AUTONOMIC NERVOUS SYSTEM

University of Hawai'i Hilo Pre-Nursing Program
NURS 203 – General Pharmacology
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LEARNING OBJECTIVES

- Understand the basic function of the autonomic nervous system (ANS)
- Know the neurotransmitters and receptors of each branch of the autonomic nervous system
- Understand if a tissue or organ is being activated by a certain branch of the ANS and what the resulting action would be
- Understand how these two systems work in concert for daily living and situation of fight or flight
AUTONOMIC NERVOUS SYSTEM — WHERE IT FITS IN

Nervous System

Central

Brain

Spinal Cord

Peripheral

Somatic (Skeletal Muscle)

Autonomic

Parasympathetic (cholinergic) ACh

Sympathetic (adrenergic) NE

Nicotinic

Muscarinic

Alpha $\alpha_1, \alpha_2$

Beta $\beta_1, \beta_2$
AUTONOMIC NERVOUS SYSTEM

Rest & Digest
Cholinergic
Acetylcholine

Fight or Flight
Adrenergic
Norepinephrine

Parasympathetic
(cholinergic) ACh

Sympathetic
(adrenergic) NE
AUTONOMIC NERVOUS SYSTEM — WHERE IT FITS IN

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(Skeletal Muscle)

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Alpha
$\alpha_1$, $\alpha_2$

Beta
$\beta_1$, $\beta_2$
AUTONOMIC NERVOUS SYSTEM (ANS)

- Parasympathetic NS
  - Nicotinic
  - Muscarinic

- Sympathetic NS
  - Alpha
  - Beta

- Nerves
  - Carrying ACh
    - Cholinergic
  - Carrying NE
    - Adrenergic

Diagram:

- Peripheral
  - Autonomic
    - Parasympathetic (cholinergic) ACh
    - Sympathetic (adrenergic) NE
  - Nicotinic
  - Muscarinic
  - Alpha $\alpha_1, \alpha_2$
  - Beta $\beta_1, \beta_2$
AUTONOMIC NERVOUS SYSTEM (ANS)
AUTONOMIC NERVOUS SYSTEM (ANS)

Ganglion: Group of nerve cell bodies. Connects pre and post ganglionic nerves.
AUTONOMIC NERVOUS SYSTEM (ANS)
AUTONOMIC NERVOUS SYSTEM (ANS)
AUTONOMIC NERVOUS SYSTEM (ANS)

Preganglionic
SNS
ACh

Post ganglionic
SNS
NE

Preganglionic
PNS
ACh

Post ganglionic
PNS
ACh
ACTIONS OF THE ANS - SNS

- Think fight or flight
  - Dilate pupils
    - Let in more light to see the bear
  - Inhibit salivation
    - This is no time to be hungry
- Relax airways
  - Increase O2 intake
- Increase heart rate
  - ....
ACTIONS OF THE ANS - PNS

- Think rest and digest
- Constrict pupils
  - Lessened sense of awareness
- Stimulate saliva
  - Let’s eat
- Constrict bronchi
  - Don’t need extra oxygen
- Decrease heart beat
  - Rest easy

Parasympathetic System

- Constricts pupils
- Stimulates flow of saliva
- Constricts bronchi
- Slows heartbeat
- Stimulates peristalsis and secretion
- Stimulates bile release
- Contracts bladder
ANS — NEUROTRANSMITTER TRANSMISSION

- Cholinergic and adrenergic transmission — from start to finish
  - Synthesis
  - Storage
  - Release
  - Action
  - Inactivation
ANS — CHOLINERGIC TRANSMISSION

- Synthesis & Storage

![Diagram showing the synthesis and storage of acetylcholine](image-url)
ANS – CHOLINERGIC TRANSMISSION

Graph of membrane potential over time showing:
- Threshold of excitation
- Resting potential
- Peak action potential
- Repolarization
- Hyperpolarization
ANS — CHOLINERGIC TRANSMISSION

Propagation
ANS – CHOLINERGIC TRANSMISSION

Graph showing the membrane potential over time with key points labeled:
1. Resting potential
2. Threshold of excitation
3. Peak action potential
4. Hyperpolarization
5. Time
Hey look, exocytosis!
ANS — ADRENERGIC TRANSMISSION

- Synthesis
  - Nerve terminal
    - Neurotransmitter
  - Adrenal medulla
    - Hormone
    - Epi and NE
ANS — ADRENERGIC TRANSMISSION
Alpha receptors - excitatory

- Alpha 1
  - Postsynaptic nerve
  - Constrict
  - Vascular smooth muscle, prostate, pupillary dilator muscle

- Alpha 2
  - Presynaptic nerve
  - Inhibit SNS outflow
  - Platelets, adrenergic and cholinergic nerve terminals, some vascular smooth muscle, and fat cells

ANS — ADRENERGIC TRANSMISSION
ANS — ADRENERGIC TRANSMISSION

- Beta receptors — inhibitory
  - Beta 1 – heart
  - Postsynaptic
  - Increase rate & increase force of contraction

- Beta 2 – lungs
  - Postsynaptic
  - Relax & increase glucose
  - Lungs, liver, & vascular smooth muscle
ANS — ADRENERGIC TRANSMISSION

- Turning off the SNS
- Reuptake
- Monoamine oxidase (MOA)
- Catechol-o-methyltransferase (COMT)
The 2 branches of the ANS are the SNS and PNS

The PNS and SNS balance each other out in terms of daily activities

Each of these systems has its own set of NTs and receptors with actions that promote its cause and attenuate the cause of its brother system
QUESTIONS
LEARNING OBJECTIVES — CHOLINERGIC AGONISTS

➢ Know the receptor location and neurotransmitter involved in direct acting and indirect acting drugs of the cholinergic agonist class
➢ Know the physiologic results of the activation or inhibition of those receptors
➢ Know the dosage forms involved in nicotine replacement therapy (NRT)
➢ Know the toxic effects of cholinergic agonists & acetylcholinesterase inhibitors
CHOLINERGIC AGONIST

- Parasympathomimetic
- Receptors
  - Nicotinic
    - Ganglia, adrenal medulla, skeletal muscle, brain
  - Muscarinic
    - Cardiac and smooth muscle, gland cells, and nerve terminals

Remember, acetylcholine is the neurotransmitter for all preganglionic nerve fibers. Even those of the sympathetic nervous system.
**CHOLINERGIC AGONIST**

- Direct vs. Indirect acting cholinergic agonists

![Diagram of cholinergic system showing direct and indirect acting agonists](image)

- **PRESYNAPTIC NEURON**
- **POST SYNAPTIC NEURON**

**INDIRECT ACTING** – Acetylcholinesterase inhibitor

**DIRECT ACTING**
MUSCARINIC RECEPTORS

- Muscarinic receptors
- Eye (lacrimal gland), saliva gland, heart, lungs, GI tract, gallbladder, bladder, AND sweat glands (sympathetic effect) AND vascular smooth muscle (no PNS innervation)
MUSCARINIC AGONISTS — DIRECT ACTING

- **Bethanechol**

  ![Chemical Structure](image)

  - **Brand name:** Urecholine
  - **Use:** Ease urinary retention in the neurogenic bladder
  - **Dosage form:** Oral tablet
  - **Distribution:** Poorly absorbed and poorly distributed to CNS, concentrates in GI tract and bladder
  - **MOA:** Increase bladder muscle tone, stimulated gastric motility
  - **Onset/Duration:** 30-90 min/~1 hr (up to 6 hrs)

- **ADRs:**
  - Cardiovascular
    - Hypotension, flushing, tachycardia
  - CNS
    - Headache, malaise, seizure
  - Dermatology
    - Sweating
  - GI
    - Abd. cramps, diarrhea, burping, rumbly tummy, nausea, salivation, vomiting
  - GU:
    - Urinary urgency
  - Ophthalmic
    - Miosis & lacrimation
  - Respiratory
    - Bronchoconstriction/asthma

- **Overdose:** Treat with atropine
Pilocarpine

- Brand name: Salagen (oral)/Isopto Carpine (ophthalmic)
- Use: Xerostomia (cancer tx/sjogrens), glaucoma
- Dosage form: Tablet/solution & gel
- Distribution: Well absorbed and distributes into the CNS
- MOA: Increased salivation/miosis, decreased intraocular pressure
- Onset/Duration: 10-60 min/ 4-8 hrs (up to 12 hrs)
- Excretion: Kidney

ADRs:
- Cardiovascular
- Flushing
- CNS
- Headache
- Dermatology
- Rash, itching
- GI
- Nausea
- GU:
  - Urinary frequency
- Ophthalmic
  - Double vision & lacrimation
- Respiratory
  - Rhinitis
NICOTINIC RECEPTORS

- Nicotinic receptors
  - Ganglia, adrenal medulla, skeletal muscle, and neuronal cells in the CNS

- CNS effects
  - At therapeutic doses – mild alerting effect
  - At increased to toxic doses – tremor, stimulation of respiratory center, convulsions, & coma

- Neuromuscular junction
  - At therapeutic doses – contraction of muscle
  - At increased to toxic doses – disorganized twitching, contraction of entire muscle, & paralysis

- Peripheral nervous system
  - Activation of the SNS and PNS at the same time
    - Cardiovascular effects – mostly SNS effects
    - GI tract – mostly PNS effects
NICOTINIC AGONISTS — DIRECT ACTING

Nicotine (NRT)
- Use: Smoking cessation
- Dosage forms: Next slide
- Distribution: Lipophilic, distributes well to tissues
- Onset/duration: Fast/24 hour – depends on dosage form
- Metabolism: Liver
- Excreted: Kidney
- ADRs: Depends on dosage form – headache, nausea, throat irritation, cough, dyspepsia
- Toxicity: Very toxic. Lethal doses seen at 30-60 mg (5 cigarettes)

Varenicline (Chantix)
- Use: Smoking cessation
- Dosage forms: Tablets – Can be dispensed in monthly packs
- Distribution: Well absorbed, not affected by food, 90% bioavailability
- Onset: Peak 3-4 hours
- Half-life: 24 hours
- Excretion: Urine 92% unchanged drug
- ADR’s:
  - CNS – HA, insomnia, abnormal dreams, suicide ideation, depression (can lead to d/c)
  - GI: Nausea and vomiting
## NRT — DOSAGE FORMS

<table>
<thead>
<tr>
<th>Product</th>
<th>Nicotine Dosage</th>
<th>Adverse Effects</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch</td>
<td>7, 14, or 21 mg/d</td>
<td>Skin reactions, vivid dreams, insomnia</td>
<td>Patch is placed on skin; user reduces dosage over time</td>
</tr>
<tr>
<td>Gum</td>
<td>2 mg or 4 mg every 1-2 h</td>
<td>Hiccups, nausea, jaw pain</td>
<td>User chews gum until it produces a tingling feeling, then parks gum between cheek and gum and chews with cravings</td>
</tr>
<tr>
<td>Lozenges</td>
<td>2- or 4-mg lozenge as needed with cravings</td>
<td>Hiccups, nausea, heartburn</td>
<td>User places lozenge in mouth where it dissolves slowly</td>
</tr>
<tr>
<td>Inhaler</td>
<td>4 mg/cartridge, 6-16 cartridges/d</td>
<td>Throat irritation, mouth irritation, nasal congestion, cough</td>
<td>Inhalation through mouthpiece delivers nicotine</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>1 spray (0.5 mg) per nostril per hour as needed with cravings</td>
<td>Nasal irritation, nasal congestion, changes in taste and smell</td>
<td>Inserted and sprayed into each nostril; used to control cravings fast for heavy smokers</td>
</tr>
</tbody>
</table>
CHOLINERGIC AGONIST — INDIRECT ACTING

Neostigmine
Pyridostigmine
Ambenonium
Physostigmine
Tacrine
Donepezil
Rivastigmine
Galantamine

Myasthenia gravis: Autoimmune disease that degrades nicotinic receptors from autoantibodies causing severe muscle weakness.

Alzheimer’s disease: Degradation of cholinergic nerves in CNS causing memory loss and cognitive function decline. Causes not known: Efficacy of these drugs is modest and doses and use are limited by adverse effects.

GI & GU disorders: Post operative ileus, congenital megacolon, urinary retention, reflux esophagitis

Antimuscarinic overdose: Plants, atropine, 1st generation antihistamines, & tricyclic antidepressants. Physostigmine completes with the antimuscarinic agent. Only used with high fever or supraventricular tachycardia.
# Acetylcholinesterase Inhibitor Effects

<table>
<thead>
<tr>
<th>Type of effects</th>
<th>Lower doses</th>
<th>Higher doses</th>
</tr>
</thead>
</table>
| Autonomic effects | • Nicotinic receptor activation  
  o SNS & PNS effects  
  o Decreased HR and BP  
  • Muscarinic receptor activation  
  o Miosis/impaired vision  
  o Bronchospasm/increased secretions  
  o Sweating/salivation  
  o Nausea/vomitation  
  o Diarrhea/abd cramps  
  o Urination | *Both SNS and PNS are activated but the effects of the PNS prevail. Patient will present with bradycardia, reduced cardiac output, variable blood pressure, severe bronchospasm, reduced respiratory function.  
  • SLUDGE  
  o Salivation, lacrimation, urination, diarrhea, GI upset, emesis  
  • DUMBELS  
  o Diaphoresis & diarrhea, urination, miosis, bradycardia/bronchospasm/bronchorrhea, emesis, lacrimation, salivation |
| Central NS effects | • Nicotinic & muscarinic receptor activation  
  o Anxiety/confusion  
  o Tremors | • Nicotinic & muscarinic receptor activation  
  o Tremors/seizures  
  o Coma  
  o Depression of respiratory center |
| Motor effects | • Nicotinic receptor activation on skeletal muscle  
  o Muscle twitching and weakness | • Nicotinic receptor activation on skeletal muscle  
  o Paralysis  
  o Respiratory failure |
ACETYLCHOLINESTERASE INHIBITOR OVERDOSE

- Lethal – due to respiratory effects
- Usually due to poisoning, chemical warfare, insecticides (organophosphates)
- Route – skin or lungs.
- First signs – Ocular symptoms followed by respiratory symptoms

Treatment
- Ventilation
- ATROPINE
- Pralidoxime (reactivated enzymes)
QUESTIONS
LEARNING OBJECTIVES — CHOLINERGIC ANTAGONISTS

➢ Know the receptor location and neurotransmitter involved in direct acting and indirect acting drugs of the cholinergic agonist class

➢ Know the physiologic results of the activation or inhibition of those receptors

➢ Know the general therapeutic uses for the cholinergic antagonists class of medications

➢ Know antidotes

➢ Know the toxicities related to the overuse of cholinergic antagonists
CHOLINERGIC ANTAGONISTS

- Antimuscarinics and Antinicotinics
- Parasympatholytics
- Receptors
  - Muscarinic
    - Cardiac and smooth muscle, gland cells, and nerve terminals
    - Sweat glands – sympathetic
  - Nicotinic
  - Ganglia & skeletal muscle
ANTICHLINERGICS
ANTICHOLINERGICS

Which of those pathways represents a direct acting drug and which represents an indirect acting drug?
ANTICHOLINERGICS

PRESYNAPTIC NEURON

POST SYNAPTIC NEURON

INDIRECT ACTING

DIRECT ACTING
ANTICHOLINERGICS – @ THE GANGLIA & ADRENAL MEDULLA

- Decreased concentrations of epinephrine and norepinephrine & antagonism of acetylcholine

- Parasympathetic
  - Constipation, tachycardia, dry mouth, nausea, vomiting, angina, urinary retention, impotence

- Sympathetic
  - Decreased blood pressure, decreased release of epinephrine and norepinephrine, decreased sweating,
ANTICHOLINERGICS — @ THE GANGLIA & ADRENAL MEDULLA

- When do we use these medications:
  - HYPERTENSIVE EMERGENCY – LIMITED
  - Dissecting aortic aneurysm
  - Controlled hypotension during surgery

Ganglion Blockers:
Mecamylamine
Trimethaphan
ANTICHOLINERGICS — NEUROMUSCULAR BLOCKERS

- Antinicotinics — decreased binding of acetylcholine to skeletal muscle

- Two types
  - Nondepolarizing & depolarizing
    - Both cause muscle paralysis but depolarizing causes ion channels to open allowing a brief period of muscle contraction.

- Somatic effects
  - Blockade of voluntary & some involuntary muscle contraction
  - DO NOT CAUSE SEDATION. DO NOT PROVIDE RELIEF OF ANXIETY.
  - MUST BE GIVEN RESPIRATORY SUPPORT
ANTICHOLINERGICS – NEUROMUSCULAR BLOCKERS

- When do we use these medications:
  - Surgery

- Non-depolarizing
  - Rocuronium
    - Competitive antagonist at nicotinic receptor
    - Reversed by neostigmine

- Depolarizing
  - Succinylcholine
    - Nicotinic agonist
    - Not metabolized at the synapse, receptor desensitization

Neuromuscular Blockers:
Succinylcholine
Rocuronium
ANTICHOLINERGICS — NEUROMUSCULAR BLOCKERS

Why CAN’T neostigmine be used as an antidote for succinylcholine?
ANTICHOLINERGICS – ANTIMUSCARINICS

- Antimuscarinics – Decreased binding of acetylcholine to muscarinic receptors

- Small dose effects
  - Reduced saliva, sweat, and bronchial secretions, increase heart rate, inhibit accommodation

- Large dose effects
  - Inhibit micturition, decreased digestive muscle tone, & decreased gastric motility

- Prototype drug - Atropine
ANTICHOLINERGICS — ANTIMUSCARINICS

Eye
- Dilation of pupil, relaxation of ciliary muscle

- Use with care in patients with glaucoma
  - Mechanism for increasing intraocular pressure???

- Even eye drops can cause systemic effects
ANTICHOLINERGICS — ANTIMUSCARINICS

- Skin and mucous membranes
  - Decreased sweating
    - Dry & hot skin
  - Decreased glandular secretions
    - Dry mouth, nose, pharynx, and bronchi

- Respiratory system
  - Decreased secretion — pharynx, nose, and bronchi
  - Relaxation of smooth muscles of airway
    - Breathe more easily
ANTICHOLINERGICS – ANTIMUSCARINICS

- Cardiovascular system effects

- Low dose
  - Slightly slowed heart rate – from depression of the cardiac center in the brain

- High dose
  - Increase in heart rate due to vagal nerve blockage, facial redness
ANTICHOLINERGICS — ANTIMUSCARINICS

**GI tract**
- Little effect on secretions
  - Stomach, intestinal, pancreatic, gallbladder
- Greater effects on food movement
  - Peristalsis, GI tone

**Urinary tract**
- Muscles of the urinary system
  - Relaxation of detrusor
- Sphincters of the urinary system
  - Constricted
- Relaxation of fundus and ureter
ANTICHOLINERGICS – ANTIMUSCARINICS

**Dose response**

- Low doses
  - Little to no adverse effect

- High doses
  - Restlessness, wakefulness, talkativeness...leading to delirium, stupor, and coma

**CNS conditions**

- Parkinson’s disease
  - Decreased tremor

- Respiratory depression
  - Increased breath rate and deeper breathing
ANTICHOLINERGICS — ANTIMUSCARINICS

- When do we use these medications?
  - Dilate eye
    - Ophthalmic exam
  - Motion sickness
    - Central action – depresses vestibular function
  - IBS & diarrhea
    - Slow GI motility
    - Can be combined with opioids
  - Urinary disorders
    - Decrease urinary leakage and incontinence
  - Parkinson’s
    - Decrease tremor & oral secretions

Muscarinic antagonists:
Scopolomine, benztropine, ipratropium, tiotropium, tolderodine, solifenacin, darifenacin
ANTICHOLINERGICS – ANTIMUSCARINICS

MAD AS A HATTER

DRY AS A BONE

RED AS A BEET

BLIND AS A BAT
QUESTIONS
LEARNING OBJECTIVES — ADRENERGIC AGONISTS

- Know the receptor location and neurotransmitter involved in direct acting and indirect acting drugs of the cholinergic agonist class
- Know the physiologic results of the activation or inhibition of those receptors
- Know what substances are considered to be catecholamines
- Understand the differences in binding affinities of the catecholamines and the physiologic results of that
- Know the receptor locations
- Understand shock and the first choice treatment of that condition
SYMPATHETIC NERVOUS SYSTEM

**M receptors on the sweat glands = increased sweating**

**M Receptors**
- Inhibit SNS

**α1 Receptors**
- Prostate gland
  - Smooth muscle contraction (urinary obstruction)
- Vascular smooth muscle
  - Most other vessels - contraction

**α2 Receptors**
- Inhibit SNS

**B1 Receptor**
- Increase HR
- Increase conduction AV node
- Increase force of contraction

**B2 Receptor**
- Lungs
  - Relaxation of bronchial smooth muscle
- Liver
  - Increased glucose production
    - Gluconeogenesis
    - Glycogenolysis
  - Vascular smooth muscle
    - Vasodilation of arteries to skeletal muscle and liver

**Vascular smooth muscle**

**Dilates pupils**
- Inhibits salivation

**Relaxes bronchi**
- Accelerates heartbeat

**Inhibits peristalsis and secretion**

**Stimulates glucose production and release**

**Secretion of adrenaline and noradrenaline**

**Inhibits bladder contraction**

**Stimulates orgasm**
SYMPATHETIC NERVOUS SYSTEM

- Neurotransmitters (catecholamines)
  - Epinephrine, Norepinephrine, Dopamine

**Dopamine**

**D**
- At low doses
  - Vasodilation of the renal and splanchnic arteries
  - NO CLINICAL SIGNIFICANCE

**B₁**
- At low-moderate doses
  - Directly – Increase cardiac contractility
  - Indirectly – Release NE from storage site in neuron
  - Increase stroke volume and cardiac output/HR mild increase at low doses
  - **DILATION OF RENAL, MESENTERIC, CORONARY, & CEREBRAL BLOOD VESSELS**

**A**
- At high doses
  - Vasoconstriction and increase in peripheral vascular resistance.
  - Reduced urinary output
SYMPATHETIC NERVOUS SYSTEM

- Neurotransmitters (catecholamines)
- Epinephrine, Norepinephrine, Dopamine

EPI = NE Affinity
EPI >> NE Affinity
NE >> EPI Affinity
SYMPATHETIC NERVOUS SYSTEM

PRESYNAPTIC NEURON

POST SYNAPTIC NEURON

MONOAMINE OXIDASE

DIRECT ACTING

INDIRECT ACTING

REUPTAKE
SYMPTOMATIC NERVOUS SYSTEM — DIRECT ACTING AGONISTS

- Medications
  - Clonidine
  - Phenylephrine
  - Norepinephrine
  - Epinephrine
  - Dobutamine
  - Isoproterenol
  - Tertbutaline
  - Albuterol
  - Dopamine

  - Alpha agonist
  - Alpha and beta agonist
  - Beta agonist
  - Dopamine agonist
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING AGONISTS (ALPHA)

- Clonidine
  - Receptor affinity
    - $\alpha_2 > \alpha_1 >>> \beta$
  - Uses: Hypertension, migraine prophylaxis, cancer pain
  - Centrally decreases blood pressure by decreasing sympathetic outflow
  - ADRs: Xerostomia, skin rash, drowsiness

- Phenylephrine
  - Receptor affinity
    - $\alpha_1 > \alpha_2 >>> \beta$
  - Can be used to raise blood pressure – REFLEX DECREASE IN HEART RATE, primary use as a decongestant or used to dilate pupils
  - ADRs: Nasal burning and discharge – local effects
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING AGONISTS (ALPHA & BETA)

- Epinephrine & Norepinephrine
  - Epinephrine agonist of all 3 receptors
  - Modest change in blood pressure
- Norepinephrine = low affinity towards beta 2
  - Large increase in blood pressure
- Epi, NE, & Dopamine – DO NOT CROSS BBB

**A₁**
Vasoconstriction = Increased blood pressure

**B₂**
Vasodilation = Decreased blood pressure

**B₁**
Increased cardiac output (increased contractility & rate) = Increased blood pressure
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING AGONISTS (ALPHA & BETA)

Epinephrine

Uses: Allergic reaction, hypotension/shock, pupil dilation during eye surgery

ADRs: Arrhythmia, anxiety, dry throat, urinary retention

Norepinephrine

Uses: First choice vasopressor in treatment of sepsis and septic shock, severe hypotension after fluid replacement

ADRs: Arrhythmia, anxiety, and difficulty breathing

*Levophed
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING AGONISTS (ALPHA & BETA)

Why is NE the first choice in the treatment of septic shock?
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING AGONISTS (BETA AGONISTS)

**Isoproterenol**

\[ \beta_1 = \beta_2 \gg \gg \gg \gg \gg \gg \alpha \]

- Non-selective beta agonist
- Potent cardiac stimulant, increases cardiac output
- Vasodilator, decreases arterial pressure
- Causes bronchodilation
- Uses: Bronchospasm associated with asthma, emphysema, and bronchitis
- ADRs: Arrhythmia, anxiety, red tinged saliva

**Tertbutaline**

\[ \beta_2 > \beta_1 \gg \gg \gg \gg \gg \gg \alpha \]

- Selective beta-2 agonists
- Cause bronchodilation
- Relaxes uterine wall
- Uses: Bronchoconstriction, premature labor
- ADRs: Increased heart rate, nervousness, trembling, headache, dry mouth
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING AGONISTS (BETA AGONISTS)

**Dobutamine**

\[ \beta_1 > \beta_2 >>>> \alpha \]
- Selective beta-1 agonist
- Cardiac stimulant
- Uses: Cardiac decompensation (heart failure), sepsis
- ADRs: Chest pain, palpitations, PVCs, headache, nausea

**Albuterol**

\[ \beta_2 > \beta_1 >>>> \alpha \]
- Selective beta-2 agonists
- Cause bronchodilation
- Uses: Bronchospasm in asthma & COPD & hyperkalemia
- ADRs: Tachycardia, excitement, nervousness, tremor
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING AGONISTS (DOPAMINE AGONISTS)

**Dopamine**  \( D_1 = D_2 >> \beta_1 >> \alpha_1 \)

- Vasoconstriction and increase in peripheral vascular resistance.
- Reduced urinary output
- Vasodilation of the renal and splanchnic arteries
- Directly — Increase cardiac contractility (beta 1)
- Indirectly — Release NE from storage site in neuron (beta 1)

- Increase stroke volume and cardiac output/HR mild increase at low doses
- **DILATION OF RENAL, MESENTERIC, CORONARY, & CEREBRAL BLOOD VESSELS** (alpha 1)
- Uses: Adjunct in the treatment of shock & facilitate diuresis and preserve renal function
- ADRs: Chest pain, arrhythmia, anxiety, headache, nausea, vomiting
SYMPATHETIC NERVOUS SYSTEM — INDIRECT ACTING AGONISTS

Indirect Acting

PRESYNAPTIC NEURON

MONOAMINE OXIDASE

Phenelzine

POST SYNAPTIC NEURON

REUPTAKE

Cocaine

Amphetamines

Ephedrine

α

β

α₂
SYMPATHETIC NERVOUS SYSTEM — INDIRECT ACTING AGONISTS — RELEASING AGENTS

Amphetamine, methamphetamine, methylphenidate
- Elevates mood and alertness
- Decreased appetite
- Uses: Amphetamine & methamphetamine
  - Drugs of abuse
- Uses: Methylphenidate
  - ADHD — potential for abuse

- ADRs: Addiction, tachycardia, blurred vision, headache, insomnia, skin rash, weight loss, dry mouth

- Lipophilic and can penetrate the BBB
SYMPATHETIC NERVOUS SYSTEM — INDIRECT ACTING AGONISTS — RELEASING AGENTS & DIRECT BINDING

Ephedrine
- Plant derived and has mild stimulant effect
- Long duration of action
- Non selective
- Uses: Primarily as a nasal decongestant, but also stress incontinence in women and pressor effects
- ADRs: Hypertension, tachycardia, nausea and vomiting, tremor, and anxiety

****pseudoephedrine — indirect action only but still a nasal decongestant and can reduce stress incontinence in women
SYMPATHETIC NERVOUS SYSTEM — INDIRECT ACTING AGONISTS — REUPTAKE AND MAOIS

**Cocaine**

Local anesthetic properties/major drug of abuse
- Inhibits the reuptake of catecholamine at the cleft
- CNS effect substantial

**Phenelzine**

Monoamine oxidase inhibitor and increases storage supply of norepinephrine in CNS
- Uses: Depression, bulimia
- ADRs: Orthostatic hypotension, headache, xerostomia, weight gain, sexual dysfunction
- Tyramine foods – dangerous hypertension
  - Pickled, cured meats, beer, aged cheese

Cocaine

- Inhibits the reuptake of catecholamine at the cleft
- CNS effect substantial
QUESTIONS
LEARNING OBJECTIVES — ADRENERGIC ANTAGONISTS

- Know the receptor location and neurotransmitter involved in direct acting and indirect acting drugs of the cholinergic agonist class
- Know the physiologic results of the activation or inhibition of those receptors
- Know the receptor locations
- Know the physiologic results of administering a selective agent over a non-selective agent
- Understand why certain agents within a drug class might be used for a particular indication and the reasons for the selection of that medication
- Understand reflex tachycardia
SYMPATHETIC NERVOUS SYSTEM

**α1 Receptors**
- Prostate gland
  - Smooth muscle relaxation (urinary obstruction)
- Vascular smooth muscle
  - Most other vessels - relaxation

**α2 Receptors**
- Inhibit SNS

**B1 Receptor**
- Decreased HR
- Decreased conduction AV node
- Decreased force of contraction

**B2 Receptors**
- Lungs
  - Contraction of bronchial smooth muscle
- Liver
  - Decreased glucose production
- Vascular smooth muscle
  - Vasoconstriction of arteries to skeletal muscle and liver

**Vascular smooth muscle**
SYMPATHETIC NERVOUS SYSTEM – ADRENERGIC ANTAGONISTS

Indirect Acting

Synthesis inhibitors

PRESYNAPTIC NEURON

Direct Acting

POST SYNAPTIC NEURON

α

β

α₂
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING ANTAGONISTS

- Medications
  - Phentolamine
  - Phenoxybenzamine
  - Prazosin
  - Terazosin
  - Doxazosin
  - Tamsulosin
  - Alfuzosin
  - Yohimbine

  Mixed alpha antagonist
  - Alpha 1 antagonist
  - Alpha 2 agonist
**SYMPATHETIC NERVOUS SYSTEM — MIXED ALPHA ANTAGONISTS**

**Phentolamine**

- $\alpha_1 = \alpha_2$
- Very non-selective and can even bind to muscarinic, H1, and H2 receptors.
- $\alpha_1$ - blocked, causing vasoconstriction
- $\alpha_2$ - blocked, allowing the continued release of catecholamine to bind beta 1
- Baroreflex
- Poor oral absorption

- Uses: Pheochromocytoma & erectile dysfunction
- ADRs: Tachycardia, arrhythmia, MI, GI stimulation (diarrhea & increased gastric acid)
SYMPATHETIC NERVOUS SYSTEM — MIXED ALPHA ANTAGONISTS

Phenoxybenzamine

$\alpha_2 > \alpha_1$

• Blocks alpha 1 & 2 as well as receptors of acetylcholine, H1, and serotonin receptors

• Decreases blood pressure – especially when HTN caused by increased SNS tone

• Baroreflex and some alpha 2 blockade = potential increase in cardiac output

• Uses: Pheochromocytoma, and surgery prep

• ADRs: Postural hypotension, tachycardia, stuffy nose, sexual dysfunction, CNS – fatigue, nausea, sedation
SYMPATHETIC NERVOUS SYSTEM — ALPHA 1 ANTAGONISTS

Prazosin, doxazosin, tamsulosin, terazosin, alfuzosin

• Uses: BPH & moderate hypertension

• Alpha 1 >>>>>> alpha 2

• All generally work by blocking alpha 1 receptors in the smooth muscle arteries, veins, and prostate. However, there are some differences within the class

• ADRs: Postural hypotension, reflex tachycardia, retention of fluid and salt, sexual dysfunction
SYMPATHETIC NERVOUS SYSTEM — ALPHA 1 ANTAGONISTS

**Prazosin**

*Use: Hypertension & PTSD*

- May increase HDL and decrease LDL

**Tamsulosin**

*Use: BPH, chronic urinary obstruction*

- Little effect on BP
- Useful in patients who may have experienced postural hypotension with other alpha 1 blockers
- Greater selectivity for alpha 1a vs alpha 1b (alpha 1a most important for prostate)
SYMPATHETIC NERVOUS SYSTEM — ALPHA 2 ANTAGONISTS

Yohimbine

Uses: Reverse sedation in dogs and deer

Other uses: Hallucinogen, aphrodisiac, erectile dysfunction, and reduced libido in women

MOA: Centrally acting alpha 2 antagonist to increase sympathetic outflow

ADRs: Nausea/vomiting, tachycardia, anxiety, agitation, tremor, sweat, renal failure, arrhythmia, seizure...

No known antidote but benzodiazepines may help in toxicities associated with agitation, hypertension, and tachycardia
SYMPATHETIC NERVOUS SYSTEM — DIRECT ACTING ANTAGONISTS — BETA ANTAGONISTS

- Medications
  - Pindolol
  - Propanolol
  - Labetalol
  - Carvedilol
  - Dobutamine
  - Metoprolol
  - Atenolol
  - Acebutalol
  - Butaxamine

- Mixed beta antagonist
- Alpha and beta antagonist
- Beta 1 antagonist
- Beta 2 antagonist
SYMPATHETIC NERVOUS SYSTEM — BETA ANTAGONISTS

Pure Antagonists
- Atenolol
- Carvedilol
- Propranolol

Partial Agonists (ISA)
- Acebutolol
- Labetalol
- Pindolol

Inverse agonists
- Metoprolol
- Bisoprolol
SYMPATHETIC NERVOUS SYSTEM — BETA ANTAGONISTS

IN GENERAL: Decrease in blood pressure, cardiac output (decrease in heart rate and contractility, lower blood pressure without creating hypotension

- Most are lipophilic, large Vd, well absorbed
- Some cross the BBB
- Some are metabolized in the liver and some are excreted in the urine as unchanged drug
- Upon administration — rise in PVR, overtime (chronic use) decrease in PVR
- Blockade of beta 2
  - Bronchoconstriction
  - Decreased lipolysis
  - Decreased blood glucose
- ADRs:
  - Sedation, sleep disturbances, depression, bronchospasm
- Taper
SYMPATHETIC NERVOUS SYSTEM — BETA ANTAGONISTS

Propranolol
- Non-selective
- Very lipophilic
- Uses: Hypertension, coronary artery disease, migraine prophylaxis, performance anxiety
  - Can cross the BBB
  - Extensive first pass metabolism (CYP 2D6 & 1A2)
  - Local anesthetic properties
  - May also be used for hyperthyroidism (thyroid storm — excessive catecholamine action on the heart)
# Sympathetic Nervous System — Beta Antagonists

<table>
<thead>
<tr>
<th>Metoprolol</th>
<th>Nadolol</th>
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<tbody>
<tr>
<td>Inverse Agonist</td>
<td>Pure Agonist</td>
</tr>
<tr>
<td>Moderately lipophilic</td>
<td>Not metabolized</td>
</tr>
<tr>
<td>Extensive first pass effect (CYP2D6)</td>
<td>Longest half life</td>
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<tr>
<td>Local anesthetic</td>
<td>• May increase with kidney disease</td>
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<tr>
<td>First choice BB in heart failure</td>
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SYMPATHETIC NERVOUS SYSTEM — BETA ANTAGONISTS

**Labetalol**

Hypertension in pregnancy
- Has ISA – less risk for bradycardia (reduced sympathetic response)

NOT TO BE USED IN ACUTE CONGESTIVE HEART FAILURE

**Timolol / Betaxolol**

Glaucoma
- Reduction in aqueous humor by ciliary body
  - Decreased production

- Timolol — non-selective
  - Bronchospasm
- Betaxolol — selective
  - First choice
SYMPATHETIC NERVOUS SYSTEM — BETA ANTAGONISTS - CONSIDERATIONS
SYMPATHETIC NERVOUS SYSTEM — BETA ANTAGONISTS — MORE CONSIDERATIONS
QUESTIONS