Autonomic Nervous System & Neuromuscular Junction Review

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Tips for Drug Learning

- Learn agents by drug classes ie. beta-blockers, Ca++-blockers etc
- Key points:
  - Clinical application
  - Mechanism of action
  - Important drug/drug interactions ie. MAOI and tyramine rich foods
  - Adverse drug reactions ie. beta-blockers – asthma, Raynaud D.
- Drugs of choice (DOC) ie. epinephrine (anaphylaxis)
- Prototype drugs, commonly prescribed ie. propranolol, atenolol; captopril, lisinopril
- Do not focus on dosage or trade names

ANS – Overview Tissues/Organs

<table>
<thead>
<tr>
<th>Sympathetic NS</th>
<th>Parasympathetic NS</th>
<th>Cardiovascular System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ</td>
<td>Action</td>
<td>Receptor</td>
</tr>
<tr>
<td>Neuronal NS</td>
<td>Nervous muscle</td>
<td>Adrenergic Muscarinic</td>
</tr>
<tr>
<td>Receptors</td>
<td>Action</td>
<td>Vascular smooth muscle</td>
</tr>
<tr>
<td>Neuronal NS</td>
<td>Nervous muscle</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>Receptors</td>
<td>Action</td>
<td>Sympathetic smooth muscle M₁/M₅</td>
</tr>
<tr>
<td>Neuronal NS</td>
<td>Nervous muscle</td>
<td>Bronchial smooth muscle M₄/M₅</td>
</tr>
<tr>
<td>Receptors</td>
<td>Action</td>
<td>Fat cells</td>
</tr>
<tr>
<td>Neuronal NS</td>
<td>Nervous muscle</td>
<td>Renal smooth muscle</td>
</tr>
<tr>
<td>Receptors</td>
<td>Action</td>
<td>Ganglia cells</td>
</tr>
<tr>
<td>Neuronal NS</td>
<td>Nervous muscle</td>
<td>Sympathetic smooth muscle M₃/M₄</td>
</tr>
<tr>
<td>Receptors</td>
<td>Action</td>
<td>Selective agents available</td>
</tr>
</tbody>
</table>

ANS – Review

1. Tissues / Organs: - receptors present, tissue / organ response
2. Transmitters: - NE, Ach, synthesis, storage, release, regulation
3. Eye: - miosis, mydriasis, cycloplegia, Glaucoma: wide- vs narrow-angle, Horner’s Syndrome
4. Drugs: - receptor selectivity, mechanism of action
5. Can predict: - clinical application, side effects, toxicity, treatment of toxicity
6. General: - learn by drug classes, important adverse reactions, not dosage
Transmitter synthesis and release

Question 1a

A 42-old woman who is a biochemist is brought to the emergency department because of a 1-hour history of severe abdominal cramps, nausea, vomiting, sweating, and difficulty breathing due to bronchospasm and congestion. On physical examination her pulse is 45/min, BP is 85/50 mm Hg and she exhibits generalized muscle weakness. Laboratory studies show no abnormalities. Exposure to which of the following is most likely?

A. atropine
B. bethanechol
C. botulinum toxin
D. isoflurophate
E. phentolamine

Question 1b

A 42-old woman who is a biochemist is brought to the emergency department because of a 1-hour history of severe abdominal cramps, nausea, vomiting, sweating, and difficulty breathing due to bronchospasm and congestion. On physical examination her pulse is 45/min, BP is 85/50 mm Hg and she exhibits generalized muscle weakness. Laboratory studies show no abnormalities. In addition to pralidoxime, which of the following is the most appropriate pharmacotherapy for this patient?

A. atropine
B. dantrolene
C. epinephrine
D. phentolamine
E. propranolol

Question 2

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. Mushrooms
B. Heroin
C. Jimson weed (belladonna alkaloids)
D. Parathion
E. Aged cheese/red wine

ANS Excess / Deficiency

- Cholinergic excess: (e.g., AchE inhibition or mushrooms)
  - Salivation, lacrimation, urination, diarrhea, emesis (diarrhea, miosis), ↓HR, sweating, cycloplegia, (paralysis)
- Cholinergic deficiency: (e.g., Atropine toxicity)
  - ↓GI motility, mydriasis, cycloplegia, ↓secretions, tachycardia, delirium, hallucinations
- Sympathetic excess: (e.g., Tyr-MAOI or Pheochrom.)
  - ↑BP, ↑HR, pupil dilation (mydriasis), ↑GI motility
- Sympathetic deficiency: (e.g., Guanethidine-block)
  - ↓BP, ↓tissue perfusion, pupil constriction (miosis)

Terminology – ANS

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

USMLE Step 1: 2003, 2005
**Question 3**

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. Edrophonium  
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>Dantrolene</td>
<td>Inhibits calcium release from SRM</td>
<td>malignant hyperthermia</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Reverses AchE inhibition</td>
<td>neostigmine, physostigmine, or organophosphates</td>
</tr>
<tr>
<td>B. Atropine</td>
<td>Reverses AchE inhibition</td>
<td>Atropine</td>
</tr>
<tr>
<td>C. Edrophonium</td>
<td>Reverses AchE inhibition</td>
<td>Pralidoxime</td>
</tr>
<tr>
<td>D. Epinephrine</td>
<td>M-agonist causes ↑ outflow</td>
<td>Emergency glaucoma</td>
</tr>
<tr>
<td>E. Pralidoxime</td>
<td>Reversible AchE inhibitor, can cross CNS</td>
<td>Reverses atropine toxicity</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Asthma</td>
<td>Timolol, Latanoprost</td>
</tr>
<tr>
<td>Terbutaline, Metaproterenol, Salmeterol (LABA)</td>
<td>β1-selective agonists</td>
<td>Ritodrine</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Bronchodilation</td>
<td>bronchodilation</td>
</tr>
<tr>
<td>Terbutaline, Metaproterenol, Salmeterol (LABA)</td>
<td>vasoconstriction</td>
<td>vasoconstriction</td>
</tr>
<tr>
<td>Albuterol</td>
<td>- bronchodilation</td>
<td>inhalation vs oral</td>
</tr>
<tr>
<td>Terbutaline, Metaproterenol, Salmeterol (LABA)</td>
<td>- less side effects</td>
<td>fetal/adrenergic receptors in several other vascular beds, and directly and indirectly stimulates β1-adrenergic receptors in the myocardium. Drug X increases blood flow through the mesenteric and renal vascular beds by activating which of the following receptors?</td>
</tr>
<tr>
<td>A. Alpha-adrenergic</td>
<td></td>
<td>A. Alpha-adrenergic</td>
</tr>
<tr>
<td>B. Beta-adrenergic</td>
<td></td>
<td>B. Beta-adrenergic</td>
</tr>
<tr>
<td>C. Dopaminergic</td>
<td></td>
<td>C. Dopaminergic</td>
</tr>
<tr>
<td>D. Muscarinic-cholinergic</td>
<td></td>
<td>D. Muscarinic-cholinergic</td>
</tr>
<tr>
<td>E. Serotoninergic</td>
<td></td>
<td>E. Serotoninergic</td>
</tr>
</tbody>
</table>

**Glaucoma**

- Open angle (wide, chronic) – treated with beta-blockers and other agents
- Closed-angle (narrow-angle) – dilated irid can occlude outflow

- Increased intraocular pressure: Untreated → blindness

- Glaucoma treatment
  1. α1-Agonist: ↑ drainage
  2. M-Agonist/AchE: ↑ drainage
  3. β-Blocker: ↓ secretion
  4. α2-Agonist: ↓ secretion
  5. Prostaglandins (PGF2α): ↑ drainage
  6. Carbonic acid inhibitors: ↓ secretion
Question 5

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

Without treatment  
Treatment With TYR  
Treatment With EPI

Correct: E


Schizophrenia

- Altered perception or expression of reality
- Affects 1% of the population
- Affects men and women equally
- Strong genetic component

- Dopamine (DA) excess theory:
  - Amphetamine exacerbates symptoms and high doses → paranoia, delusions, auditory hallucination. Effects blocked by DA antagonist chlorpromazine.

Antipsychotic Pharmacotherapy:
Typical: chlorpromazine, haloperidol  
Atypical: risperidone, olanzapine, sertindole

Question 6

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

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


Beta-Adrenoceptor Blocking Agents (-olol)
(Drugs A-M are β1-selective except Labetalol & Carvedilol)

-10  0  10  20
-20 HR IncreaseBronchiolar resistance

EPI Drug  
EPI  
Drug X

Beta-Adrenoceptor Blocking Agents
(-olol)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial-Agonist Activity</th>
<th>Local Anesthetic Action</th>
<th>Vasodilatation</th>
<th>Elimination Half-Life</th>
<th>Agonist-Beta Block Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lineolol</td>
<td>High</td>
<td>Yes</td>
<td>Low</td>
<td>Low</td>
<td>3-4 days</td>
<td>100%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>High</td>
<td>Yes</td>
<td>Low</td>
<td>Low</td>
<td>4-24 hours</td>
<td>90%</td>
</tr>
<tr>
<td>Labetalol</td>
<td>High</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>2-3 days</td>
<td>80%</td>
</tr>
<tr>
<td>Pindolol</td>
<td>High</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>2-3 days</td>
<td>80%</td>
</tr>
<tr>
<td>Timolol</td>
<td>High</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>2-3 days</td>
<td>90%</td>
</tr>
</tbody>
</table>

Parkinson’s Disease

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

Treatment:

- MAO inhibitors: bromocriptine, pramipexole
- L-Dopa
- Anticholinergics: benztropine
- Decarboxylase inhibitor: carbidopa
- COMT inhibition


Question 7

The histograms show changes in HR and bronchiolar 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>or ≥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 |
| Dₐ₂-Agonist | - Hypertensive crisis iv, ie. Fenoldopam |
| Reserpine | - 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

**Acetylcholinesterase & Irreversible Inhibition**

**DFP, Isoflurophate, Malathion, Parathion**

<table>
<thead>
<tr>
<th>2-PAM</th>
<th>Pralidoxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cns action</td>
<td>Aging</td>
</tr>
<tr>
<td>30-40 min</td>
<td>Nerve gas</td>
</tr>
<tr>
<td>secs / min</td>
<td>secs / min</td>
</tr>
<tr>
<td>Parathion, Malathion (prodrugs)</td>
<td>4 – 6 hr</td>
</tr>
</tbody>
</table>

**Deadly Nightshade**

**Approx 5,000 per yr**

- Mainly atropine
- Devil’s apple
- Stink 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 degraded
- normal nerve terminal and transmitter
- wider synaptic junction

**Diagnosis:** Edrophonium (Tension, 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.

**Neuromuscular Junction**

**Succinylcholine (non-competitive):**
- depolarizing (only agent)
- cannot reverse, short-acting, fasciculations
- atypical pseudo-AchE, hyperkalemia (burn or trauma, develops slowly), malignant hyperthermia

**Tubocurarine (competitive):**
- non-depolarizing
- reversible, long-acting,
- relaxed paralysis (flaccid)
- some ganglia blockade and histamine release
Competitive (nondepolarizing) NMBs - Others

- **Pancuronium**
  - more potent than tubocurarine (x5)
  - reduced histamine release than curare
  - lack of ganglionic blockade

- **Rocuronium**
  - fast onset (1-2min), 30-40min duration, hypersensitivity

- **Atracurium** (~10 isomers)
  - hydrolysis by AchE
  - replaced by cisatracurium, Hoffmann degradation, organ independent

- **Gallamine**
  - also some muscarinic block

- **Mivacurium**
  - fast onset (2-4min), short acting (12-18min), hydrolysis by AchE, some histamine release

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### Hyperkalemia

- **Hyperkalemia**
- burn & trauma
- usually small ↑K+
- cardiac arrest
- support: dialysis glucose / insulin

### Malignant Hyperthermia

- more likely with halothane
- 60% mortality
- ↑Ca** → ↑ body temp
- tachycardia
- dysrhythmia
- ↑HR, muscle rigidity

**Treatment:**
- Dantrolene
- drug of choice
- ↓Ca** release

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### NMJ Blocking Agents – Other Actions

<table>
<thead>
<tr>
<th>Drug</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>Metaocurine</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>cisAtracurium</td>
<td>None</td>
<td>None</td>
<td>Minimal</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>90-120</td>
<td>Kidney, Liver</td>
</tr>
<tr>
<td>Metaocurine</td>
<td>4-6</td>
<td>90-120</td>
<td>Kidney</td>
</tr>
<tr>
<td>Gallamine</td>
<td>4-6</td>
<td>90-120</td>
<td>Kidney, Liver</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>4-6</td>
<td>90-120</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>cisAtracurium</td>
<td>2-4</td>
<td>30-40</td>
<td>Hoffmann</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>Pimecuroin</td>
<td>2-4</td>
<td>90-100</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>alpha_1</td>
<td>vasoconstriction</td>
<td>↑TPR ↑BP</td>
</tr>
<tr>
<td>beta_1</td>
<td>↑ heart rate</td>
<td>↑CO ↑BP</td>
</tr>
<tr>
<td>beta_2**</td>
<td>vasodilation</td>
<td>↓TPR ↓BP</td>
</tr>
<tr>
<td>M_2 (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 ++ ++++ o

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 i.e. phentolamine)
• Norepinephrine in presence of atropine (↑BP, ↑HR)

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

Cardiovascular Actions – Low dose

Question 8

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 9

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

Benign Prostate Hypertrophy (BPH)

Enlarged prostate leads to difficulty in urination
Alpha-receptor blocker (ie Prazosin) causes prostate relaxation
Relaxed prostate improves urination

Question 10

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 11

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

Sympathetic Nervous System Review

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

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