Part 1: Acetyl Choline (Cholinergic) Receptor Pharmacology

Part 2: Norepinephrine (Adrenergic) Receptor Pharmacology

PHRM 203
Allison Beale
Cholinergic Receptor Types

• **Muscarinic (metabotropic, GPCR)**
  – Neuronal
    • CNS, Autonomic ganglia, pre-synaptic nerve terminals
  – Cardiac
    • Heart tissue
  – Glandular
    • Smooth muscle and glands

• **Nicotinic (ionotropic, LGIC)**
  – Muscular
    • Somatic NMJ
  – Neuronal
    • CNS, Autonomic ganglia

Atropine ⊗’s

Curare ⊗’s
Muscarinic Receptors

- G-protein coupled (GPCR) with 2nd messenger
  - Different 2nd messengers allow various responses
- Five types, M₁ - M₅
- Agonist = muscarine
- Antagonist = atropine

All 5 subtypes are found in all tissues


Muscarinic Receptor Sites

• **Parasympathetic**
  - **Heart** – cardiac pace maker conduction (*Vagus nerve*)
  - **Exocrine glands (secretions)** - bronchorrhea, salivation, hyperamylasemia, lacrimation, rhinorrhea, gastric acid, bile, etc. (*Vagus, facial, glossopharyngeal, trigeminal nerves*)
  - **Smooth muscles** - bladder stimulation, sphincter relaxation, bronchospasm, miosis, GI motility, vasodilation (*Vagus, oculomotor, trigeminal nerves*)

• **Sympathetic**
  - **Sweat glands**, *piloerector muscles & arterioles in skeletal muscles*
  - *On the sympathetic post-ganglionic neuron pre-synaptic membrane to allow parasympathetic feedback*

• **CNS**
Cranial Nerves with mixed Sensory, Motor & PNS activity

- **Occulomotor (CN III)**
  - Miosis
- **Trigeminal (CN IV)**
  - Oral & nasal mucous glands, taste receptors
- **Facial (CN VII)**
  - Salivary & lacrimal glands, nasal mucous glands
- **Glossopharyngeal (CN IX)**
  - Parotid (salivary) glands
- **Vagus (CN X)**
  - Smooth muscle, glandular, nerve conduction functions in heart, lung, GIT, pancreas, kidney, liver, gall bladder

Of the 12 Cranial Nerves, 5 have mixed functions, mnemonic:

Some Say Marry Money But My Brother Says Big Brains Matter Most

S = sensory, M = motor, B = both
ACh Agonists

• Direct
  – Bind to the receptor directly
    • Bethanechol & pilocarpine (mAChR)
    • Varenicline - Chantix (nAChR)

• Indirect
  – Increase the synaptic [ACh] by:
    • Inhibiting AChE
      – Preventing breakdown of ACh
      – AntiAChE agents, eg OPs, Donepezil, Tacrine
    • Increasing the release of ACh from the terminal
      – Black Widow toxin (Latrotoxin)

Agonists may cause depression by ↑’ing REM sleep. REM associated with ↑ ACh & ↓ NE & 5-HT

Muscarinic agonists must be used with great caution in patients with: Asthma, epilepsy, peptic ulcers, coronary insufficiency, hypotension, bradycardia, hyperthyroidism, and Parkinson’s because of Parasympathetic effects
Muscarinic agonist
Poisoning Mnemonics

• **SLUDGE**
  – Salivation, lacrimation, urination, diarrhea, **GI upset** and emesis

• **DUMBELS** *(sometimes, D-DUMB-BELS)*
  – Defecation/Diaphoresis (sweating), urination, **miosis**, bronchospasm & bronchorrhea, emesis, lacrimation, salivation.

Muscarinic effects also include:  muscle spasms, bradycardia, GI cramps, headache and disorientation or **CNS depression**
If you see this icon: 🚭, or the drug name is red
   KNOW that drug
   Look for it on Drug Lists

When you see this icon: 🛋️️
   Notice the Pregnancy Category
   Important drugs are PC-X

When you see this icon: 😨
   Notice the sound alike or look alike names
   FYI: Handouts in the Course Index

Drugs with this icon:
   Make people dizzy, disoriented, &/or weak – or otherwise increase the risk of falls.
# Direct-acting Cholinergic Agonists (muscarinic)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bethanechol (Urecholine)</strong></td>
<td>Non-obstructive urinary retention, neurogenic bladder</td>
</tr>
<tr>
<td><strong>Carbachol</strong></td>
<td>Glaucoma</td>
</tr>
<tr>
<td><strong>Cevimeline</strong></td>
<td>Dry mouth symptoms in Sjögren’s syndrome</td>
</tr>
<tr>
<td><strong>Pilocarpine</strong> (Isopto Carpine, Salagen)</td>
<td>Glaucoma (drops) &amp; dry mouth in Sjögren’s syndrome &amp; following radiotherapy (tablets)</td>
</tr>
</tbody>
</table>

* Gtt = drops (from Latin, guttae)  🎨 = Know this drug, be able to recognize it and say what it does.

Adapted from: Focus on Nursing Pharmacology, 4th Ed. AM Karch. Lippincott Williams & Wilkins 2008.
Glaucoma = optic nerve damage caused by ↑d intraocular pressure.

Focus on Glaucoma

www.nei.nih.gov/health/glaucoma

Glaucoma treatment:
- α Agonists
- β Blockers
- Carbonic anhydrase inhibitors
- ACh agonists
- Prostaglandin analogs

Normally, fluid is produced by the ciliary bodies, flows through the pupil and is drained to the blood, if the iris is pushed forward, the fluid can’t drain and pressure↑
# Glaucoma Medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Effect(s)</th>
<th>Generic name</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic agonist</td>
<td>↑ Drainage</td>
<td>Pilocarpine</td>
<td>Isopto Carpine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbachol</td>
<td>Isopto Carbachol</td>
</tr>
<tr>
<td>α-2 Agonist</td>
<td>↓ Fluid production</td>
<td>Apraclonidine</td>
<td>Iopidine</td>
</tr>
<tr>
<td></td>
<td>↑ Drainage</td>
<td>Brimonodine</td>
<td>Alphagan</td>
</tr>
<tr>
<td>β Blocker</td>
<td>↓ Fluid production</td>
<td>Timolol</td>
<td>Istalol, Betimol</td>
</tr>
<tr>
<td>(all except timolol are non-selective)</td>
<td></td>
<td>Betaxolol</td>
<td>Betoptic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metipranolol</td>
<td>OptiPranolol</td>
</tr>
<tr>
<td>Carbonic anhydrase Θ’rs</td>
<td>↓ Fluid production</td>
<td>Brinzolamide</td>
<td>Azopt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dorzolamide</td>
<td>Diamox Sequels</td>
</tr>
<tr>
<td>Prostaglandin analogs</td>
<td>↑ Drainage</td>
<td>Bimatoprost</td>
<td>Lumigan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latanoprost</td>
<td>Xalatan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Travaprost</td>
<td>Travatan</td>
</tr>
</tbody>
</table>
Focus on 
*Sjögren’s Syndrome*

• Autoimmune disease
  – Ab produced against secretory glands
    • Dry eyes and mouth
      – Lots of other symptoms, e.g., GERD...
    • Associated with Lupus, Rheumatoid arthritis, Hashimoto’s thyroiditis, etc.
  • 4M Americans *Dx’d* (very common)
    – 9/10 are women
    – Mostly >40 yrs old

Treatment: mACh agonist e.g., pilocarpine (Salagen)
## Indirect Cholinergic Agonists

Adapted from: Focus on Nursing Pharmacology, 4th Ed. AM Karch. Lippincott Williams & Wilkins 2008.

<table>
<thead>
<tr>
<th>Drug (Anti-AChE agents)</th>
<th>Indications (Atropine = antidote to poisoning)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambenonium</td>
<td>Myasthenia gravis (A)</td>
</tr>
<tr>
<td>Donepezil (Aricept) ![ ]</td>
<td>Alzheimer’s Disease</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>Myasthenia gravis (also as antidote to <strong>non-depolarizing</strong> NMJ blockers *)</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>Neostigmine (Prostigmin) ![ ]</td>
<td>Myasthenia gravis (also as antidote to <strong>non-depolarizing</strong> NMJ blockers *)</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Myasthenia gravis (also as antidote to <strong>non-depolarizing</strong> NMJ blockers *)</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>Tacrine (Cognex)</td>
<td>Alzheimer’s</td>
</tr>
</tbody>
</table>

* NOT succinylcholine whose effects will be ↑↑

Anti-AChE effects antagonized by corticosteroids - .:. shouldn’t co-administer!
Focus on: **Myasthenic Syndromes**

- Two basic types, many, many syndromes
  1. Autoimmune, Ab-mediated (*Myasthenia gravis*)
     - Ab ⊗ nicotinic ACh receptor (at NMJ) or ⊗ AChE
     - LEMS (Lambert-Eaton Myasthenic Syndrome) Ab ⊗ *Voltage-gated Ca++ channels* (VGCC)
       - LEMS patients *usually* have small cell carcinoma of lung
  2. Genetic (congenital)
     - Presynaptic: Smaller or fewer synaptic vesicles
     - Postsynaptic: Defective or missing ACh receptors
     - Synaptic: Defective or missing AChE
Focus on: Myasthenic Syndromes

- Symptoms:
  - Muscle weakness and fatigue (1st symptoms usually *droopy eyelids*, difficulty swallowing or slurred speech)
  - Use IV EDROPHONIUM (Tensilon®) to Dx

1. Myasthenic crisis
   - Episodes of severe weakness

2. Cholinergic crisis
   - Toxicity due to med during period of improvement

Use **NEOSTIGMINE** or **EDROPHONIUM** to differentiate the two.
Indirect Cholinergic Agonists

• **Anti-AChE agents**
  – Irreversible agents are all Organophosphates, but not all OP’s are irreversible!!
    • Form covalent bond with AChE, some hydrolyze slowly
  – Phosphoric acid esters
    • Easily absorbed and X the BBB
  – Affect ACh levels at mAChR & nAChR

Anti-AChE drugs used 1o to treat myasthenia gravis & Alzheimer’s

Poisoning = SLUDGE
Antidote = Atropine
Focus on: Alzheimer’s Disease

- 5M + people affected - No cure
- Most common cause of dementia
- Therapeutic agents
  - Anti-AChE agents
    - Donepezil (Aricept), Galantamine (Reminyl), Rivastigmine (Exelon) & Tacrine (Cognex)
  - Anti-NMDA (glutamate receptor) agent
    - Memantine (Namenda)
- Typical ADRs
  - Nausea, vomiting, loss of appetite and increased frequency of bowel movements.

AD patients have fewer nAChR
Very Indirect Cholinergic Agonists

- **Anti-5-PDE agents**
  - 5-phosphodiesterase (5-PDE) is the enzyme responsible for cyclic GMP breakdown.
    - cGMP = 2nd messenger
    - Effect = *same as more ACh available to stimulate receptors!*
    - Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra)
    - Rapid PO absorption, CYP3A4 metabolism, active metabolites
    - Drug interactions with nitroglycerin and adrenergic antagonists (doxazosin), + the inhibitors of CYP3A4

Sildenafil indicated for erectile dysfunction & pulmonary arterial hypertension
# Muscarinic Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
</table>
| **Atropine**       | ↓ secretions; bradycardia, pylorospasm, ureteral colic, relaxing the bladder, emotional lability after head trauma, antidote for cholinergic drugs, and used to dilate pupil  
                      *Poisoning: Hot as a poker, Blind as a bat, Dry as a bone, Leaping like a hart, Red as a beet, Mad as a hatter*                                                                 |
| Dicyclomine        | Irritable or hyperactive bowel and bladder syndromes                                                                                                                                    |
| Glycopyrrolate     | ↓ Gastric secretions; antidote for neuromuscular blockers used in surgery                                                                                                               |
| Ipratropium        | Maintenance of COPD; asthma therapy adjunct                                                                                                                                               |
| Propantheline      | Adjunct to ulcer therapy (↓ Gastric secretions) and antispasmodic                                                                                                                      |
| **Scopolamine**    | Motion sickness; ↓ secretions; obstetric amnesia, adjunct to ulcer therapy; pupil dilation                                                                                          |

**Urinary antispasmodics like Solifenacin (VesiCare), for overactive bladder syndrome, are also antimuscarinics**
Nicotinic Receptors

• Ligand-gated ion channels
  – Trigger RAPID neural and neuromuscular transmissions
  – Na⁺, K⁺, or Ca++]

• Two basic types
  – Neuronal (N⁰)
  – Muscular (Nₘ)
  – 17 subunits

• Agonist = Nicotine

• Antagonist = Curare

FDA Medwatch 2009
Both Varenicline & Bupropion have a ■: Neuropsychiatric events include suicide

Varenicline (Chantix)

Bupropion (Wellbutrin, Zyban) blocks nAChR & NE/DA reuptake
Direct acting **Nicotinic** agonist action

Varenicline (Chantix) is a partial nicotinic agonist


www.cnsforum.com/content/pictures/imagebank/ hirespng/rcpt_sys_nic_ag1.png
Nicotinic Receptor Sites

- CNS
- ANS
  - Parasympathetic & Sympathetic
    - Autonomic ganglia
  - Somatic
    - Neuromuscular junction (NMJ)

Note: the Adrenal Medulla is a SNS Ganglion. SNS preganglionic cholinergic neurons stimulate nicotinic receptors on the Chromafin cells of the Adrenal Medulla.
## Nicotinic Antagonists: NMJ Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>Adjunct to general anesthesia, Intubation,</td>
<td>No IM, may cause histamine release</td>
</tr>
<tr>
<td></td>
<td>mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td><img src="image" alt="" /></td>
<td>Vagalytic effect →↑ HR</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Intubation, mechanical ventilation</td>
<td>Avoid use in neonates (may be fatal); may cause permanent muscle damage</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Surgery, MG Dx, Electro-Shock Therapy</td>
<td>May cause histamine release, hypotension, ↑ secretions, ganglion blockade</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>Surgery, intubation, mech. Vent.</td>
<td>May cause myalgia, ↑ intraocular pressure (avoid in glucoma); ↑ intragastric pressure (which may cause emesis); malignant ↑ $B_{To}$</td>
</tr>
</tbody>
</table>

**Nursing consideration:** NMJ blockers have **no effect on pain or consciousness**, so patient may become very fearful as paralysis ensues & they can not communicate painful sensations.
Cholinergic neuron

- Saxitoxin, Locals
- Neostigmine, Donepezil
- Bethanechol, Pilocarpine etc
- Atropine, Scopolamine
- Botulinum
- Vesamicol
- BWV
- Carbachol, Arecoline
- Pancuronium, Succinylcholine
- Hemicholinium
- Amlodipine, Diltiazem, Verapamil, CCBs
- Digoxin

ACETYL CoA + CHOLINE

ACHT

ACH

ADP, 3Na⁺, ATP, 2K⁺
Time to shift gears… On to the Adrenergic neurons which use norepinephrine as the neurotransmitter

Part 2
**Adrenergic Receptors**

*Neurotransmitter = NE* (Epi and DA to lesser extent)

<table>
<thead>
<tr>
<th>Receptor Metabotropic</th>
<th>Activation causes “fight or flight” responses:</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_1 )</td>
<td>Contraction of smooth muscle (vasoconstriction); ↑heart contractility, etc.</td>
</tr>
<tr>
<td>( \alpha_2 )</td>
<td>( \ominus ) Glands (( \ominus ) insulin release by pancreas); modulate CNS (on presynaptic neuron, ( \ominus )NT release) and clotting (on platelet membrane ( \ominus ) platelet aggregation)</td>
</tr>
<tr>
<td>( \beta_1 )</td>
<td>( \oplus ) Renin secretion (from kidney); ↑HR, contractility &amp; conduction in heart smooth muscle</td>
</tr>
<tr>
<td>( \beta_2 )</td>
<td>Glycogenolysis, smooth muscle relaxation (e.g., bronchodilation), ↑uptake of ( K^+ ) in skeletal muscles</td>
</tr>
<tr>
<td>( \beta_3 )</td>
<td>Lipolysis</td>
</tr>
</tbody>
</table>
ADRENERGIC SIGNAL TERMINATION

1. **Breakdown** by enzymes (MAO and COMT)
2. **Reuptake** into vesicles
3. **Diffusion** into extracellular fluid & blood
4. Binding to receptor & taken up by effector
5. Stimulation of receptor that $\Theta$NE release
   - ACh, Histamine, 5-HT, NE
6. **Angiotensin II** alters presynaptic membrane
   - $\downarrow$ NE release and reuptake
7. $\downarrow$ local $T^o$ $\downarrow$NE release, but $\uparrow$ receptor affinity
8. Autocoid & ion feedback $\Theta$NE release
   - AMP, ADP, ATP, Adenosine, H$^+$, K$^+$

MAO = monoamine oxidase
COMT = catechol-O-methyl transferase

Selegiline (Eldepryl)
Entacapone (Comtan)
### Mixed α And β Agonists

*Adapted from: Focus on Nursing Pharmacology 4th Ed., by AM Karch. Lippincott Williams & Wilkins. 2008*

**Sympathomimetic!**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine ✷</td>
<td>CHF (synthetic catecholamine)</td>
</tr>
<tr>
<td>✷ Dopamine</td>
<td>Shock</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Hypotensive episodes, seasonal rhinitis/asthma (nasal decongestant)</td>
</tr>
<tr>
<td>✷ Epinephrine</td>
<td>Shock, to prolong regional anesthetic effects</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>Shock (if NE or DA can’t be used), prevention of hypotension with spinal anesthesia</td>
</tr>
<tr>
<td>✷ Norepinephrine</td>
<td>Shock, cardiac arrest</td>
</tr>
</tbody>
</table>

**catecholamines = catechol + tyrosine backbone. TYR → L-DOPA → DA → NE → E**
## α-specific Agonists

Adapted from: *Focus on Nursing Pharmacology 4th Ed.*, by AM Karch. Lippincott Williams & Wilkins. 2008

### α1 = Sympathomimetic!  
### α2 = Sympatholytic!

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine (Catapres) α2</td>
<td>Essential hypertension, chronic pain (analgesic), alcohol &amp; opiate withdrawal, an aide to smoking cessation, ADHD adjuvant. <em>Off label: Tourette’s &amp; tics.</em></td>
</tr>
<tr>
<td>Guanfacine α2 (Tenex, Intuniv)</td>
<td>Essential hypertension, ADHD</td>
</tr>
<tr>
<td>Dexmedetomidine (Precedex) α2</td>
<td>IV ICU sedation (pre- &amp; peri-surgery)- incompatible with diazepam and amphotericin B</td>
</tr>
<tr>
<td>Phenylephrine (Neo-Synephrine) α1&amp;2</td>
<td>Cold and allergies; shock and shock-like conditions; supraventricular tachycardias, glaucoma; allergic rhinitis; otitis media</td>
</tr>
<tr>
<td>Oxymetazoline α1&amp;2</td>
<td>Nasal decongestant (in lots of OTCs, has STRONG rebound effects)</td>
</tr>
</tbody>
</table>
Direct acting NON-Catecholamines

**Clonidine**

- $\alpha_2$ agonist
  - Oral anti-HT
  - Transdermal patch
  - Severe pain w/opioid
- ADRs
  - Dry mouth, dizziness, sedation, constipation, bradycardia, weight gain
- Incompatible with
  - TCAs, $\beta$-blockers

$\alpha_2$ agonists = Sympatholytic!

- **Serious withdrawal syndrome**
  - Nervousness, agitation, severe *increase in BP* and plasma catecholamines
  - Effects reversed by phentolamine or clonidine
Direct acting NON-Catecholamines

• Phenylephrine (PE) 🎥
  – 1º an \( \alpha_1 \) agonist
  • Vasoconstrictor
    – Increase BP during anesthesia, vascular failure or shock
    – Prolong spinal anesthesia
    – Decongestant
  • Lasts longer than epinephrine or ephedrine

Phenylephrine 🎥 & replaced PSEUDOEPHEDRINE (ephedrine) in OTC cold/allergy meds.

PO, Topical, Parenteral (IV, SC, etc.)
Direct acting NON-Catecholamines

• **Oxymetazoline**
  – A topical nasal decongestant
  – $\alpha_1$ and partial $\alpha_2$ agonist
  – **OVERUSE** $\Rightarrow$ strong rebound effect
  – *In lots of OTCs*

Afrin = oxymetazoline
Neo-Synephrine = phenylephrine
**β-specific Agonists**

Adapted from: Focus on Nursing Pharmacology 4th Ed., by AM Karch. Lippincott Williams & Wilkins. 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Issues/ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoproterenol (Isuprel)</td>
<td>Shock, cardiac arrest; treatment of heart block in transplanted hearts; prevention of bronchospasm during surgery</td>
<td>Anxiety, restlessness, arrhythmias (tachycardia), coughing, pulmonary edema, sweating, pallor</td>
</tr>
<tr>
<td>β₁ &amp; β₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ocrine (isosorbide dinitrate)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sympathomimetic!**

IV, metered inhaler

Don’t co-administer sympathomimetics with β blockers, MAOIs, COMT-Is, TCAs, SNRIs
## Sympathomimetic Bronchodilators

Adapted from: Focus on Nursing Pharmacology 4th Ed., by AM Karch. Lippincott Williams & Wilkins. 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol aka <em>salbutamol</em> (Proventil) – fast acting  <img src="https://example.com/beta_2" alt="beta_2_agonist_icon" /></td>
<td>These are <em>beta_2</em> agonists. Most <em>beta_2</em> receptors are in the lungs, but up to 50% are in heart muscle.</td>
</tr>
<tr>
<td>Formoterol (Foradil) - LABA</td>
<td>CV ADRs: arrhythmias &amp; ischemia.</td>
</tr>
<tr>
<td>Isoetharine (generic)</td>
<td>CNS ADRs: seizures.</td>
</tr>
<tr>
<td>Pirbuterol (Maxair)</td>
<td>Lung ADRs: edema &amp; worsening of asthma symptoms (leading to death).</td>
</tr>
<tr>
<td><strong>Salmeterol</strong> (Serevent) - LABA  <img src="https://example.com/beta_2" alt="beta_2_agonist_icon" />  LABA = long-acting <em>beta_2</em> agonist</td>
<td>Metabolic ADRs: hyperglycemia &amp; hypokalemia.</td>
</tr>
<tr>
<td>Terbutaline (Brethaire)  <img src="https://example.com/beta_2" alt="beta_2_agonist_icon" /> (also fast acting)</td>
<td>Other: hypersensitivity</td>
</tr>
</tbody>
</table>

β2 agonists shouldn’t be used with diuretics, MAOI or tricyclic antidepressants, or with β-blockers.
Direct acting NON-Catecholamines

• Albuterol (Proventil) and Terbutaline (Brethaire) 🕷
  – $\beta_2$ agonist
  – Use: asthma (fast acting bronchodilator)
  – ADRs
    • CV effects, seizures, hypokalemia
  – Use caution in patients with
    • Diabetes, Heart disease, epilepsy, hyperthyroidism
  – Incompatibility issues with
    • MAO-I, TCAs, $\beta$-blockers, diuretics

Terbutaline 🕷 tolbutamide (Orinase) and terbinafine (Lamisil)

Sympathomimetic!

www.bedfordlabs.com
Selective $\beta_2$ Agonists

- **Salmeterol and formoterol**
  - 3rd generation $\beta_2$ agonists (LABA)
  - *1/6 of population has hypersensitive receptor*
    - Highest prevalence among African Americans
    - In this population, Asthma is worsened by $\beta$ agonists
      - *Can cause death* (rebound bronchoconstriction)
      - FDA “Black box” warning
    - Must be Rx’d with corticosteroid to control inflammation
      - Example: Advair Diskus: salmeterol + fluticasone
  - ADRs & cautions
    - Seizures, arrhythmias, adrenal suppression, oral candidiasis, altered taste, staining of teeth. Use with caution in patients with diabetes, glaucoma, hyperthyroidism, liver disease.
Indirect Acting Agents

- **Amphetamine**
  - \(\uparrow\)'s the amount of NE & DA released
  - Blocks reuptake of NE & DA.
  - Direct \(\alpha\) & \(\beta\) effects

CNS stimulants for ADHD include *dextroamphetamine (Adderall)* & *methylphenidate (Ritalin, Concerta)* – both are C-II

<p>|</p>
<table>
<thead>
<tr>
<th>Sympathomimetic!</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\uparrow) BP, HR &amp; (B_t^o)</td>
</tr>
<tr>
<td>(\downarrow) sleep &amp; appetite</td>
</tr>
<tr>
<td>(\text{}) Abuse potential; suicide risk</td>
</tr>
<tr>
<td>(\text{}) Abrupt cessation leads to withdrawal syndrome</td>
</tr>
<tr>
<td>(\text{}) Incompatible with MAO-I’s</td>
</tr>
<tr>
<td>(\text{}) Not for patients with HT, heart defects, arrhythmias, seizures, or depression/mental illness</td>
</tr>
</tbody>
</table>
Sympathomimetic amines in the diet

- Lots of MAO-A in intestines to prevent absorption
- **Tyramine** Beware of when using MAO-Is!
  - Aged cheese, avocados, eggplant, figs, grapes, oranges, vegemite, sauerkraut, shrimp paste, processed or cured meats, all soy products, alcoholic drinks (varies), protein diet supplements, brewer’s yeast
Adrenergic Antagonists

Sympatholytics

• Block $\alpha_1$ & $\alpha_2$ receptors
• Block $\alpha_1$ selectively
• Block $\beta_1$ & $\beta_2$
• Block $\beta_1$ selectively
• Block $\alpha$ & $\beta$ receptors

Sympatholytics tend to cause orthostatic hypotension and sexual dysfunction.
Adrenergic Antagonists

• Sympatholytics
  – Adrenergic antagonists (α and/or β blockers)
  – Ganglionic-blocking agents (anticholinergic agents)
  – Sympathetic neuronal blockers

• Management of
  – CV disease
    • E.g., β- blockers like propranolol
  – Glaucoma
    • E.g., β-blockers like timolol
  – Migraine headache
    • E.g., dihydroergotamine (α, 5-HT & Dopamine receptor blocker) & off label bupropion (NE/5-HT reuptake inhibitor)
  – Urinary retention
    • E.g., α blockers like prazosin or phentolamine (off label)
**Nonselective $\beta$ antagonists** (Block $\beta_1$ & $\beta_2$)

Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karsh, Lippincott, Williams & Wilkins. 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadolol</td>
<td>Hypertension, angina, migraine</td>
</tr>
<tr>
<td>Carteolol</td>
<td></td>
</tr>
<tr>
<td>Penbutolol</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Pindolol</td>
<td></td>
</tr>
<tr>
<td><strong>Propranolol (Inderal)</strong></td>
<td>Hypertension; angina, hypertrophic subaortic stenosis, arrhythmias (e.g., due to digitalis), pheochromocytoma, migraine, stage fright, essential tremor, thyrotoxicosis (off label)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Ventricular arrhythmias, maintaining sinus rhythm with atrial fibrillation</td>
</tr>
<tr>
<td>Timolol</td>
<td>Hypertension; open-angle glucoma</td>
</tr>
</tbody>
</table>

**Propranolol: PO, IV (for arrhythmias)**
**Selective $\beta$ antagonists:** Block only $\beta_1$

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol (Tenormin)</td>
<td>MI, angina, HT</td>
<td>PO, IV</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>Hypertension, ocular hypertension, open-angle glucoma</td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>Supraventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>Metoprolol (Lopressor, Toprol)</td>
<td>HT, angina, MI, Congestive HF- Off label - anxiolytic, hyperthyroidism</td>
<td>PO, IV</td>
</tr>
</tbody>
</table>
General β Blocker Issues

• **Diabetics**
  – ↑ Blood glucose
  – Mask hypoglycemia symptoms

• **Hypotension**
  – Fall hazard

• **↑ Sensitivity to cold**
  – ↓ Circulation in fingers and toes

• **↑ Reaction to allergy shots**

• **Asthmatics**
  – Bronchospasm

• **Thyroid patients**
  – Mask hyperthyroid symptoms
  – PPT thyroid storm

• **Heart patients**
  – Lead to heart failure
    • Especially with CCBs

• **Interfere with lab tests**
  – Glaucoma
    • ↓ intraocular pressure
  – Clinical chem changes
    • ↑ BUN, K+, serum transaminases and alkaline phosphatase

**Boxed warning: rebound angina/MI**
Metoprolol Considerations

⚠️ Incompatible with Amphotericin B.

 cautiously CYP Θ’rs, digoxin, CCBs (diltiazem & verapamil), MAO-I’s, hydralazine, NSAIDs, oral antidiabetic drugs, IV lidocaine, prazosin, rifampin, Beta 2 agonists (albuterol, terbutaline), ma huang

 appréhender Take with food

 ↑ uric acid levels & liver enzymes

⚠️ Bradycardia, heart failure, fatigue, dizziness, nausea

⚠️ Caution in patients with diabetes, asthma or hepatic disease

⚠️ Rebound angina/MI

⚠️ metaproterenol (Alupent)

⚠️ Toprol ⚠️ Topamax (topiramate) & Tegretol (carbamazepine)
**Nonselective α & β antagonists** (Block α & β)
Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karsh, Lippincott, Williams & Wilkins. 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amiodarone</strong></td>
<td>Life threatening ventricular arrhythmias (blocks Na(^+) &amp; K(^+) channels, too - see anti-arrhythmics lecture)</td>
</tr>
<tr>
<td>Bretylium tosylate</td>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>HT, CHF</td>
</tr>
<tr>
<td>Guanadrel</td>
<td>HT not responding to diuretics</td>
</tr>
<tr>
<td>Guanethididine (Ismelin)</td>
<td>HT, renal hypertension</td>
</tr>
<tr>
<td>Labetalol (Normodyne)</td>
<td>Severe HT. Off label for: clonidine withdrawal and pheochromocytoma</td>
</tr>
</tbody>
</table>

**Sympatholytics!**

PO, IV
### Nonselective $\alpha$ antagonists Block $\alpha_1$ & $\alpha_2$

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentolamine (Regitine, Oraverse)</td>
<td>• Dx of pheochromocytoma*, Hypertensive crisis in pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>• Dermal necrosis/ischemia following extravascularization of vasopressive substances (e.g., Epi, NE or DA).</td>
</tr>
<tr>
<td></td>
<td>• <strong>Off label</strong> for clonidine or propranolol withdrawal &amp; for hypertensive crisis due to MAOI/sympathomimetic interaction; ED</td>
</tr>
</tbody>
</table>

*Pheochromocytoma = neuroendocrine tumor of the adrenal medulla that secretes excess Epi and NE. Usually not malignant.
Selective $\alpha$ antagonists: Block $\alpha_1$

Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karsh, Lippincott, Williams & Wilkins. 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>Benign prostatic hyperplasia (BPH)</td>
</tr>
<tr>
<td><strong>Doxazosin (Cardura)</strong></td>
<td>Hypertension (HT) and BPH  PO</td>
</tr>
<tr>
<td>Prazosin</td>
<td>HT and BPH</td>
</tr>
<tr>
<td><strong>Tamsulosin (Flomax)</strong></td>
<td>BPH (not HT!)  PO</td>
</tr>
<tr>
<td>Terazosin</td>
<td>HT and BPH</td>
</tr>
</tbody>
</table>

*Sympatholytics!*

*No longer recommended in HF patients due to increased risk of CHF*
α₁ Antagonist Issues

• Profound hypotension
  – Fall hazard

• Arrhythmias
  – Tachyarrhythmias

• Flushing

• Nausea

• Priapism (α₁ blockers)

Doxazosin

⚠️ Arrhythmias, leukopenia, neutropenia, dizziness, hypotension, sleepiness, abnormal vision, myalgia, nausea, constipation, fluid retention

ℹ️ 1st dose syncope!!

⚠️ doxapram, doxorubicin, doxepin. Cardura
⚠️ coumadin, K-Dur, Cardene and Cordarone