above. Arrows indicate the range of receptors that the drugs can stimulate (at usual therapeutic doses).

■ Therapeutic Applications

- **Alpha$_1$ activation**
  - ***Vasoconstriction***
    - **Blood vessels of skin, viscera and mucous membranes**
      - » **Stops bleeding (epinephrine topically)**
      - » **Nasal decongestion relieved by vasoconstriction**
      - » **Helps with local anesthesia- slows absorbance by vasoconstriction**
      - » **Elevation of blood pressure**
    - **Mydriasis- dilation of pupil**
- **Adverse reactions**
  - **Hypertension**
  - **Necrosis due to lack of blood flow (extevasation around IV)**
  - **Bradycardia- slow heart**

- **Alpha$_2$ Activation**
  - ***Located pre-synaptically***
  - ***Activation inhibits NE release***
    - **Activation of alpha$_2$ receptors in the periphery <u>does not</u> have any clinical consequence**
    - **Activation of alpha$_2$ receptors in CNS very important**
      - » **Causes reduction of sympathetic response in heart and blood vessels and cause slowing of heart rate and vasodilation**
- **Beta$_1$ activation**
  - ***Activate Beta$_1$ in heart to initiate beating in heart that has stopped (cardiac arrest)***
  - ***Increase in force of contraction***
  - ***Improve blood flow when shock occurs***
  - ***Enhances impulse conduction through A-V node (AV heart block)***

- **<u>Precautions & Contraindications</u>**
  - **Severe allergy: by blocking Beta$_1$ receptors in heart and Beta$_2$ receptors in lung by propranolol, the ability of epinephrine to be used to counter anaphylaxis will be impaired**
  - **Diabetes: blockage of glycogenolysis will prevent one mechanism for correcting hypoglycemia in diabetes**
  - **Cardiac, respiratory & psychiatric disorders**
- **<u>Drug Interactions</u>**
  - **Calcium channel blockers**
  - **Insulin**

- **Summary**
  - **Alpha$_1$-Adrenergic Antagonists**
    - ***Pre-administration assessment***
      - **Therapeutic Goal**
        - » **Reduction of blood pressure**
        - » **Reduction of symptoms in patients with BPH**
      - **Baseline Data**
        - » **Determine blood pressure**
        - » **Determine degree of nocturia, daytime frequency, intermittency, terminal dribbling, urgency, size and force of stream, sensation of incomplete voiding**
      - **Identifying high risk patients**
        - » **Only contraindication is hypersensitivity to these drugs**
    - ***Route & Administration***
      - **Oral-take 1st at bedtime to avoid "first-dose effect"**
      - **Most may be taken with food**

  - **On-going evaluation**
    - ***Essential hypertension- monitor BP***
    - ***BPH- evaluate for improvement of symptoms***
- **Beta-adrenergic Antagonists**
  - **Pre-administration assessment**
    - ***Therapeutic goal***
      - **Indications are: hypertension, angina pectoris and cardiac dysrhythmias**
    - ***Baseline Data***
      - **Hypertension (standing and supine)**
      - **Angina pectoris**
      - **Cardiac dysrhythmias (baseline EKG)**
    - ***ID High Risk Patients- contraindicated for:***
      - **Patients with sinus bradycardia or AV heart block**
      - **Asthma, diabetes, severe allergic reactions**
      - **Depression or those taking Ca^{++} channel blockers**

- ***Route & Administration***
  - **Oral (for most), IV for propranolol and some others**
  - **Dose should be given 1-2 times per day**
- ***Ongoing Evaluation***
  - **Hypertension**
  - **Agina pectoris**
  - **Cardiac dysrhythmias**
- ***Minimizing adverse reactions***
  - **Bradycardia: if severe withhold medication and notify physician**
  - **AV heart block: do not give beta blockers to patients with AV block greater than first degree**
  - **Heart failure: inform patients about early signs (shortness of breath, night coughs, swelling of extremities, …)**
  - **Warn against abrupt discontinuation**
  - **Inform about signs of hypertension**
  - **Warn diabetic patients about NOT using tachycardia as an early sign of hypoglycemia (masked by beta blockers)**

■ Beta$_2$ activation

- ***Action in lung and uterus***
  - **Asthma- beta$_2$ activation causes bronchodilation**
  - **Terbutaline is more selective for beta$_2$ receptors**
  - **Inhalation therapy minimizes systemic effects**
  - **Delay of pre-term labor- relaxes uterine smooth muscle**
- ***Adverse effects***
  - **Hyperglycemia- promotes breakdown of glycogen in liver and skeletal muscles to glucose**
  - **Tremor- activation of beta$_2$ receptors in muscle enhances contraction**

Properties of Adrenergic Agonists

- **Epinephrine**
  - Catecholamine
  - Activates all 4 types of receptors
  - ***Therapeutic uses***
    - Delay absorption of local anesthetics
    - Control superficial bleeding
    - Reduce nasal congestion
    - Elevate blood pressure
    - Induces mydriasis
    - Overcome AV block & restores cardiac function
    - Bronchiolar dilation in patients with asthma
    - Treatment for anaphylactic shock
  - ***Administered***
    - Topically, IV, inhalation NOT ORALLY
    - Short ½ life

Adverse effects of epinephrine

- ***Hypertensive crisis***
- ***Dysrhythmias***
- ***Angina pectoris***
- ***Necrosis following extravasation***
- ***Hyperglycemia***

Drug interactions- Do Not Use With:

- **MAO inhibitors**
- **Tricyclic antidepressants**
- **General anesthetics**
- **Alpha adrenergic blocking agents**
- **Beta adrenergic blocking agents**

- **Isoproterenol**
  - *Reacts with $beta_1$ and $beta_2$ receptors*
  - **Therapeutic uses**
    - *Cardiovascular- AV heart block and increase output*
    - *Asthma- bronchiolar dilation*
- **Dopamine**
  - *Dopamine and $beta_1$ receptors: and $alpha_1$ at high doses*
  - *Receptor specificity is dose dependent*
  - **Therapeutic uses**
    - *Shock*

Chapter 19: Adrenergic Antagonists

- **Adrenergic Antagonists**
  - **Cause direct blockade of adrenergic receptors**
    - *Reversible (competitive) block*
  - **2 major groups**
    - *Alpha-adrenergic blocking agents*
    - *Beta-adrenergic blocking agents*

Therapeutic applications of alpha blockade

- ***Essential hypertension***
  - **Block alpha receptors on arterioles and veins causing vasodilation**
- ***Reversal of toxicity from alpha agonists***
- ***Benign prostatic hyperplasia (BPH)-***
  - **benefits result from reduced contraction of smooth muscle in bladder neck and prostatic capsule**
- ***Pheochromocytoma-***
  - **catecholamine secreting tumor in adrenal gland: result in persistent hypertension**
- ***Raynaud's Disease***
  - **Peripheral vascular disorder**
  - **Spasms in toes and fingers**
  - **Antagonist suppress symptoms by preventing vasocontriction**

Adverse effects of Alpha blockers

- ***Orthostatic hypotension***
  - **Reduces blood flow to brain causing dizziness, lightheadedness and fainting (syncope)**
  - **Due to vasodilation of veins lowering blood flow to brain**
- ***Reflex tachycardia***
  - **Increase heart rate by stimulating baroreceptor reflex which causes and increased heart rate to compensate**
- ***Nasal Congestion***
  - **Dilates vessels of nasal mucosa**
- ***Inhibition of ejaculation***
  - **Alpha$_1$, sympathetic reaction needed**
- ***Sodium retention***
  - **Decreased blood pressure decreases filtering by kidneys and causes retention of water and salt**

Other Adrenergic Antagonists

- Table 19-1

Beta adrenergic antagonists

- Therapeutic Properties
  - *Result primarily from blockage of beta$_1$ receptor in heart*
    - Reduced heart rate
    - Reduced force of contraction
    - Reduced velocity of impulse conduction through AV node
  - *Angina Pectoris - pain in region of heart when oxygen supply too low to meet needs of heart*
    - Exertion
    - Intense emotion
  - *Hypertension*
    - Reduction of peripheral vascular resistance

- ***Cardiac Dysrhythmias***
  - **Due to high electrical activity in the SA node and atria**
    - » **Decrease rate of SA node discharge**
    - » **Suppress conduction of atrial impulses through the AV node**
- ***Myocardial infarction (MI)***
  - **Reduction of pain, infarct size, mortality and risk of re-infarction**
  - **Must occur soon after MI**
- ***Heart Failure***
- ***Hyperthyroidism***
  - **Blocks increased sympathetic activity to heart**
- ***Migraine***
  - **Prophylaxis in lowering frequency of migraines**

- **Adverse Effects of beta$_1$ blockade**
  - ***Bradycardia***
  - ***Reduced cardiac output***
  - ***Heart failure***
  - ***AV block***
  - ***Long-term use can sensitize heart to catecholamines. If withdrawn abrutly angina pain and/or ventricular dysrhythmias can develop= rebound excitation. Withdraw drug gradually***
- **Adverse effects of beta$_2$ blockade**
  - ***Bronchoconstriction***
  - ***Inhibition of glycogenolysis (detrimental to patients with diabetes***

- **Propranolol**
  - *Blocks beta$_1$ and beta$_2$ receptors*
  - *Reduces heart rate*
  - *Decreases force of ventricular contraction*
  - *Suppress impulse through AV node*
  - – **Net effect= reduction in cardiac output**
- **Beta$_1$ blockade**
  - *In kidney: suppresses secretion of renin*
- **Beta$_2$ blockade**
  - *Lung: bronchoconstriction*
  - *Blood vessels (only certain ones) : vaso-constriction*
  - *Skeletal muscle & liver: block glycogenolysis*

- **Summary of Implications**
  - – **Alpha1-adrenergic Antagonists**
    - *Pre-administration assessment*
      - – **Therapeutic Goal**
        - » **Reduction of blood pressure**
        - » **Reduction of symptoms of BPH**
      - – **Baseline Data**
        - » **Determine blood pressure**
        - » **Determine degree of nocturia, daytime frequency, intermittency, terminal dribbling, urgency, reduction in force and size of stream, sensation of incomplete voiding**
      - – **Identifying high risk patients**
        - » **Only contraindication is hypersensitivity to drugs**
      - – **Route & Administration**
        - » **Oral-- May be taken with food**
        - » **Initial dose at bedtime to minimize "first dose" effect**

- Ongoing Evaluation
  - » Hypertension
  - » BPH- monitor for improvement
- Minimizing Effects
  - » Orthostatic hypotension- inform patients about lightheadedness and dizziness and to move slowly from sitting to standing
  - » First-dose effect- warn about driving after first dose for 12-24 hours. Take first dose at bedtime

– Beta-Adrenergic Antagonists

- *Pre-administration assessment*
  - Therapeutic goal
    - » Hypertension, angina pectoris and cardiac dysrhythmias
  - Baseline Data
    - » Hypertension
    - » Angina pectoris
    - » Cardiac dysrhythmias

- Identifying High Risk Patients: contraindicated for:
  - » Patients with sinus bradycardia of AV block greater than first degree
  - » Caution inpatients with hart failure
  - » Patients with asthma, bronchospasms, diabetes or severe allergic reactions
  - » Caution in patients with depression
  - » Caution in patients using Ca^{++} channel blockers
- Route and Administration
  - » Oral (all except esmolol) and IV
  - » For hypertension administer 1-2 times per day
  - » Warn about abrupt discontinuation
- On-going evaluation
  - » Hypertension
  - » Angina pectoris
  - » Cardiac dysrhythmias

- Minimizing adverse effects
  - » Bradycardia- beta blockers can reduce heart rate. If severe withhold medication and notify physician
  - » AV block- beta blockers can decrease AV conduction. Do not give to patients with greater than 1st degree blockage of AV node
  - » Heart failure- inform patients about early signs of heart failure (shortness of breath, night coughs, swelling of extremities, etc…)
  - » Rebound cardiac excitation- abrupt withdrawal can cause tachycardia. Warn patients
  - » Postural hypotension- warn patients about moving slowly from sitting to standing positions
  - » Diabetics- warn patients about NOT using tachycardia as an early sign of hypoglycemia since beta blockers may hide this symptom
  - » CNS effects- warn patient about possible depression, insomnia and nightmares

Chapter 20: Indirect-Acting Antiadrenergic Agents

- Drugs that prevent stimulation of peripheral adrenergic receptors but do so by mechanisms that DO NOT involve direct interaction with peripheral receptors
  - *Act to decrease norepinephrine release*
  - *Act within CNS to reduce outflow of impulses along sympathetic nerves*
- Net result
  - *Reduction in stimulation of peripheral adrenergic receptors (similar to drugs that block receptors)*

■ Reserpine

- ***Naturally occurring compound from shrub indigenous to India***

– **Primary Indication**

- ***Hypertension***
  - **Can produce severe depression**

– **Mechanism of Action**

- ***Depletes norepinephrine fro post-ganglionic sympathetic neurons (decreases stimulation of all adrenergic receptors– effects similar to combinatin of alpha and beta adrenergic blockade)***
  - **Affects stored NE by exposing to degradation by MAO**
  - **Suppresses synthesis of NE by blocking uptake of dopamine**
  - **Also depletes serotonin (depression effects)**

- ***Peripheral effects***
  - **Slows heart rate and reduces cardiac output, and causes vasodilation**
  - **Results in decreased blood pressure**
- ***Effects on CNS***
  - **Sedation**
  - **Causes sense of indifference to environment**
  - **Severe depression**
  - **Effects due to reduction in levels of seretonin and catecholamines from brain neurons**
- ***Therapeutic uses***
  - **Hypertension**
  - **Psychotic states (schizophrenia)- used rarely now**
- ***Adverse effects***
  - **Depression**
  - **Bradycardia, orthostatic hypotension, nasal congestion**
  - **Increase acid formation in stomach and increase peristalsis**

Centrally acting Alpha$_2$ Agonists

- Used primarily in hypertension
  - Reduce firing of sympathetic neurons and reduce release of NE from sympathetic nerves
  - Reduces pain of cancer (route is epidural infusion {marketed under Duraclon})
- Drugs of choice
  - *Clonidine*
    - » Antihypertensive that acts within CNS
    - » Lipid soluble
- Route & Administration
  - Administered by mouth or transdermal patch
- Adverse effects
  - Drowsiness
  - Xerostomia (dry mouth)
  - Rebound hypertension
  - Embryotoxic

Summary

- Pre-administration assessment
  - Therapeutic Goal
    - » Reduction in blood pressure
  - Baseline Data
    - » Determine blood pressure
  - ID high risk patients
    - » Contraindicated for patients with active peptic ulcers
    - » History of depression
- Route & Administration
  - Oral
  - Give with food to reduce gastric upset
- Evaluation of therapeutic effects
  - *Hypertensive effects may take 1 week or more*
  - *Monitor blood pressure*

- *Minimizing adverse effects*
  - Depression: inform patients about signs of depression (insomnia, loss of appetite, change in mood)
  - Orthostatic hypotension-: inform patients to move slowly from sitting to standing

– **Summary of Clonidine**

- *Pre-administration assessment*
  - Therapeutic goal
    - » Reduction of blood pressure
  - Baseline data
    - » Blood pressure
  - ID high risk patients
    - » Embryotoxic- do not give to pregnant women
  - Route and Administration
    - » Oral and transdermal
    - » Take at bedtime to avoid sedation during day
    - » Put patch on hairless, intact, skin on upper arm
    - » Apply new patch every 7 days

Chapter 21: CNS Pharmacology

■ **Treatment of:**

– **Medical Uses**

- *Mental illness*
- *Suppression of seizures*
- *Relief of pain*
- *Production of anesthesia*

– **Non-Medical Uses**

- *Stimulant & depressant*
- *Euphoriant*
- *Mind altering abilities*

- **Neurotransmitters**
  - Brain has more than 12 neurotransmitters
  - Other sites have not had neurotransmitters identified yet
    - *Dopamine*
    - *Norepinephrine*
    - *Serotonin*
    - *Enkephalins*
  - Blood-Brain Barrier
    - *Impedes entry of drugs into brain*
    - *Passage is limited to lipid soluble drugs*
    - *Drugs cross by use of specific transport systems*
      - Drugs that are protein bound and drugs that are highly ionized cannot cross blood-brain barrier

- *Protects brain from injury due to drugs*
- *Prevents drugs that need to get in from getting into CNS*
- *Blood-Brain barrier not completely developed at birth*
  - Newborns more susceptible to drug actions than adults

- Production of effects in CNS
  - *Not known but hypothesized*
- Adaptation of CNS to prolonged exposure
  - *May be beneficial or harmful*
  - *Therapeutic effects*
    - Drug must be taken for weeks before effects seen. May be due to adaptive changes in brain, not from direct effects of drug
    - Decreased side-effects by adaptations of brain
    - Tolerance and physical dependence

- » **Tolerance- a decreased response during prolonged use of drug (decreased receptor levels, increased degradation of drug)**
- » **Physical dependence- state during which an abrupt removal of drug will lead to severe withdrawal symptoms). Brain must ADAPT back to "normal" and during this time there are withdrawal symptoms**

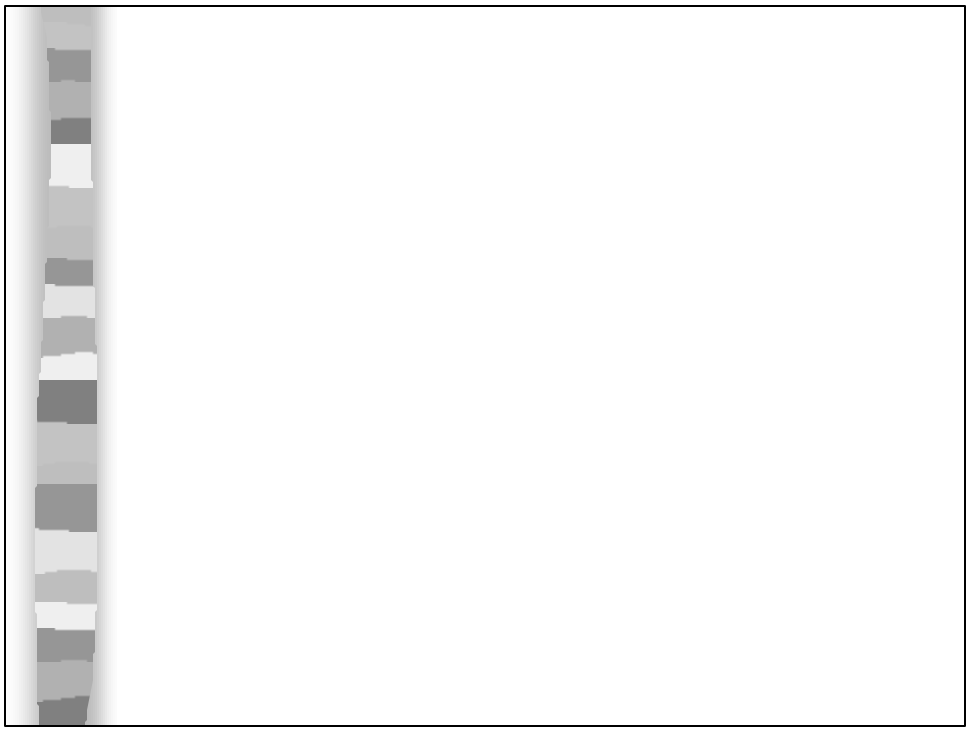
- ***New drug development***
  - **Lack of proper animal models**
  - **Mentally healthy patients cannot be used to assess potential of anti-psychotic agents**

Chapter 22: Drugs for Parkinson's Disease

- **Parkinson's Disease**
  - **A neurodegenerative disorder**
  - **Extrapyramidal system-**
    - ***Dyskinesias- disorder of movement (leads to akinesia)***
    - ***Affects over 1 million Americans***
  - **Symptoms**
    - ***Tremor***
    - ***Rigidity***
    - ***Postural instability***
    - ***Slowed movement***
  - **Cause**
    - ***Loss of dopaminergic neurons in substantia nigra***

- **Symptoms of PD**
  - ***Result from disruption of neurotransmission within the striantum***
  - ***Requires a balance between 2 transmitters***
    - **Dopamine: inhibitory transmitter→ neurons that release dopamine inhibit neurons that release gamma-aminobutyric acid (GABA, an inhibitory transmitter)**
    - **Acetylcholine: excitatory transmitter → neurons that release ACh excite the neurons that release GABA**
    - **Neurons that supply dopamine originate in the *substantia nigra***
  - ***In PD there is a degeneration of the neurons that supply dopamine to the striatum (why is unknown), and ACh stimualtion is not balanced by dopamine, and too much GABA released***

- **Therapeutic Goal**
  - ***Improve patient's ability to carry out daily activities***
  - ***Drugs provide only symptomatic relief, not a cure***
  - ***Selegiline- only drug that may alter progression of disease***
- **Treatment strategy**
  - ***To regain balance of dopamine and ACh***
    - **Use agents that directly or indirectly activate dopamine receptors**
    - **Use agents that block ACh receptors**
  - ***See Table 22-1 for drugs that are used in PD***



■ Levodopa

– Beneficial effects

- ***75% of patients respond with a 50% reduction in symptoms***
- ***If patient fails to respond to levodopa, then it should be questioned as to whether PD is the diagnosis***
  - **May take months to fully respond-- inform patient of this**
- ***Long-term treatment disappointing***
  - **1st two years symptoms controlled, by end of 5 years deterioration occurs. Due to progression of disease, not due to tolerance or adaptation???**
  - **Gradual loss vs abrupt loss of effect → can be minimized in two ways**
    - » **Shortening the dosing interval**
    - » **Giving drug that prolongs ½ life (tolcapone)**
    - » **Giving a direct-acting dopamine agonist**

- **Mechanism of action of Levodopa**
  - ***Promotes synthesis of dopamine in striatum***
  - ***Enters brain by active transport***
    - **Once in brain it is taken up by the few remaining dopaminergic nerve terminals that remain**
    - **Converted to dopamine by enzyme decarboxylase, the activity of which is enhanced by pyridoxine (vitamin B6)**
    - **Balances Ach**
  - ***Administered orally and rapidly absorbed from small intestine (food delays absorption)***
    - **Only 2% of dose reaches brain**
  - ***Adverse Effects (1º in elderly)***
    - **Nausea and vomiting**
    - **Dyskinesias- 80% develop other involuntary movements (head bobbing, tics, grimacing) w/I first year**
    - **Cardiovascular effects: hypotension**
    - **Psychosis: 20% of patients**

  - ***Drug holidays***
    - **Stimulation may improve after long-term use with a holiday (10 day interruption)**
- **Drug and food interactions**
  - **Antipsychotic drugs: agents that block dopamine receptors should not be used (many of current drugs do this)**
  - **MAO inhibitors: levodopa can cause a hypertensive reaction (MAO inactivates dopamine and NE, and levodopa increases these, therefore an inhibitor of MAO would increase these too much)**
  - **Anticholinergic drugs: since excessive levels of ACh contribute to symptoms, anticholinergic drugs would enhance therapeutic effects**
  - **Foods with high protein content compete with levodopa for absorption in intestine and lower levodopa absorption**
  - **Carbidopa- (Sinemet) enhances effect of levodopa by inhibiting decarboxylases in periphery**

- ***With Carbidopa :***
  - **Can decrease dose of Levodopa by 75%**
  - **Reduces nausea and vomiting by reducing dopamine production in periphery**
  - **No adverse effects of Carbidopa**
- ***Dose and Administration***
  - **Combination tablets (sustained release)= Sinemet**

- **Summary**- Levadopa and Carbidopa
  - **Pre-Administration Assessment**
    - ***Therapeutic Goal***
      - **Improve patient's ability to carry out activities of daily living**
    - ***Baseline Data***
      - **Assess overt manifestations of PD**
        - » **Bradykinesia, akinesia, postual instability, tremor, rigidity)**
    - ***ID high risk patients***
      - **Contraindicated for patients with malignant melanoma (can activate neoplasm)**
      - **Contraindicated for patients taking MAO inhibitors**
      - **Caution in patients with cardiac disease and psychiatric disorders**

- ***Route and Administration***
  - **Oral**
  - **Can be taken with food, but avoid foods with high protein content**
- ***On-going evaluation***
  - **Evaluating therapeutic effects: improvements in handling every day activities**
  - **Managing acute loss of effect (after long-term usage)**
- ***Minimizing Adverse Effects***
  - **Nausea and vomiting: inform patient that taking drug with food can alleviate these symptoms**
  - **Dyskinesias: inform patients about possible movement disorders**
  - **Dysrhythmias: inform patients about signs of excessive cardiac stimulation**
  - **Orthostatic hypotension: inform patient**
  - **Psychosis: inform patient**

Chapter 23: Drugs for Epilepsy

- **Epilepsy**
  - **Disorders characterized by excessive excitability of neurons with CNS**
    - ***Brief unconsciousness***
    - ***Violent convulsions***
    - ***2.3 million people in US have diagnosed epilepsy***
    - ***300,000 are under age 14***
    - ***50% of people can be seizure free by using drugs and 25% can have reduced symptoms***
  - **Seizure- all types of epileptic events**
  - **Convulsion- abnormal motor responses**
    - ***Jerking movements in grand mal seizure***

Seizures

- Initiated by high-frequency discharge from a group of excitable neurons called a FOCUS
  - *Focus caused by:*
    - Congenital defects
    - Hypoxia at birth
    - Head trauma
    - Cancers
  - *Symptoms depend upon location of FOCUS and how discharge spreads to other portions of brain*

Types of seizures

- Partial (focal) seizures
  - *Simple partial seizures*
    - Convulsions in single limb or muscle group
  - *Complex partial seizures*
    - Involve impairment of consciousness
- Generalized seizures
  - *Produce immediate loss of consciousness*
    - Tonic-Clonic seizures (Grand Mal): discharge throughout total cerebral cortex
      - » Major convulsions
      - » Muscle rigidity (tonic phase)
      - » Synchronous muscle jerks (clonic phase)
    - Absence seizures (Petit Mal):
      - » Loss of consciousness for brief time (10-30 sec)
      - » Mild eye blinking
      - » Occur in children and disappear by teens

Antiepileptic Drugs & how they work

- AEDs suppress discharge of neurons within a seizure FOCUS
- Suppress propagation of seizure activity from FOCUS to other areas of brain
  - *Act through:*
    - Suppression of sodium influx:
      - » reversibly bind to sodium channels
    - Suppression of calcium influx:
      - » T-type calcium channels in hypothalamus; drugs block this channel to prevent absence seizures
    - Potentiation of GABA
      - » Inhibitory transmitter (GABA) and by augmenting GABA responses (binding to receptors, promoting GABA release, inhibiting enzyme degradation of GABA, or re-uptake

Therapeutic Goal

- *Reduce seizures to allow patient to live normal life*
- *Eliminate seizures (ideal)*

- Select drug for specific disorders (T 23-1)

■ Making Diagnosis

- **Requires**
  - ***Physical neurologic and lab evaluations and complete history***
    - **Age of onset of seizures**
    - **Frequency and duration of seizure activity**
    - **Precipitating factors**
    - **Times when seizures occur**
    - **EEG for diagnosis of seizure type**
  - ***Until drug evaluation done make sure patient does not participate in activities that could be dangerous if seizure occurs***
    - **Trial period**
    - **Dosage adjustments**
    - **Measurement of plasma levels of drug**
    - **Seizure frequency chart**

- **Promote Compliance in Patient**
  - ***Educate patient and family***
  - ***Monitoring plasma drug levels***
  - ***Seizure frequency chart***
- **Spontaneous remission**
  - ***Some forms of epilepsy will spontaneously go away***
  - ***Withdrawal of drugs must be done over and extended period of time (6 weeks to several months). If patient using two drugs then they must be withdrawn sequentially not simultaneously***

■ Antiseizure therapy during pregnancy

- **Some risk of *in utero* exposure to AEDs**
  - ***First trimester most important***
  - ***Must balance risks involved***
    - **To mother and health**
    - **To baby and harm from convulsions *vs* medication**
  - ***Women with major seizures should continue medication throughout pregnancy***
    - **Take lowest effective dose**
- **Considerations**
  - ***Renal excretion and hepatic metabolism increase during pregnancy (increase dosage needed?)***
  - ***Valproic acid and carbamjazepine associated with higher incidence of neural tube defects***
    - **Treatment with folic acid (5 mg/day) reduces this**

Chapter 24: Drugs for Muscle Spasm and Spasticity

- **Muscle spasm**
  - Involuntary contraction of a muscle of muscle group
    - ***Painful***
    - ***Decreases level of functioning***
      - Epilepsy
      - Hypocalcemia
      - Acaute and chronic pain syndromes
      - Trauma: muscle inury

■ Spasms due to muscle injury

- *Immobilization of affected muscle*
- *Application of cold compresses*
- *Whirlpool baths*
- *Physical therapy*

– **Drug therapy**

- *Analgesic anti-inflammatory agents*
  - **Aspirin**
- *Centrally acting muscle relaxants*
  - **High doses suppress spinal motor reflexes (too high to be used in humans)**
  - **Sedative properties of drugs**
    - » **Diazepam and Tizanidine– enhance pre-synaptic inhibition of motor neurons in CNS**
    - » **Diazepam - enhances effects of GABA**
    - » **Tizanidine- promotes ingibition by acting as an agonist at pre-synaptic alpha$_2$ receptors**

■ Adverse effects

– **CNS depression-**

- *drowsiness, dizziness, lightheadedness*

– **Hepatic toxicity**

- *Assess liver function before and after treatment*

– **Physical dependence-**

- *With chronic high dose therapy, if drugs abruptly withdrawn*

■ Drugs for Spasticity

– **CNS origin: due to MS and cerebral palsy**

- *Heightened muscle tone*
- *Spasm*
- *Loss of dexterity*
- *Traumatic spinal cord injury and stroke*

Drug action

- Baclofen
  - *May mimic action of GABA*
- Diazepam (Valium)
  - *Mimic action of GABA*
- Dantrolene
  - *Acts directly on skeletal muscle by suppressing release of calcium from SR*
    - No effect on smooth muscle and cardiac muscle

Summary

- Therapeutic Goal
  - *Releif of signs and symptoms of muscle spasm*
- Identify high risk patients
  - *Avoid chlorzoxazone, metaxalone and tizanidine in patients with liver disease*
- Minimize adverse effects
  - *CNS Depression- inform patient*
  - *Hepatic toxicity- determine liver function before and after treatment*
  - *Do not use*
    - Alcohol
    - Antihistamines
  - *Withdraw gradually*

Chapter 25: Drugs for Headache

- **Headache**
  - **Induced by:**
    - ***Stress*** ***eye disorders***
    - ***Fatigue*** ***hypertension***
    - ***Acute illness*** ***hyperthyroidism***
    - ***Alcohol*** ***infection***
  - **OTC medications can treat mild headaches**
  - **Determine cause of headaches**
    - ***can cause be eliminated***

- **Migraine**
  - ***Unilateral, throbbing or nonthrobbing head pain, often associated with nausea, vomiting, photophobia and phonophobia***
  - ***Usually develop in morning***
  - ***Persists for hours to days***
  - **Migraine with aura (classic migraine)**
    - ***Visual flashes***
  - **Migraine without aura (common migraine)**
    - ***80% of people get this***
    - ***60-70% are women in late teens → 30 years***
    - ***Worse during menstruation and subside during pregnancy and cease after menopause***

- **Pathophysiology**
  - **Result from**
    - ***Inflammation and dilation of intracranial blood vessels***
      - **Calcitonin gene related peptide (CGRP) and serotonin (5-HT)**
        - » **CGRP- promotes migraine**
        - » **Plasma level rises during migraine attack**
        - » **Sumatriptan, lowers elevated levels of CGRP**
        - » **CGRP causes release of inflammatory neuropeptides**
        - » **5-HT suppresses migraine**
        - » **Plasma levels drop by 50% with migraine**
        - » **Reserpine lowers levels of 5-HT and causes an attack**
        - » **Treatment with 5-HT or sumatriptan stimulate 5-HT receptors and suppress migraine**