Antihypertensive Drugs

What is Hypertension:
A common, incurable, persistent, but usually asymptomatic disease whose treatment provides no obvious benefit.
Introduction

Thirty percent of people with high blood pressure don’t know they have it.

Of all people with high blood pressure, 11 percent aren’t on therapy (special diet or drugs), 25 percent are on inadequate therapy, and 34 percent are on adequate therapy.
Average 14 readings: two per session, taken morning and evening for 7 days.
BP variations

Increased BP variability is associated with increased organ damage and cardiovascular morbidity.

“White Coat” or isolated office hypertension.

Masked hypertension.

Morning surge of BP.

During Sleep: “Non dipping’ and “extreme dipping”.
### Table 11–1 Classification of Hypertension on the Basis of Blood Pressure.

<table>
<thead>
<tr>
<th>Systolic/Diastolic Pressure (mm Hg)</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120/80</td>
<td>Normal</td>
</tr>
<tr>
<td>120–135/80–89</td>
<td>Prehypertension</td>
</tr>
<tr>
<td>≥ 140/90</td>
<td>Hypertension</td>
</tr>
<tr>
<td>140–159/90–99</td>
<td>Stage 1</td>
</tr>
<tr>
<td>≥ 160/100</td>
<td>Stage 2</td>
</tr>
</tbody>
</table>

From the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA 2003;289:2560.
Benefits of Lowering BP

Antihypertensive therapy has been associated with:

- 35% to 40% mean reduction in stroke incidence.
- 20% to 25% reduction in myocardial infarction.
- More than 50% reduction in HF.
Multiplication of risk of coronary heart disease

Number of cases / 1000 over 8 years

- without risk: x1
- hypertension: x2.3
- cholesterol: x4.5
- glucose: x1.5
- smoking: x1.4
- LVH: x1.5
Non-pharmacologic Treatment

Lifestyle Modifications:

- Weight reduction
- Diet rich in potassium and calcium and sodium reduction.
- Dietary Approaches to Stop Hypertension (DASH) eating plan (1600-mg sodium) has effects similar to single drug therapy.
- Physical activity.
Goals of Therapy

Maximal protection against cardiovascular consequences with minimal bother to the patient.

Stroke, coronary, and renal complications increase when BP is vigorously lowered (Why?)
Sites of action of antihypertensive drugs.
Sites of action of antihypertensive drugs.

- CO (Cardiac output)
  - HR (Heart rate)
    - β-blockers
    - CCB (Calcium channel blockers)
  - SV (Stroke volume)
    - SVR (Systolic vascular resistance)
      - Direct innervation
        - α₁-blockers
        - Central α₂-agonists
      - Circulating regulators
        - α₁-blockers
        - Central α₂-agonists
        - ACE inhibitors
        - AT₁ antagonists
    - Local regulators
      - Endothelin antagonists
      - Sodium nitroprusside
      - ACE inhibitors
      - AT₁ antagonists

- BP (Blood pressure)
  - CCB (Calcium channel blockers)

- Contractility
  - Preload
    - β-blockers
    - CCB (Calcium channel blockers)

- Venous tone
  - α₁-blockers
  - Sodium nitroprusside
  - ACE inhibitors
  - AT₁ antagonists

- Intravascular volume
  - Na⁺/H₂O retention
    - Diuretics
    - ACE inhibitors
    - AT₁ antagonists
**Table 27-5 Classification of Antihypertensive Drugs by Their Primary Site or Mechanism of Action**

**Diuretics (Chapter 25)**

1. Thiazides and related agents (hydrochlorothiazide, chlorthalidone, chlorothiazide, indapamide, methylclothiazide, metolazone)
2. Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)
3. K⁺-sparking diuretics (amiloride, triamterene, spironolactone)

**Sympatholytic drugs (Chapter 12)**

1. β receptor antagonists (metoprolol, atenolol, betaxolol, bisoprolol, carteolol, esmolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, timolol)
2. α receptor antagonists (prazosin, terazosin, doxazosin, phenoxybenzamine, phentolamine)
3. Mixed α-β receptor antagonists (labetalol, carvedilol)
4. Centrally acting adrenergic agents (methyldopa, clonidine, guanabenz, guanfacine)
5. Adrenergic neuron blocking agents (guanadrel, reserpine)

**Ca²⁺ channel blockers** (verapamil, diltiazem, nisoldipine, felodipine, nicardipine, isradipine, amlodipine, clevidipine, nifedipine²)

**Angiotensin-converting enzyme inhibitors** (Chapter 26; captopril, enalapril, lisinopril, quinapril, ramipril, benazepril, fosinopril, moexipril, perindopril, trandolapril)

**AngII receptor antagonists** (Chapter 26; losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan, olmesartan)

**Direct Renin Inhibitor** (Chapter 26; aliskiren)

**Vasodilators**

1. Arterial (hydralazine, minoxidil, diazoxide, fenoldopam)
2. Arterial and venous (nitroprusside)
## Hemodynamic Effects of Antihypertensive Drugs

<table>
<thead>
<tr>
<th></th>
<th>HEART RATE</th>
<th>CARDIAC OUTPUT</th>
<th>TOTAL PERIPHERAL RESISTANCE</th>
<th>PLASMA VOLUME</th>
<th>PLASMA RENIN ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>−↓</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Sympatholytic agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrally acting</td>
<td>−↓</td>
<td>−↓</td>
<td>↓</td>
<td>−↑</td>
<td>−↓</td>
</tr>
<tr>
<td>Adrenergic neuron blockers</td>
<td>−↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>−↑</td>
</tr>
<tr>
<td>α receptor antagonists</td>
<td>−↑</td>
<td>−↑</td>
<td>↓</td>
<td>−↑</td>
<td>↔</td>
</tr>
<tr>
<td>β receptor antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ISA</td>
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<td>−↓</td>
<td>−↑</td>
<td>↓</td>
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<tr>
<td>ISA</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>−↑</td>
<td>−↓</td>
</tr>
<tr>
<td><strong>Arteriolar vasodilators</strong></td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Ca²⁺ channel blockers</td>
<td>↓ or ↑</td>
<td>↓ or ↑</td>
<td>↓</td>
<td>−↑</td>
<td>−↑</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
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<tr>
<td><strong>AT₁ receptor antagonists</strong></td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Renin inhibitor</strong></td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↓ (but [renin] ↑)</td>
</tr>
<tr>
<td>Drug</td>
<td>Half-life (h)</td>
<td>Bioavailability (percent)</td>
<td>Suggested Initial Dose</td>
<td>Usual Maintenance Dose Range</td>
<td>Reduction of Dosage Required in Moderate Renal Insufficiency</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>---------------------------</td>
<td>------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>35</td>
<td>65</td>
<td>2.5 mg/d</td>
<td>5–10 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Atenolol</td>
<td>6</td>
<td>60</td>
<td>50 mg/d</td>
<td>50–100 mg/d</td>
<td>Yes</td>
</tr>
<tr>
<td>Benazepril</td>
<td>0.6²</td>
<td>35</td>
<td>5–10 mg/d</td>
<td>20–40 mg/d</td>
<td>Yes</td>
</tr>
<tr>
<td>Captopril</td>
<td>2.2</td>
<td>65</td>
<td>50–75 mg/d</td>
<td>75–150 mg/d</td>
<td>Yes</td>
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<tr>
<td>Clonidine</td>
<td>8–12</td>
<td>95</td>
<td>0.2 mg/d</td>
<td>0.2–1.2 mg/d</td>
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<tr>
<td>Diltiazem</td>
<td>3.5</td>
<td>40</td>
<td>120–140 mg/d</td>
<td>240–360 mg/d</td>
<td>No</td>
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<tr>
<td>Guanethidine</td>
<td>120</td>
<td>3–50</td>
<td>10 mg/d</td>
<td>25–50 mg/d</td>
<td>Possible</td>
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<tr>
<td>Hydralazine</td>
<td>1.5–3</td>
<td>25</td>
<td>40 mg/d</td>
<td>40–50 mg/d</td>
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<td>Hydrochlorothiazide</td>
<td>12</td>
<td>70</td>
<td>25 mg/d</td>
<td>25–50 mg/d</td>
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<tr>
<td>Lisinopril</td>
<td>12</td>
<td>25</td>
<td>10 mg/d</td>
<td>10–20 mg/d</td>
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<td>Losartan</td>
<td>1–2³</td>
<td>36</td>
<td>50 mg/d</td>
<td>25–100 mg/d</td>
<td>No</td>
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<tr>
<td>Methyldopa</td>
<td>2</td>
<td>25</td>
<td>1 g/d</td>
<td>1–2 g/d</td>
<td>No</td>
</tr>
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<td>Metoprolol</td>
<td>3–7</td>
<td>40</td>
<td>50–100 mg/d</td>
<td>200–400 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>4</td>
<td>90</td>
<td>5–10 mg/d</td>
<td>40 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>12</td>
<td>Nd⁴</td>
<td>5 mg/d</td>
<td>10–40 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>2</td>
<td>50</td>
<td>30 mg/d</td>
<td>30–60 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Prazosin</td>
<td>3–4</td>
<td>70</td>
<td>3 mg/d</td>
<td>10–30 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3–5</td>
<td>25</td>
<td>80 mg/d</td>
<td>80–480 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Reserpine</td>
<td>24–48</td>
<td>50</td>
<td>0.25 mg/d</td>
<td>0.25 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Verapamil</td>
<td>4–6</td>
<td>22</td>
<td>180 mg/d</td>
<td>240–480 mg/d</td>
<td>No</td>
</tr>
</tbody>
</table>
Diuretics (Saluretics)

- Widely recommended as first-line therapy, especially in the elderly, the obese, and black patients.
- Better at reducing coronary heart disease, HF, stroke, and mortality.
- Inexpensive.
- Combine well with others.
- Lower doses, with sodium restriction, cause fewer metabolic side effects, but retain antihypertensive activity.
- All have same efficacy in lowering BP, although not same diuretic activity.
Diuretics (Saluretics)

Early Effects (3-4 days):
- Diuresis lowers blood volume and cardiac output.
- Mainly affects the systolic BP.

Late Effects (3-4 weeks):
- Decreased Na⁺ & Cl⁻, lowers blood vessel contractility. Appear even with low doses.

Increase Plasma Renin

Side Effects:
Diuretics (Saluretics)

Thiazide diuretics:

Effective in mild and moderate Ht with normal renal and heart function.

- Hydrochlorothiazide.
- Chlorthalidone: long acting.
- Bendrofluazide.
- Indapamide: vasodilating and lipid neutral. Also induces regression of LVH.
Diuretics (Saluretics)

Loop Diuretics:

Needed in severe Ht, in renal insufficiency, and in heart failure or cirrhosis.

- Furosemide: not ideal, short acting.
- Torsemide: free of metabolic side effects.

Potassium-sparing diuretics:

Useful in heart failure.

- Spironolactone:
- Eplerenone.
- Ameloride.
- Triamterene
VASODILATORS

- Work directly on arterial blood vessels, or veins (organic nitrates and nitroprusside).
- Actions not antagonized by known blockers.
- Reduce peripheral resistance, which will elicit compensatory mechanisms leading to tolerance, resistance or pseudoresistance.
- Usually other drugs are combined with vasodilators to avoid this problem.
Compensatory responses to vasodilators

Vasodilator drugs

Decreased systemic vascular resistance

Decreased arterial pressure

Increased renin release

Increased angiotensin II

Increased systemic vascular resistance

Increased heart rate

Increased cardiac contractility

Decreased venous capacitance

Increased cardiac output

Increased arterial pressure

Increased sympathetic nervous system outflow

Increased renal sodium excretion

Increased aldosterone

Sodium retention, increased plasma volume

Decreased renal sodium excretion


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<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release of nitric oxide from drug or endothelium</td>
<td>Nitroprusside, hydralazine, nitrates, histamine, acetylcholine</td>
</tr>
<tr>
<td>Reduction of calcium influx</td>
<td>Verapamil, diltiazem, nifedipine</td>
</tr>
<tr>
<td>Hyperpolarization of smooth muscle membrane through opening of potassium channels</td>
<td>Minoxidil, diazoxide</td>
</tr>
<tr>
<td>Activation of dopamine receptors</td>
<td>Fenoldopam</td>
</tr>
</tbody>
</table>
Hydralazine:

- Oldest vasodilator (1950s), was withdrawn and then came back.
- Arteriolar dilator, works by release of NO.
- Tachyphylaxis (Tolerance or Peusdoresistance).
- Activates baroreceptor reflex.
- Metabolized by acetylation.
- Drug-induced lupus syndrome.
- Other side effects.
- Replaced by CCBs.
- Used in heart failure, combined with isosorbide dinitrate.
VASODILATORS

Diazoxide:
- Thiazide derivative, but not a diuretic.
- Potent arterial dilator, works by opening potassium channels.
- Causes excessive hypotension.
- Used in emergencies by rapid I.V. bolus injection.
- Rapidly bound to albumin.
- Onset 10-30 seconds.
- Duration 2-4 hours.
- Does not require constant monitoring.
VASODILATORS

Sodium Nitroprusside:

- Cyanide-containing molecule.
- Useful in emergencies, surgery and heart failure.
- Relaxes both arterial and venous smooth muscle, works by release of NO.
- No excessive reflex increase in cardiac output.
- Might increase C.O. if there is failure.
VASODILATORS

Sodium Nitroprusside:
- Short half life.
- Action is immediate, requires constant monitoring in ICU.
- Drug is light sensitive.
- Thiocyanate levels and acid-base balance: weakness, nausea, tinnitus, flushing, lactic acidosis and anoxia.
Minoxidil:

- K+ channel-opener: increases efflux leading to hyperpolarization.
- Prolonged arterial relaxation.
- Superior to hydralazine.

For severe intractable hypertension, or renal insufficiency, usually in combination with a diuretic and β blocker.

- Hypertrichosis, so useful for baldness.
- Pericarditis.
Fenoldopam:

- Dopamine D₁ agonist, which results in vasodilation, renal vessel dilation, and natriuresis.
- Rapidly metabolized, short acting.
- Used by continuous infusion in emergencies or postoperatively.
Calcium Channel Blockers

More effective than others in protection against stroke.

Primarily act to reduce PVR, aided by at least an initial diuretic effect, especially with the short-acting DHPs.

Effective in the elderly.

Equally effective in blacks and nonblacks.

Cause no metabolic disturbances
Calcium channel blockers

Phenylalkylamines
- Verapamil

Benzothiazepines
- Diltiazem

Dihydropyridines

1st generation
- Nifedipine

2nd generation
- Isradipine
- Nicardipine
- Felodipine

3rd generation
- Amlodipine
<table>
<thead>
<tr>
<th></th>
<th>PVR</th>
<th>HR</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>- -</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>(Reflexly)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>- -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Verapamil</td>
<td>- -</td>
<td>- -</td>
<td>--</td>
</tr>
</tbody>
</table>
Angiotensin - Converting Enzyme Inhibitors (ACEI)

Angiotensin II:
- Potent vasoconstrictor by itself.
- Facilitates release of NE.
- Central actions to increase BP.
- Promotes release of aldosterone.
- Regulates tubular function.
- Regulates intra-renal blood flow.
Angiotensin - Converting Enzyme Inhibitors (ACEI)

- Inhibit ACE in the lungs.
- Also inhibit kinin metabolism.
Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system.

Angiotensinogen

\[ \text{Renin} \quad \longrightarrow \quad \text{Angiotensin I} \quad \longrightarrow \quad \text{Angiotensin-converting enzyme (kininase II)} \quad \longrightarrow \quad \text{Angiotensin II} \quad \longrightarrow \quad \text{Vasoconstriction} \]

- ARBs

\[ \text{Increased peripheral vascular resistance} \]

\[ \text{Increased blood pressure} \]

\[ \text{Aldosterone secretion} \quad \longrightarrow \quad \text{Increased sodium and water retention} \]

\[ \text{Increased blood pressure} \]

\[ \text{inactive metabolites} \]

\[ \text{Increased prostaglandin synthesis} \]

\[ \text{Increased peripheral vascular resistance} \]

\[ \text{Decreased blood pressure} \]

Kininogen

\[ \text{Kallikrein} \quad \longrightarrow \quad \text{Bradykinin} \quad \longrightarrow \quad \text{Vasodilation} \]

Aliskiren

ACE inhibitors

Spironolactone, eplerenone
Angiotensin - Converting Enzyme Inhibitors (ACEI)

- Captopril  -------------- Prototype.
- Enalapril
- Quinapril
- Lisinopril.
- Benazepril
- Fosonopril

All are similarly effective

Might differ in toxicity
Angiotensin - Converting Enzyme Inhibitors (ACEI)

**Therapeutic Benefits:**

- Effective in high-renin hypertension (20%), HF and Ischemic Heart Disease.
- Do not increase HR.
- Useful in diabetic nephropathy by dilating efferent arterioles thus reducing intraglomerular pressure and consequently protects against progressive glomerulosclerosis.
- No need for a diuretic but can be added.
- Can be combined with CCBs.
- Should not be combined with Beta blockers.
- No metabolic effects.
- * Contraindicated in pregnancy and bilateral renal artery stenosis.
Angiotensin - Converting Enzyme Inhibitors (ACEI)

Side Effects:

Captopril is SH containing drug, so very toxic (bone marrow suppression, disguesia, proteinuria, allergic skin rash, fever).

- Hypotension (First Dose Phenomena) especially with renovascular hypertension.
- K+ retention, especially in the presence of renal dysfunction or when combined with K+ sparing diuretics or ARBs.
- Cough (10% of patients).
- Angioedema.
Angiotensin II Receptor Blockers (AT-1)

- Result in more complete inhibition of angiotensin actions (Chymase ?) with no effects on bradykinins.
- May be only indicated when ACEI are intolerable.
- Most expensive, but fastest growing class of antihypertensive drugs.
- Free of side effects, especially cough.
- May be better than ACEI in protection against stroke (activation of AT-2 receptor facilitates collateral vessels and neuronal resistance).
Angiotensin II Receptor Blockers (AT-1)

- Losartan.
- Valsartan.
- Candesartan.
- Irbesartan.
- Telmisartan (additional peroxisome proliferator-activated receptor-\(g\) agonist activity).
- Eprosartan.
Renin Enzyme Inhibitors

- Aliskiren.
Sympatholytics or Adrenergic Blockers

- **Alpha Adrenergic Antagonist**
  - Non selective Antagonists
  - $\alpha_1$ -Selective Antagonists.

- **Beta Adrenergic Blockers**

- **Adrenergic Neurone Blockers.**

- **Ganglionic Blockers**
Non selective Alpha Adrenergic Antagonist

- **Phentolamine**
- **Phenoxybenzamine**
  - Block both $\alpha_1$ and $\alpha_2$ receptors, so cause reflex tachycardia and increased contractility.
  - Used only for pheochromocytoma.
**α1**-selective Alpha Adrenergic Antagonists

Prazosin

Terazocin

Doxazosin

First - Dose Phenomenon.

All are free of metabolic effects, but can cause drowsiness, diarrhea, postural hypotension, tachycardia, and tolerance due to fluid retention.

Effective in moderate hypertension as well as benign prostatic hypertrophy.
Beta Adrenergic Blockers

Antihypertensive Mechanisms:

1. Decrease HR, SV, and consequently C.O.
2. Decrease Rennin Release
3. Central Action
4. Inhibit NE release
Beta Adrenergic Blockers

Preparations: 30

- **Propranolol**: Prototype, 1957
- **Timolol**: Lipophilic
- **Nadolol**: Long acting
- **Pindolol**: ISA
- **Acebutolol**: ISA
- **Esmolol**: Short half life
- **Metoprolol**: $\beta_1$ selective
- **Atenolol**: $\beta_1$ selective
- **Betaxolol**: $\beta_1$ selective
- **Bisoprolol**: $\beta_1$ selective
Beta Adrenergic Blockers

**Therapeutic Effectiveness:**
- Effect not immediate.
- High - rennin hypertension
- Combination or monotherapy
- Hyperkinetic hearts
- Used in other cardiovascular conditions
- Ineffective in blacks
- No postural hypotension
Beta Adrenergic Blockers

Side Effects:

- Bronchospasm, especially with the non-selective
- Heart Failure?
- CNS: fatigue, depression, impotence, etc
- Impair lipid and glucose metabolism
- Masked hypoglycemia!!!
- Claudication
- Withdrawal Syndrome
Vasodilating Beta Adrenergic Blockers

- **Labetalol:**
  - $\beta$, $\alpha_1$ (20% of $\beta$) antagonist & $\beta_2$ partial agonist.
  - Useful for pheochromocytoma and emergencies.

- **Carvedilol:**
  - $\beta$, $\alpha_1$ (10% of $\beta$) antagonist.

- **Esmolol:**
  - $\beta_1$ selective, rapidly metabolized.
  - Used by continuous IV infusion.

- **Nebivolol**
Adrenergic Neurone Blockers

Guanethidineline
Bethanidine
Debrisoquin
Guanadrel

- Hydrophilic.
- Uptake 1.
- Block NE release.
- Displace NE from vesicles ------- MAO.
- Cause depletion of NE.
Life Cycle of Norepinephrine
Adrenergic Neurone Blockers

Reserpine (Rauwolfia Alkaloids):

- Lipophilic
- Binds to the sympathetic vesicles.
- Prevents DA uptake into vesicles.
- Amines are metabolized by MAO.
- Depletes: NE, 5HT, ACTH, DA.
- Old fashioned, slow onset and offset, very cheap.
Ganglionic Blockers

Trimethaphan
Pentolinium
Mecamylamine

- Block transmission in both sympathetic and parasympathetic systems.
- Act immediately and are very efficacious.
- Effect rapidly reversed, so used for short term control of BP, e.g. intraoperatively or emergency.
- Many side effects.
Table 16-2. Predominant Autonomic Tone at Various Neuroeffector Junctions and the Effect Produced by Ganglionic Blockade

<table>
<thead>
<tr>
<th>Site</th>
<th>Effect of ganglionic blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tissues predominantly under parasympathetic (cholinergic) tone</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardium</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Atrium; S-A node</td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Iris</td>
<td></td>
</tr>
<tr>
<td>Ciliary muscle</td>
<td>Cycloplegia</td>
</tr>
<tr>
<td>GI tract</td>
<td>Decrease in tone and motility; constipation</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>Dry mouth</td>
</tr>
<tr>
<td><strong>Tissues predominantly under sympathetic (adrenergic) tone</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardium</td>
<td>Decrease in contractile force</td>
</tr>
<tr>
<td>Ventricles</td>
<td></td>
</tr>
<tr>
<td>Blood vessels</td>
<td></td>
</tr>
<tr>
<td>Arterioles</td>
<td>Vasodilation; increase in peripheral blood flow; hypotension</td>
</tr>
<tr>
<td>Veins</td>
<td>Vasodilation; pooling of blood; decrease in venous return; decrease in cardiac output</td>
</tr>
<tr>
<td>Sweat glands*</td>
<td>Decrease in secretion</td>
</tr>
</tbody>
</table>

*Anatomically sympathetic; transmitter is ACh.
Centrally Acting Antihypertensive Drugs

Vasomotor Center:

- $\alpha$ Receptor activation decreases BP
- $\beta$ Receptor activation increases BP

Nucleus Tractus Solitarius
Nucleus Ambiguus
Rostral Ventral Medulla
Autonomic and hormonal control of cardiovascular function

VASOMOTOR CENTER

Parasympathetic autonomic nervous system

Sympathetic autonomic nervous system

Baroreceptors

Peripheral vascular resistance

Heart rate

Contractile force

Venous tone

Mean arterial pressure

Cardiac output

Stroke volume

Venous return

Blood volume

Hormonal feedback loop

Renal blood flow/pressure

Renin

Angiotensin

Aldosterone

Automonic feedback loop


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Centrally Acting Antihypertensive Drugs

Common Properties:
- Cross BBB.
- Reduce preganglionic sympathetic activity.
- Orthostasis is unusual, due to preservation of peripheral sympathetic activity.
- CNS side effects.

Nov-14
Munir Gharibe MD, PhD, MHPE
Centrally Acting Antihypertensive Drugs

1. Propranolol
2. Reserpine.
3. \(\alpha\)-Methyl Dopa:

Old drug, thought to work by forming a pseudo transmitter which works peripherally.

Central \(\alpha\) agonist.

\(\alpha\) MD------ \(\alpha\) MDA ------- \(\alpha\) MNE.

Lowers BP but not CO or renal blood flow.

Can cause lactation and positive Coomb’s test.

Safe in pregnancy.
4. Clonidine:

- Imidazoline derivative, tried initially as a nasal decongestant.
- Central $\alpha$ agonist.
- I.V: Biphasic Effect: peripheral then central actions.
- Oral.
- Transdermal Patch(7 days).
Step Therapy of Hypertension

- **Stage A**: High risk with no symptoms
- **Stage B**: Structural heart disease, no symptoms
- **Stage C**: Structural disease, previous or current symptoms
- **Stage D**: Refractory symptoms requiring special intervention

- Hospice
- VAD; transplantation
- Inotropes
- Aldosterone antagonist, nesinidine
- Consider multidisciplinary team
- Revascularization, mitral-valve surgery
- Cardiac resynchronization if bundle-branch block present
- Dietary Na⁺ restriction, diuretics, and digoxin
- ACE inhibitors and β blockers in all patients
- ACE inhibitors or AT₁ blockers in all patients; β blockers in selected patients
- Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or AT₁ blockers in some patients
- Risk-factor reduction, patient and family education

Source: Brunton LL, Lazo JS, Parker KL; Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 11th Edition; http://www.accessmedicine.com

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Causes of Resistant Hypertension

- Improper blood pressure measurement, “White Coat Hypertension”.
- Noncompliance.
- Psychological stresses, secondary hypertension, sleep disorders
- Volume overload and pseudotolerance.
- Excess sodium intake
- Volume retention from kidney disease.
- Inadequate diuretic therapy.
Causes of Resistant Hypertension

- Inadequate doses.
- Inappropriate combinations.
- NSAID; cyclooxygenase 2 inhibitors.
- Cocaine, amphetamines, other illicit drugs.
- Sympathomimetics, e.g. decongestants, anorectics.
Causes of Resistant Hypertension

- Oral contraceptives
- Adrenal steroids
- Cyclosporine
- Erythropoietin
- Licorice (including some chewing tobacco)
- Excess alcohol intake.
Figure 16.4
Munir Gharabeh MD, PhD, MHPE
Treatment of hypertension in patients with concomitant diseases.