**Tips for Drug Learning**
- Learn agents by drug classes, e.g., beta-blockers, Ca++-blockers etc.
- Key points:
  - Mechanism of action
  - Important drug-drug interactions (e.g., MAOI and tyramine rich foods)
  - Adverse drug reactions
  - Important drugs (e.g., epinephrine (anaphylaxis), beta-blockers – asthma, Raynaud D.)
  - Drugs of choice (DOC) (e.g., ephedrine or pseudoephedrine, clonidine, captopril, lisinopril)
- Do not focus on dosage or trade names.

**Autonomic Nervous System & Neuromuscular Junction Review 2007**
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**Drug Extensions**
- valsalan (A-II blockers)
- mivacurium (NMJ blockers)
- simvastatin (HMG CoA reductase inhibitors)
- lisinopril (ACE inhibitors)
- terazosin (Alpha1-blockers)
- prazosin

**ANS – Review – Core Concepts**
1. Tissues/Organs: receptors present, tissue/organ response
2. Transmitters: NE, Ach, synthesis, storage, release, regulation, clinical application, side effects, toxicity, treatment of toxicity
4. Drugs: receptor selectivity, mechanism of action
5. Can predict: clinical application, side effects, toxicity, treatment of toxicity, important adverse reactions, not dosage
6. General: learn by drug classes, important adverse reactions, not dosage
Receptors of the ANS

<table>
<thead>
<tr>
<th>Adrenoceptors</th>
<th>Cholinceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td></td>
</tr>
<tr>
<td>α-</td>
<td>Vascular smooth muscle</td>
</tr>
<tr>
<td>α-</td>
<td>Nerve terminals</td>
</tr>
<tr>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>β₁-</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>β₁-</td>
<td>Bronchiol smooth muscle</td>
</tr>
<tr>
<td>β₂-</td>
<td>Fat cells</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Renal smooth muscle (D₁-)</td>
</tr>
</tbody>
</table>

Selective agents available

ANS – Review Tissues/Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Adrenergic</th>
<th>Cholinergic</th>
<th>Non-Cholinergic</th>
<th>2nd Messengers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>α₁</td>
<td>M₁</td>
<td>M₂</td>
<td>NO = Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>M₁</td>
<td>M₁</td>
<td>NO = Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>M₃</td>
<td>M₃</td>
<td>NO = Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>M₃</td>
<td>M₃</td>
<td>NO = Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>α₁</td>
<td>M₂/M₃</td>
<td>M₁</td>
<td>NO = Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>M₃</td>
<td>M₃</td>
<td>NO = Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>α₁</td>
<td>M₁</td>
<td>M₂/M₃</td>
<td>NO = Nitric oxide</td>
</tr>
</tbody>
</table>

ANS Excess / Deficiency

- Cholinergic excess: (ie. AchE inhibition or mushrooms)
  - salivation, lacrimation, urination, diarrhea, emesis (slude), miosis, ↓HR, sweating, cycloplegia (paralysis)
- Cholinergic deficiency: (ie. Atropine toxicity)
  - ↓GI motility, mydrias, cycloplegia, ↓secretions, tachycardia, delirium
- Sympathetic excess: (ie. Tyr-MAOI or Pheochromo.)
  - ↑BP, ↑HR, pupil dilation (mydrias), ↓GI motility
- Sympathetic deficiency: (ie. Guanethidine-block)
  - ↓BP, ↓tissue perfusion, pupil constriction (miosis)

Terminology – ANS

i. clammy: → PNS excess, ie. ↑secretion (sweating)
ii. wheezy: → PNS excess, ie. difficulty in breathing (↑bronchial resistance, ↑secretion)
iii. flushed: → PNS deficiency ie. vasodilation, thermoregulation (atropine toxicity)
iv. cramps: → muscle contraction ie. abdominal (↑PNS)
v. palpitations: → SNS excess ie. hypertension, hypertensive crisis, MAOI-Tyramine or pheochromocytoma

Question 1

A 32-year-old man is brought to the emergency department because of confusion, wheezing, vomiting and diarrhea for the past 6 hours. He is sweating and salivating profusely. There is generalized muscle weakness. Which of the following substances is the most likely cause of these findings?

A. Glutethimide
B. Heroin
C. Jimson weed (belladonna alkaloids)
D. Parathion
E. Phencyclidine (PCP)

USMLE Step 1: 2003, 2005

Question 2

A 59-year old man develops excessive sweating and salivation, diarrhea, and bradycardia while being treated with neostigmine for myasthenia gravis. Which of the following is the most appropriate therapy for these symptoms and signs?

A. Atropine
B. Carbachol
C. Endrophonium
D. Epinephrine
E. Pralidoxime

USMLE Step 1: 2003, 2005
**Drugs of Choice**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Therapeutic use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Blocks hypotensive reaction in low doses</td>
<td>α-adrenergic, phenoxybenzamine causes for effects of released histamine (phenothiazines, PPI)</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Inhibits calcium release from SR</td>
<td>Malignant hyperthermia</td>
</tr>
<tr>
<td>Reverse toxic effects of AchE inhibitors ie. neostigmine, physostigmine, or organophosphates</td>
<td>Reverse achE inhibition</td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td>M-agonist causes ↑ outflow</td>
<td>Emergency glaucoma</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Reversible achE inhibitor, can cross CNS</td>
<td>Regenerate achE enzyme</td>
</tr>
<tr>
<td>Pralidoxime</td>
<td>Reversible achE inhibitor</td>
<td>Reverse atropine toxicity</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>A very useful group, differ in selectivity (β₁- vs β₂-), LA-action, partial agonist activity (ISA). CI: heart failure (unstable CHF, depression, significant bradycardia or bronchospasm), asthma, diabetes</td>
<td>Hypertension, angina, arrhythmias, CHF, tremor, migraine, hyperthyroidism, panic stress, (CHF)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>A-M β₁-selective</td>
<td>Labetalol, Carvedilol (α-β-blockers) can reduce both BP &amp; HR, or α-blockers (ie. phenoxybenzamine or phentolamine only reduce BP)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>α-β-agonist, physiologically counters the effects of released histamine (ie. bronchospasm, ↓ BP)</td>
<td>Hypertensive crisis ie. tyramine effect, pheochromocytoma, α-blocker or Labetalol, Carvedilol β-blocker, most common agent used for chronic glaucoma ↓ secretion</td>
</tr>
</tbody>
</table>

**Asthma**

- **Albuterol**
- **Terbutaline,** **Metaproterenol**
  - β₂-selective agonists
  - bronchodilation
  - less side effects

Ritodrine - premature labor

**Glaucoma**

Increased intracranial pressure: Untreated → blindness

Glaucoma: Open angle (wide, chronic) – treated with beta-blockers and other agents
- Closed-angle (narrow-angle) – dilated iris can occlude outflow
Pilocarpine or surgical removal of part of iris (iridectomy)

1. α-Agonist: Outflow
2. M-Agonists: Outflow
3. β-Blocker: ↓ Secretion
4. α₂-Agonist: ↓ Secretion
5. Prostaglandins: ↓ Outflow
6. Carbonic acid inhibitors: ↓ Secretion

**Horners Syndrome**

Destruction of sympathetic innervation to the iris
- loss of preganglionic fibers or
- loss of postganglionic fibers
- parasympathetic innervation left unopposed

Horners Syndrome (note sagging left eyelid and miosis)

**Question 3**

The circles represent the size of the pupils of a patient's right and left eyes, both without treatment and with two different treatments. Which of the following is compatible with the findings shown for the left eye?

A. Blockade of α-adrenergic rec.
B. Blockade of β-adrenergic rec.
C. Blockade of muscarinic rec.
D. Inhibition of cholinesterase
E. Sympathetic denervation

**Question 4**

Which of the following drugs applied topically produces mydriasis without producing cycloplegia?

A. Atropine  
B. Neostigmine  
C. Phentolamine  
D. Phenylephrine  
E. Pilocarpine


---

**Tyramine Interaction with MAO Inhibitors**

Can cause hypertensive crisis (↑BP, ↑HR)

Aged cheese & red wine are rich in tyramine

---

**Beta-Adrenoceptor Blocking Agents (-olol)**

(Drugs A-M are β1-selective except Labetalol & Carvedilol)

<table>
<thead>
<tr>
<th>Drug</th>
<th>β1 Selectivity</th>
<th>Peripheral Argon Activity</th>
<th>Local Anesthetic Action</th>
<th>Block Activity</th>
<th>Elimination Half-Life</th>
<th>Approximate Bioavailability</th>
</tr>
</thead>
</table>
| Atenolol | S | No | Yes | Low | 24 Hours | 90%
| Metoprolol | S | No | No | Low | 6-8 Hours | 90%
| Timolol | S | No | No | Low | 1-2 Hours | 90%
| Nebivolol | S | Yes | No | Low | 2-6 Hours | 70%
| Nadolol | S | No | Yes | Low | 24 Hours | 90%
| Propranolol | S | No | No | Low | 24 Hours | 90%
| Prazosin | S | No | No | High | 1-2 Hours | 90%
| Phentolamine | S | No | No | Low | 12 Hours | 90%
| Doxazosin | S | No | No | High | 12 Hours | 90%
| Hydralazine | S | No | No | Low | 12 Hours | 90%

*Partial agonist at β2 receptors.  Labetalol and tablets + selective β2-blocker.  Bioavailability is dose-dependent.

---

**Pheochromocytoma**

Tumor: ↑ synthesis, ↑ release of NE & EPI into the circulation.

Result: ↑ BP, THR → hypertensive crisis

Treatment: - surgical removal for solid tumor  
- α-β-blocker ie. Labelotol, Carvedilol  
- α-blocker ie. phenoxbenzamine or phentolamine  
- inhibitor of tyrosine hydroxylase ie. α-methyl-p-tyrosine  
- β-blocker only after α-blockade

**Rule of Ten**

10% Pheochromocytomas are:

- Malignant  
- Bilateral  
- Extra-Adrenal  
- In Children  
- Familial  
- Recur (within 5 to 10 years)  
- Present after stroke

---

**Parkinson’s Disease**

- General population 1:1000, over 60 1:75  
- Tremor, stiffness, or clumsiness, usually involving one side difficulty walking, fatigue, depression  
- Progressive destruction of the dopaminergic nigrostriatal pathway  
- Elevated cholinergic activity

**Treatment:**

- MAO inhibitors:  
- Dopamine agonists: bromocriptine  
- L-Dopa  
- Anticholinergics: benztropine  
- Decarboxylase inhibitor: carbidopa  
- Amantadine: Inhibit D-uptake, M-rec, NMDA-block, release dopamine

---

**Question 5**

The histograms show changes in HR and bronchial resistance produced by the administration of epinephrine alone, drug X alone, and epinephrine together with drug X. Drug X is most likely to be?

A. Isoproterenol  
B. Metoprolol  
C. Nadolol  
D. Pindolol  
E. Propranolol

USMLE Step 1: 2003, 2005
**Hypertension (JNC VII – 2003)**

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

*Requires three measurements (repeat visits)*

BP lowest in the morning → ↑ during the day

- **β-Blockers**: Frontline agents
- **α-Blockers**: Hypertensive crisis, special circumstances
- **α2-Agonists**: Useful, not frontline ie. Clonidine
- **Reserpine**: Resistant hypertension, significant side effects, rarely used
- **Guanethidine**: Resistant hypertension, significant side effects, rarely used

**β-Blockers: Contraindications/Cautions**

- **Supersensitivity**: Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol). Gradual withdrawal
- **Asthma**: Blockade of pulmonary β2-receptors. β1-selective agents preferred
- **Diabetes**: Compensatory hyperglycemic effect of EPI in hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred
- **Raynauds D**: - may induce
- **Caution in Congestive Heart failure**: β-blockers can precipitate latent heart failure by removing compensatory increase in sympathetic effects on heart.

**Note CI**: unstable CHF, depression, significant bradycardia or bronchospasm

---

**Deadly Nightshade**  
 Approx 5,000 per yr

- Mainly atropine
- Devil’s apple
- Slink weed
- Devil’s cherries

**Datura**

- Mainly scopolamine & hyoscyamine
- Thorn apple
- Jimson weed

**Myasthenia gravis**  
 Autoimmune disease

- 1:10,000 (250,000 USA)
- Antibodies to NMJ nicotinic receptors leads to degradation
- Simplified synaptic folds
- Normal nerve terminal and transmitter
- Wider synaptic junction
- Diagnosis: Edrophonium (Tensilon, short acting) is used for diagnosis and determination of maintenance dose
- Treatment: Neostigmine has direct (stimulates receptor) and indirect actions (inhibition of AchE). No CNS activity.

**Acetylcholinesterase & Irreversible Inhibition**

- DFP, Isofluriphrate, Malathion, Parathion

- 2-PAM
  - Pralidoxime
  - No CNS action
  - Aging 30-40 min
  - Nerve gas secs / min
  - Parathion, Malathion (prodrugs)
  - 4 – 6 hr

**Wild Mushrooms - Amanita**

- 10,000 cases per year
- Muscarine poisoning
- 5,000 mushroom species
- 100 "bad", 10 "deadly"
Prototype Drugs

ie. Propranolol
Metoprolol, Atenolol
Tubocurarine
Succinylcholine
Clonidine
etc

Neuromuscular Junction

Succinylcholine (non-competitive):
- depolarizing (only agent), cannot reverse, short-acting, fasciculations
- atypical pseudo-AchE, hyperkalemia, malignant hyperthermia

Tubocurarine (competitive):
- non-depolarizing, reversible, long-acting, relaxed paralysis, some histamine release & ganglia block

Rocuronium (competitive):
- non-depolarizing, fast acting, 30-40min duration

Mivacurium (competitive):
- non-depolarizing, short acting, hydrolysis by AchE

NMJ Blocking Agents – Other Actions

<table>
<thead>
<tr>
<th></th>
<th>Ganglia</th>
<th>Muscarinic Receptors</th>
<th>Histamine Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>Stimulates</td>
<td>Stimulates</td>
<td>Slight</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Blocks</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Metacurine</td>
<td>Blocks weakly</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Gallamine</td>
<td>None</td>
<td>Blocks strongly</td>
<td>None</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>None</td>
<td>Blocks weakly</td>
<td>None</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Atracurium</td>
<td>None</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>None</td>
<td>None</td>
<td>Slight</td>
</tr>
</tbody>
</table>

Onset, Duration and Elimination of Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Mode of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>1-2</td>
<td>6-8</td>
<td>Hydrolysis by AchE</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, Liver</td>
</tr>
<tr>
<td>Metacurine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td>Gallamine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, Liver</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>2-4</td>
<td>30-40</td>
<td>Kidney, Liver</td>
</tr>
<tr>
<td>Atracurium</td>
<td>2-4</td>
<td>30-40</td>
<td>Hydrolysis by AchE</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1-2</td>
<td>30-40</td>
<td>Liver</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>2-4</td>
<td>80-100</td>
<td>Kidney, Liver</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>2-4</td>
<td>12-18</td>
<td>Hydrolysis by AchE</td>
</tr>
</tbody>
</table>

ANS – Cardiovascular Receptors

Blood Pressure = Cardiac Output X TPR
Cardiac Output = Heart rate X Stroke volume

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Response</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha₁</td>
<td>vasoconstriction</td>
<td>↑ TPR ↑ BP</td>
</tr>
<tr>
<td>beta₁</td>
<td>↑ heart rate</td>
<td>↑ CO ↑ BP</td>
</tr>
<tr>
<td>beta₂ **</td>
<td>vasodilation</td>
<td>↓ TPR ↓ BP</td>
</tr>
<tr>
<td>M₂ (vagus)</td>
<td>↓ heart rate</td>
<td>↓ CO ↓ BP</td>
</tr>
<tr>
<td>M (vascular) **</td>
<td>vasodilation</td>
<td>↓ TPR ↓ BP</td>
</tr>
</tbody>
</table>

** not innervated

Cardiovascular – Resting & Reflex Response

Resting: BP 120/80 mmHg    HR 70 bpm
No tone: BP 60/40 mmHg     HR 75 bpm

vagus (-10 bpm)  beta₁ (+5 bpm)

Resting     After ↑BP After ↓BP
alpha₁       ++++    o    ++++
beta₁        +     o      +
beta₂ **      +     ++    o
vagus        ++    +++   +

note: athletic individual has low HR (high vagal tone)
Cardiovascular Responses

Moderate/high doses:
- NE: ↑BP, ↓HR (reflex)
- EPI: ↑BP, ↑HR
- ISO: ↓BP, ↑HR
- ACH: ↓BP, ↓HR

- Epinephrine reversal (EPI response in presence of α-blocker ie. phentolamine)
- Norepinephrine in presence of atropine (↑BP, ↑HR)

Cardiovascular Actions – Low dose

Key Diagrams

NE, PE, EPI, ISO
α-blocker, β-blocker
NE + atropine
NE + α-blocker
NE + β-blocker
PE + atropine
EPI + α-blocker
EPI + β-blocker

Cardiovascular Actions – High dose

Phenylephrine
α-agonist, PP constant
Epinephrine
α-β-agonist, ↑PP
Isoproterenol
β-agonist, ↑PP
Epinephrine Reversal
Phentolamine
α-antagonist
↑PP, ↑BP, ↑HR (reflex)
In the presence of phentolamine, epinephrine now causes ↓BP

Question 6

A 65-year old woman on holidays is stung by a bee. She goes to the first aid station where she receives an intramuscular injection of epinephrine. A few minutes later she develops a pounding headache, and blood pressure is measured at 250/150 mmHg. Which of the following drugs might the patient have previously taken that could account for this unexpected effect?

A. atropine
B. clonidine
C. alpha-methyldopa
D. prazosin
E. propranolol

Question 7

A new agent (X) was tested for its cardiovascular actions in three anaesthetized animals.

i. Control animal
ii. Animal treated with a ganglion blocker
iii. Animal treated with a muscarinic blocker

Drug X caused a 50 mmHg rise in BP in the control animal, no change in BP in the ganglion blocker treated animal and a 75 mmHg rise in the muscarinic blocker treated animal. Drug X is a drug similar to?

A. Acetylcholine
B. Atropine
C. Mecamylamine
D. Epinephrine
E. Nicotine
Question 8
A new agent (Y) was tested for its cardiovascular actions in three anaesthetized animals.

i. Control animal
ii. Animal treated with a ganglion blocker
iii. Animal treated with a muscarinic blocker

Drug Y caused a 40 mmHg fall in BP in the control animal, a 50 mmHg fall in BP in the ganglion blocker treated animal and no change in BP in the muscarinic blocker treated animal. Drug Y is a drug similar to?

A. Acetylcholine
B. Edrophonium
C. Mecamylamine
D. Pralidoxime
E. Nicotine

Question 9
A 60-year-old asthmatic man comes in for a check-up and complains that he is having some difficulty in voiding urine. Physical examination indicates that the man has a blood pressure of 160/100 mmHg and a slightly enlarged prostate. Which of the following medications would be useful in treating both the hypertension and the enlarged prostate?

A. prazosin
B. propranolol
C. clonidine
D. atenolol
E. isoproterenol

Benign Prostate Hypertrophy (BPH)
Enlarged prostate leads to difficulty in urination
Alpha-receptor blocker (ie Prazosin) causes prostrate relaxation
Relaxed prostrate improves urination

Question 10
A 30 yr male has been treated with several autonomic agents for 4 weeks. He is now admitted to the emergency department showing signs of drug toxicity. Which of the following signs would distinguish between an overdose of a ganglionic blocker versus a muscarinic blocker?

A. Mydriasis
B. Tachycardia
C. Postural hypotension
D. Blurred vision
E. Dry mouth, constipation

Actions on the Eye
Glaucoma treatment
1. α-Agonist ↑Outflow
2. M-Agonists ↑Outflow
3. β-Blocker ↓Secretion
4. α2-Agonist ↓Secretion
5. Prostaglandins ↑Outflow
6. Carbonic acid inhibitors ↓Secretion

Question 12
Which of the following characteristics of amphetamines is most likely to be responsible for increasing blood pressure?

A. Indirect release of endogenous catecholamines
B. Inhibition of catecholamine metabolism
C. Metabolism to false neurochemical transmitters
D. Potent alpha1-adrenergic agonism
E. Potent beta1-adrenergic agonism