# Drugs Acting at Synaptic and Neuroeffector Junctional Sites

## Autonomic and Neuromuscular Pharmacology

**Subcommittee:**

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<table>
<thead>
<tr>
<th>Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology</th>
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</thead>
<tbody>
<tr>
<td><strong>Recommended Curriculum Equivalent:</strong> 1.0 hr</td>
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<tr>
<td><strong>Introduction and History</strong></td>
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<tr>
<td>Neuronal Drugs</td>
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<tr>
<td>BOTULINUM TOXIN</td>
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<tr>
<td>COCAINE</td>
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<tr>
<td>entacapone</td>
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<tr>
<td>metyrosine</td>
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<td>reserpine</td>
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## Learning Objectives

**Physiology and pathophysiology**

- Describe the anatomical projections of the sympathetic and parasympathetic autonomic nervous system.
- Describe the evidence for the development of the concept of neurotransmitters, co-transmitters and end-organ specificity.
- Describe homeostasis, fight-or-flight, and rest-and-repair with regard to the autonomic nervous system.
- Describe the central control of the autonomic nervous system.
- List and describe the responses of end organs to activation of each division of the autonomic nervous system.
- Describe the concept of dominant tone.

**Mechanisms of action**

- Explain the mechanism and drugs that block uptake of choline into cholinergic neurons.
- List drugs that Inhibit Catechol-o-methyl transferase peripherally.
- List drugs that block storage vesicle transport systems.
- Describe the mechanism by which drugs Inhibit reuptake of NE into adrenergic neurons.
- Describe the mechanism by which drugs deplete NE by interfering with synthesis.

**Notes**

Define words containing the suffixes, -ergic, -mimetic, - lytic, and –ceptive.
**Clinical Pharmacology**  Botulinum toxin only marginally effective for prophylaxis against chronic migraine headache. Not approved for treatment of episodic migraine headache.

<table>
<thead>
<tr>
<th>Relevance</th>
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</thead>
<tbody>
<tr>
<td><strong>USMLE topic</strong>  Central and peripheral nervous system</td>
<td><strong>Principles of therapeutics</strong>  Botulinum toxin  Drugs affecting the autonomic nervous system  Treatment for substance abuse disorders  Antiparkinsonian drugs</td>
</tr>
<tr>
<td><strong>AAMC Medical School Objectives</strong>  Project Report X Patient Safety-Table 1</td>
<td><strong>Topic C</strong>  Drug treatment of common conditions</td>
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<td>Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology</td>
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<td><strong>Recommended Curriculum Equivalent:</strong> 3.0 hr</td>
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**Drug Classes and Drugs to consider**

<table>
<thead>
<tr>
<th>Direct Acting Cholinergic Ester-Agonists</th>
<th>Direct Acting Cholinergic Alkaloid Agonists</th>
<th>Cholinergic Indirect Acting</th>
<th>Related Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACETYLCHOLINE BETHANECHOL</td>
<td>PILOCARPINE</td>
<td>ECHOTHIOPHATE EDROPHONIUM</td>
<td>PRALIDOXIME obidoxime sarin VX series</td>
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<tr>
<td></td>
<td></td>
<td>NEOSTIGMINE</td>
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<tr>
<td></td>
<td></td>
<td>malathion</td>
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<td>parathion</td>
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<td>physostigmine</td>
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</tbody>
</table>

**Learning Objectives**

**Physiology and pathophysiology**
Describe synthesis, storage, release, and inactivation of cholinergic agonists.
List the steps in the synthesis, storage, release and inactivation of acetylcholine, and drugs that interface with those processes.
List the location of nicotinic and muscarinic receptors and their subtypes.
Compare the two major cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) as to anatomical locations, sites of synthesis and function.

**Mechanism of action**
Explain the mechanism of actions, including 2nd messenger systems of acetylcholine and related drugs.
Explain the differences in onset and duration of action and route of administration for different groups of anticholinesterases.
Explain the chemical makeup of the active site of AChE (anionic and esteratic) as to attraction, attachment and rates of breakdown of various substrates and inhibitors.
Distinguish the mechanism by which pralidoxime reactivates phosphorylated AChE.

**Actions on organ systems**
Describe the responses to activation of these receptors.
Explain the reason why anticholinesterases classified as reversible or irreversible.

**Pharmacokinetics**
Describe the variations of pharmacokinetics of cholinergic drugs.
Relate the onset of action of anticholinesterases, routes of administration, and the duration of action of anticholinesterases with sites and type of attachment to the enzyme.
Explain why anticholinesterases are reversible or irreversible, and indicate which anticholinesterases are in each category.
Explain the role of cholinesterase “aging” in the enzyme-inhibitor interaction.
### Adverse effects, drug interactions and contraindications

List the adverse effects of cholinergic drugs.
List and describe the rationale for contraindications of cholinergic drugs.
Describe the adverse effects, and their relevance, of the two classes of neuromuscular blocking drugs.

### Therapeutic uses

List the therapeutic uses of cholinergic agonists.
Describe the effects of accumulated acetylcholine at muscarinic and nicotinic receptors in the periphery and the central nervous system.
List therapeutic uses for and adverse side effects of anticholinesterases.
Explain why anticholinesterase agents can be used as insecticides (malathion, parathion) and chemical warfare agents (sarin, VX series).
Explain why pralidoxime is not effective reactivating all phosphorylated AChE.
Explain the concept of differential toxicity of malathion and parathion in different species.

### Notes

Clinical Pharmacology
Pilocarpine may cause mental impairment when used topically, especially in the elderly.

### Relevance

**USMLE topic**
Central and peripheral nervous system
Pharmacodynamic and pharmacokinetic processes

**Principles of therapeutics**
Drugs affecting the autonomic nervous system
Neuromuscular junction agonists
Antiglaucoma drugs
Mechanisms of toxicology

**AAMC Medical School Objectives**
Project Report X Patient Safety-Table 1

**Topic C**
Drug treatment of common conditions
Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology

Recommended Curriculum Equivalent: 2.0 hr

Drug Classes and Drugs to consider

<table>
<thead>
<tr>
<th>Antagonists at Muscarinic Receptors</th>
<th>Antagonists at Nicotinic Receptors</th>
<th>Drugs Acting at Autonomic Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATROPINE</td>
<td>MIVACURIUM</td>
<td>mecamylamine</td>
</tr>
<tr>
<td>ipratropium</td>
<td>nicotine</td>
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<tr>
<td>scopolamine</td>
<td>SUCCINYLCHOLINE</td>
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<tr>
<td>tolterodine</td>
<td>TUBOCURARINE</td>
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Learning Objectives

Physiology and pathophysiology
List the locations of and the differences between muscarinic and nicotinic receptors. Explain the rationale for historical uses in treatment of hypertension and autonomic hyperreflexia.

Mechanism of action
Describe nicotine’s agonist and antagonist properties.

Actions on organ systems
Contrast and compare the depolarizing and the competitive Neuromuscular Junction blocking drugs.

Adverse effects, drug interactions and contraindications
Explain why muscarinic antagonists cause xerostomia, blurred vision, photophobia, tachycardia, anhidrosis, difficulty in micturition, hyperthermia, glaucoma and mental confusion in the elderly.
Explain why muscarinic antagonists are contraindicated in glaucoma, obstructive disease of the gastrointestinal tract or urinary tract, intestinal atony.
List the adverse side effects of drug acting at autonomic ganglia.
List the adverse side effects and drug interactions at the NMJ.

Therapeutic uses
Explain the rationale for the therapeutic use of muscarinic antagonists in diseases such as bronchoconstriction, excessive salivation, and motion sickness. Explain the rationale for the therapeutic use to produce mydriasis and cycloplegia.
Explain why nicotine is not used clinically (except as a smoking deterrent), and its historical, social and toxicological significance.
Explain the differential uses of competitive versus depolarizing Neuromuscular Blocking Drugs and their limitations.

Notes

Clinical Pharmacology
All anticholinergic drugs relatively contraindicated in the elderly due to risk of increased mental impairment.

Relevance
**USMLE topic**
Central and Peripheral Nervous System

**Principles of therapeutics**
Mechanisms of action and use of drugs for treatment of disorders of the nervous system – neuromuscular junction agonist and antagonists
Drugs affecting the autonomic nervous system

**AAMC Medical School Objectives Project Report X Patient Safety**
**Table 1**

**Topic C**
Drug treatment of common conditions, and diseases using frequently prescribed drugs for the treatment and prevention of disease

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**Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology**

<table>
<thead>
<tr>
<th>Drug Classes and Drugs to consider</th>
<th>Recommended Curriculum Equivalent: 3.5 hr</th>
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</table>
| Nonselective 
Alpha Adrenergic Agonists | Selective 
Alpha \(_2\) 
Adrenergic Agonists |
| DOPAMINE 
EPINEPHRINE 
NOREPINEPHRINE 
phenylephrine 
pseudoephedrine | BRIMONIDINE 
CLONIDINE 
METHYLDOPA |
| Nonselective Alpha\(_1\), Alpha\(_2\) 
Antagonists | Selective 
Alpha\(_1\) Adrenergic 
Antagonists |
| phenoxybenzamine 
phentolamine | PRAZOSIN 
tamsulosin 
terazosin |
| | Indirect and Mixed Acting 
Agents |
| | AMPHETAMINE 
ephedrine 
methamphetamine 
tyramine |

**Learning Objectives**

**Physiology and pathophysiology**

List steps in the synthesis, storage, release and inactivation of norepinephrine and epinephrine.

Describe types and subtypes of adrenergic receptors, their locations, and physiologic response to activation.

Describe receptor selectivity of norepinephrine and epinephrine.

Describe the differences between direct and indirect acting adrenergic drugs.
## Mechanism of action
Describe the property of intrinsic activity as a characteristic of Direct Agonists binding to receptors.
Describe the mechanism by which Indirect Agonists release neurotransmitters from neuron.
Describe the importance of Antagonists binding to receptors without intrinsic activity.

## Actions on organ systems
Explain why alpha-1 adrenergic antagonists are used to treat hypertension and benign prostatic hypertrophy.
Explain why alpha-1 adrenergic agonists are important in the treatment of nasal congestion, hypotension, paroxysmal atrial tachycardia, and are used to cause mydriasis and vasoconstriction (with local anesthetics).
Explain the mechanism for the use of alpha-2 adrenergic agonists in the treatment of hypertension, and for topical treatment of glaucoma.

## Adverse effects, drug interactions and contraindications
List the adverse side effects of alpha1 and alpha2 agonists.
Explain drug interactions with oxytocic drugs and monamine oxidase inhibitors.
List the contraindications for alpha1 adrenergic agonists.
List the adverse side effects of nonselective alpha and selective alpha adrenergic antagonists.

## Therapeutic uses
Explain why alpha-1 adrenergic agonists are important in the treatment of nasal congestion, hypotension, paroxysmal atrial tachycardia, and are used to cause mydriasis and vasoconstriction (with local anesthetics).
Explain the mechanism for the use of alpha-2 adrenergic agonists in the treatment of hypertension, and for the topical treatment of glaucoma.
Explain the limitations of the use of nonselective alpha-1, alpha-2 adrenergic antagonists in the treatment of hypertension.

## Notes
Clinical Pharmacology
A recent trend to use a combination of methylphenidate and modified release clonidine to treat ADHD in older children. However, this should not be considered a first-line drug regimen. Caution in that clonidine should not be discontinued abruptly due to risk of rebound hypertension. Clonidine use is sometimes associated with adverse CNS activity including depression and psychosis. Adverse CNS events have also been observed in patients prescribed methyldopa.

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<td>Autonomic drugs</td>
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<td>Stimulants, amphetamines</td>
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| AAMC Medical School Objectives Project Report X Patient Safety | **Topic C**  
Drug treatment of common conditions, and diseases using frequently prescribed drugs for the treatment and prevention of disease |
# Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology

**Recommended Curriculum Equivalent:** 1.5 hr

## Drug Classes and Drugs to consider

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<tr>
<th>Nonselective Beta Adrenergic Agonists</th>
<th>Selective Beta Adrenergic Agonists</th>
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<tbody>
<tr>
<td>Isoproterenol</td>
<td>ALBUTEROL</td>
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<tr>
<th>Nonselective Alpha_1, Alpha_2 Antagonists</th>
<th>Selective Alpha_1 Adrenergic Antagonists</th>
<th>Indirect and Mixed Acting Agents</th>
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<tbody>
<tr>
<td>phenothiazine</td>
<td>PRAZOSIN</td>
<td>AMPHETAMINE</td>
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<tr>
<td>phenolamine</td>
<td>tamsulosin</td>
<td>ephedrine</td>
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<td>terazosin</td>
<td>methamphetamine</td>
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<td>tyramine</td>
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## Learning Objectives

### Mechanism of action
- Compare and contrast the pharmacology of the nonselective beta-adrenergic agonists, epinephrine and isoproterenol.
- Compare and contrast the pharmacology of the beta selective adrenergic agonists, isoproterenol, albuterol, salmeterol, and dobutamine.
- Compare and contrast the pharmacology of the beta-adrenergic antagonists, propranolol, metoprolol, and atenolol.
- Compare and contrast the pharmacology of the nonselective alpha and beta blocking drug labetalol, with selective beta blocking drugs.

### Adverse effects, drug interactions and contraindications
- List the adverse side effects of beta_2 adrenergic agonists.
- List the adverse side effects of beta adrenergic antagonists.

### Therapeutic uses
- Explain the mechanisms for the use of selective beta-adrenergic agonists in diseases such as cardiac decompensation, asthma, premature labor, bronchospasm and emphysema.

## Notes

**Clinical Pharmacology** There is no beta adrenergic blocking drug that has not been associated with reactive bronchconstriction. Thus caution is advised in adult patients with a history of pediatric asthma. Use of these agonists as effective tocolytics in humans is not supported by good clinical evidence.

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