Adrenergic receptor antagonists

- Drugs that have high affinity but no (or low negative or positive) intrinsic activity

- Competitive vs irreversible antagonists
  i.e. phentolamine vs phenoxybenzamine

- Factors that determine the effect of antagonists in vivo
  - absence or presence of intrinsic activity
  - pre-existing “tone” at receptor
  - net effect at pre- vs postsynaptic receptors
  - selectivity for receptor subtype
  - compensatory reflex adjustments
Alpha-adrenergic receptor antagonists

- Clinical applications:
  - Hypertensive crisis pheochromocytoma ADHD excess Rx tyramine crisis (MAO inhibitors)
  - Chronic hypertension
  - Benign prostrate hypertrophy

Pheochromocytoma

Tumor: ↑synthesis, ↑release of NE & EPI into the circulation.
Result: ↑BP, ↑HR → hypertensive crisis
Treatment: - surgical removal for solid tumor
- α- / β-blocker ie. Labetatol
- α-blocker ie, phenoxybenzamine 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
Benign Prostate Hypertrophy (BPH)

Enlarged prostate leads to difficulty in urination
Alpha1-receptor blocker (ie Prazosin) cause prostate relaxation
Relaxed prostate improves urination

Postural (Orthostatic) Hypotension

- Venous return falls, blood pressure falls (>20mmHg SBP, >10mmHg DBP)
- Sympathetic activity increases
  - Constriction of great veins
  - Constriction of arteries (↑ TPR)
  - Increase in heart rate (> 20bpm)

Reflex mediated

No reflex

Reflex
Alpha-adrenergic receptor antagonists

Phenoxybenzamine
- irreversible alpha1-blocker (5-10 fold)
- also block Ach, histamine, serotonin (side effects)
- also inhibit Uptake I & II (side effects)
- ↓ blood pressure, postural hypotension, tachycardia
- useful in long-term & acute pheochromocytoma

Phentolamine & Tolazoline
- non selective $\alpha_1 = \alpha_2$ antagonist activity
- cardiovascular: vasodilation, reflex ↑ HR
- enhance NA release (alpha2-blockade)
- toxicity: hypotension, tachycardia, arrhythmias, myocardial infarction

Alpha-adrenergic receptor antagonists

• Prazosin, Terazosin, Doxazosin (-azosin; competitive)
- selective $\alpha_1$ - $\alpha_2$-receptors (1000 fold)
- cardiovascular effects: reduced peripheral resistance, lowered vascular return, no reflex tachycardia

• Therapy: treat primary hypertension,
  - benign prostrate hypertrophy

Toxicity: postural hypotension, headache, nausea
↓ plasma lipids, dizziness, drowsiness

Yohimbine (herbal, OTC): $\alpha_2$-blocker, for impotence
not clinically available
Cardiovascular effects:
• reduced peripheral resistance
• lowered vascular return
• postural hypotension (main)
• tachycardia (reflex, usually) → arrhythmias

Others:
• headache, dizziness, nausea, drowsiness
• Impotence (Phenoxybenzamine)
• ↓ plasma lipids

Toxicity - Alpha-blockers

Beta-adrenergic receptor antagonists

• Clinically a more useful class of drugs than $\alpha$-adrenoceptor antagonists.

• $\beta$-Adrenoceptor antagonists vary in respect to:

• Relative affinity for beta1- and beta2-adrenoceptors
  - propranolol ($\beta_1$, $\beta_2$) vs atenolol ($\beta_1$)

• Intrinsic $\beta$-activity (ISA): also act as agonists at $\beta$-adrenoceptors, propranolol (no) vs pindolol (yes)

• local anaesthetic activity (LA-action, MSA):
  - their ability to stabilize membranes
  - propranolol (yes) vs atenolol (no)

• lipid solubility: propranolol (high) vs atenolol (low)
Beta-Adrenoceptor Blocking Agents (-olol)
(Drugs A-M are β1-selective exp. Labetalol & Carvedilol)

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anaesthetic Action</th>
<th>Local Solubility</th>
<th>Elimination Half-Life</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β₁</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3-4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6-8 hours</td>
<td>40</td>
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<tr>
<td>Betaxolol</td>
<td>β₁</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14-22 hours</td>
<td>50</td>
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<tr>
<td>Bisoprolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>9-12 hours</td>
<td>80</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
<td>85</td>
</tr>
<tr>
<td>Celiprilol</td>
<td>β₂</td>
<td>Yes¹</td>
<td>No</td>
<td>...</td>
<td>4-5 hours</td>
<td>70</td>
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<tr>
<td>Esmolol</td>
<td>β₂</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
<td>...</td>
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<tr>
<td>Labetalol²</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-5 hours</td>
<td>30</td>
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<tr>
<td>Metoprolol</td>
<td>β₁</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>2-4 hours</td>
<td>50</td>
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<tr>
<td>Nebivolol</td>
<td>β₁</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>14-24 hours</td>
<td>33</td>
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<tr>
<td>Pindolol</td>
<td>β₁</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>5 hours</td>
<td>&gt;90</td>
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<tr>
<td>Propranolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Sotalol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
<td>50</td>
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<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4-5 hours</td>
<td>50</td>
</tr>
</tbody>
</table>

¹Partial agonist effects at β₁ receptors. ²Labetalol also causes α₁-selective blockade. ³Bioavailability is dose-dependent.

Clinical uses: Beta-Blockers - Hypertension

- **Hypertension**: frontline class
  - gradual ↓ TPR in spite of long-term ↓ cardiac output
  - non-selective and β₁-selective drugs are effective

- **Mechanism of action**: Multiple sites
  - CNS action to reduce sympathetic tone
  - block of cardiac β-ARs
  - block of presynaptic β-ARs to ↓ NE release
  - decrease in renin release

---

![Graph showing changes in CO, TPR, and BP over days of treatment](image-url)
Clinical uses: Beta-Blockers

- **Angina (non-selective or β1-selective)**
  - Cardiac: $\downarrow$O$_2$ demand more than O$_2$ supply
  - Exercise tolerance ↑ in angina patients

- **Arrhythmia (β1-selective, LA-action)**
  - $\downarrow$ catecholamine-induced increases in conductivity and automaticity in heart, and $\downarrow$ serum K+ (action in skeletal muscle)

- **Glaucoma (non-selective)**
  - $\downarrow$ aqueous humor formation (Timolol)

- **Congestive Heart Failure (non-selective or β1-selective)**
  - CI: unstable CHF, bronchospasm, depression, bradycardia

- **Other**
  - block of tremor of peripheral origin (β2-AR in skeletal muscle)
  - migraine prophylaxis (mechanism unknown)
  - hyperthyroidism: $\downarrow$ cardiac manifestation (only propranolol)
  - panic attacks, stage fright

---

### Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-selective β,β₂</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carteolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA; long acting; also for glaucoma</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>α-blocking activity</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; α-blocking activity</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>long acting</td>
<td></td>
</tr>
<tr>
<td>Penbutolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA</td>
<td></td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; MSA</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA; prototypical beta-blocker</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>also K-channel blocker</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>primarily used for glaucoma</td>
<td></td>
</tr>
</tbody>
</table>

| **β₁-selective** | | | | | | |
| Acebutolol | X | X | | | ISA |
| Atenolol | X | X | X | X | CI: Pregnancy |
| Betaxolol | X | X | X | | MSA |
| Bisoprolol | X | X | X | X | |
| Esmolol | X | | | | short acting; operative arrhythmia |
| Metoprolol | X | X | X | X | MSA |
**Clinical uses: Beta-Blockers**

- **Angina (non-selective or β1-selective)**
  - Cardiac: \(\downarrow\) O\(_2\) demand more than O\(_2\) supply
  - Exercise tolerance \(\uparrow\) in angina patients

- **Arrhythmia (β1-selective, LA-action)**
  - \(\downarrow\) catecholamine-induced increases in conductivity and automaticity in heart, and \(\downarrow\) serum K\(^+\) (action in skeletal muscle)

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  - panic attacks, stage fright

**Mixed Alpha- and β-Receptor Blockers**

- **Labetalol**
  - hypertensive crisis, chronic hypertension, CHF
  - competitive antagonist at both α- & β-receptors
  - \(\beta1 = \beta2\) activity > \(\alpha\)-activity
  - some intrinsic β-adrenoceptor activity

- **Carvedilol**
  - newest agent
  - no intrinsic β-adrenoceptor activity
  - chronic hypertension, congestive heart failure
**β-Blockers: Untoward Effects, Cautions**

- Supersensitivity: Abrupt withdrawal → Rebound HT, less with β-blockers with partial agonist (ie. pindolol).

- Cardiac: ↓reserve, fatigue, dizziness

- Asthma: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective better

- Diabetes: Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred

- Raynaud D: Decreased peripheral circulation

- CNS: nightmares, mental depression, insomnia

- Elderly: ↓Effectiveness, ↑adverse effects (ie. depression)

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**Dopamine antagonists**

Haloperidol, chlorpromazine:

- used for treatment of: schizophrenia & nausea

- SE: tachycardia, hypo/hypertension

- need to discontinue gradually.
**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 \( \rightarrow \) paranoia, delusions, auditory hallucination. Effects blocked by DA antagonist chlorpromazine.

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

**Quality of transmitter in nerve terminals altered**

- **Direct inhibition of synthesis**
  - Alpha-methyl-p-tyrosine (inhibits tyrosine hydroxylase (rate limiting step in NE synthesis
  - treat pheochromocytoma (acute & chronic)

- **False transmitters (not norepinephrine)**
  - Alpha-methyl-DOPA \( \rightarrow \) alpha-methyl-NE (alpha2-action)
    - Alpha-methyl-m-tyrosine \( \rightarrow \) metaraminol
      - metaraminol also has activity at \( \alpha \)-receptor (\( \alpha \)-NE)
      - Tyramine + MAO inhibition \( \rightarrow \) octopamine
Synthesis of “False Transmitters”

Utilize the same enzymes as those involved in norepinephrine synthesis

Result in changes in the quantity and quality of transmitter in the storage vesicles

Reserpine

- Inhibits NE uptake into storage vesicle from cytosol, "leaky" vesicle (also depletes 5-HT stores)

Use: Antihypertensive (last resort)

Major side effects: lethargy, diarrhea, depression (very long lasting)
Inhibition of transmitter release

- Guanethidine (inhibits release, reuptake inhibitor)
- Bretylium (also K+ channel blocker, some LA action)
- Uses: hypertension (last resort)
- Side effects: diarrhea, nasal congestion, impotence

Dwight Eisenhower

Sympathetic Nervous System Review

- NE = Norepinephrine
- K+ = Potassium
- LA = Local Anesthetic
- α = Alpha
- β = Beta
- PDE = Phosphodiesterase
- COMT = Catechol-O-Methyltransferase
- M = Muscarinic
- D = Dopaminergic
- TCA = Tricyclic Antidepressants

Secondary messengers
- cAMP
- cGMP
- Ca^2+

Receptors and Actions
- β1: Cardiac, smooth muscle
- β2: Smooth muscle, other tissues
- α1: Vascular smooth muscle, blood vessel constriction
- α2: Vascular smooth muscle, blood vessel constriction
- M1: Smooth muscle, bronchioles
- M2: Smooth muscle, gut
- D1: Dopaminergic, brain
- D2: Dopaminergic, brain

Enzymes
- PDE: Phosphodiesterase
- COMT: Catechol-O-Methyltransferase
- MAO: Monoamine Oxidase

Membrane Transporter
- Carrier: Cotransporter (NE reuptake)
- Protein: Molecule transport

Action Potentials
- Action Potential: Neural signal
- Voltage Gated: Sodium, Calcium, Potassium

Membrane Potential
- Resting Potential: Neuron at rest
- Excitation: Increased membrane permeability
- Inhibition: Decreased membrane permeability

Synaptic Transmission
- Synapse: Communication between neurons
- Pre-synaptic: Release of neurotransmitter
- Post-synaptic: Receptor stimulation
- Synaptic Vesicles: Store neurotransmitter

Neurotransmitters
- Acetylcholine (ACh)
- Dopamine (DA)
- Serotonin (5-HT)
- Norepinephrine (NE)
- Glutamate (Glu)
- GABA

Receptors
- alpha1-3: Vascular smooth muscle
- beta1-2: Cardiac, smooth muscle
- D1/D2: Dopaminergic
- M1/M2: Muscarinic

Endogenous Ligands
- Dopamine (DA)
- Norepinephrine (NE)
- Beta-Adrenergic Receptor (β)
- Muscarinic Receptor (M)

Pharmacological Actions
- Sympathomimetics: Stimulate sympathetic nervous system
- Sympatholytics: Inhibit sympathetic nervous system
- Anticholinergics: Block acetylcholine receptors
- β-Blockers: Block β-adrenergic receptors

Pharmacological Properties
- Selectivity: Target specificity
- Potency: Effectiveness of drug
- Duration: Time of action

Adverse Effects
- Cardiac: Bradycardia, hypotension
- CNS: Dizziness, confusion
- Gastrointestinal: Constipation, dry mouth
- Renal: Urinary retention, diuresis
- Other: Sweating, cold extremities

Drug Interactions
- Alpha-blockers: Decrease antihypertensive effect of other drugs
- Beta-blockers: Alter cardiovascular response
- MAO inhibitors: Interact with other drugs

Pharmacokinetics
- Clearance: Rate of drug removal from bloodstream
- Volume of distribution: Amount of drug distributed within body
- Half-life: Time to reduce drug concentration by 50%

Therapeutic Index
- Ratio: Safety margin between therapeutic and toxic doses