### Agents used in HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hypertension</th>
<th>CHF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindications/Cautions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>CHF (unstable CHF, bronchospasm, significant bradycardia); or in diabetes, asthma (use β1-selective), depression, rebound HT</td>
</tr>
<tr>
<td>Ca++-Channel blockers</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>CHF, Gingival hyperplasia, reflex tachycardia, constipation</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>Low GFR, renal stenosis, glossitis, tetrogenic, cough (ACEI), taste, ↑renal mechanics, angioedema</td>
</tr>
<tr>
<td>Diuretics</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>Low GFR, hypokalemia → CG; glucose intolerance → diabetes</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>✔ ✔</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>Many Rx interactions, low TI, [K+]↑, important, low K+→↑toxicity</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>Flushing, dizziness, headache, reflex tachycardia, combo Rx</td>
</tr>
<tr>
<td>Na+ Channel blockers</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>Effects enhanced in depolarized tissue, damaged tissue. Phase 0</td>
</tr>
<tr>
<td>Nitrates</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>Tolerance, flushing, dizziness, headache, reflex tachycardia</td>
</tr>
</tbody>
</table>
Raynaud’s Syndrome

- Excessive sympathetic tone in nerves supplying hands and feet. Minor cold, or even thought of cold, causes pronounced vasoconstriction that can be severe enough to cause necrosis of tissues.
- Discoloration of the fingers and/or toes when the patient is exposed to changes in temperature (cold or hot) or emotional events.
- Abnormal spasm of blood vessels causes diminished blood supply.
- Initially, the digit(s) turn white because of diminished blood supply.
- Then turn blue because of prolonged lack of oxygen.
- Finally, the blood vessels reopen, causing a local “flushing” phenomenon, which turns the digit(s) red.
- Three-phase color sequence (white to blue to red), most often upon exposure to cold temperature.
- Treatment if severe: Ca++ blockers.

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.
Renal Stenosis

Primary cause of 2° HT

Decreased renal blood flow
- ↓ renal BP
- ↑ renin release
- ↑ aldosterone
- ↑ Na+, water retention
- ↑ systemic BP

Treatment
- insertion of stent

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. Labetalol
- 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 prostrate leads to difficulty in urination
Alpha-receptor blocker (ie Prazosin) cause prostrate relaxation
Relaxed prostrate improves urination

Glaucoma

Increased intraocular 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)

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
Miosis, Mydriasis & Cycloplegia

Miosis: pin point pupils
Mydriasis: dilated pupils (bella-donna agents)
Cycloplegia: loss of accommodation (blurred vision)

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Drug</th>
<th>Pupillary Response</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Sympathomimetic ie. phenylephrine</td>
<td>Dilation (mydriasis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Parasympathomimetic ie. pilocarpine</td>
<td>Constriction (miosis)</td>
</tr>
<tr>
<td>Normal</td>
<td>Parasympatholytic ie. atropine</td>
<td>Mydriasis, cyclopegia</td>
</tr>
<tr>
<td>Horner’s syndrome</td>
<td>Cocaine 4-10%</td>
<td>No dilation</td>
</tr>
<tr>
<td>Preganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
<td>Dilation</td>
</tr>
<tr>
<td>Postganglionic Horner’s</td>
<td>Hydroxyamphetamine</td>
<td>No dilation</td>
</tr>
<tr>
<td>Adie’s pupil</td>
<td>Pilocarpine 0.05-0.1%</td>
<td>Constriction</td>
</tr>
<tr>
<td>Normal</td>
<td>Opioids (oral or intravenous)</td>
<td>Pinpoint pupils</td>
</tr>
</tbody>
</table>

Eye - Horner’s Syndrome

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

Horner’s Syndrome (note sagging left eyelid and miosis)
Adies Pupil & Iritis

**Adies Pupil**

**Iritis**

Muscarinic blocker to dilate pupil to prevent attachment to lens. Steroid to treat inflammation.

Fig. 12.9  Tonic pupil: the left pupil is dilated compared to the right.

This 31 year old woman had been aware of pupillary asymmetry for some time. She presented with left facial numbness, the etiology of which was not established. It rapidly resolved. Examination showed a typical left tonic pupil. The triceps and ankle jerks were depressed.

Botulinum toxin -Action

Inhibits Ach release
Single treatment can last 3-4 months

Exposure to Botulinum Toxin

**Before**

Facial wrinkles, FDA Approval: Apr 2002

**After**
Botulinum toxin - Strabismus

Parkinson’s Disease

- general population 1:1000, over 60 1:75
- tremor, stiffness, or clumsiness,
- difficulty walking, fatigue, depression
- usually involve one side
- destruction of dopaminergic neurons
- elevated cholinergic activity

**Treatment:**
- MAO inhibitors:
- Dopamine agonists: bromocriptine, pramipexole
- L-Dopa
- Anticholinergics: benzotropine
- Decarboxylase inhibitor: carbidopa
- COMT inhibitor
Tyramine Interaction with MAO Inhibitors

Can cause hypertensive crisis (↑BP, ↑HR)

Aged cheese & red wine are rich in tyramine

MAOI and Tyramine Crisis

↑Blood pressure, ↑Heart rate

Treatment: α-blocker or labetalol (α-, β-blocker)

Normally dietary tyramine is metabolized by MAO

With MAO inhibition, octopamine is produced and stored in vesicles with NE

Aged cheese, red wine are rich in tyramine
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

Chronic Obstructive Pulmonary Disease (COPD)

Features:
- Damage to lungs
- Develops slowly
- No cure
- 4th US Cause of death
- Smoking common cause

Treatment (inhaled):
- Beta2-agonists
- M-receptor blockers
- Glucocorticosteroids
- Oxygen
**Asthma**

- **Albuterol**
- **Terbutaline, Metaproterenol**

- **β₂-Selective agonists**
  - bronchodilation
  - Inhalation vs oral
  - less side effects

- **Ritodrine**
  - premature labor

**Anaphylaxis**

- **Epinephrine**

  - bronchoconstriction
  - ↑ secretions
  - ↓ blood pressure

- **Epinephrine**
  - bronchodilation
  - vasoconstriction

**Neurologic**
- Dizziness, weakness, syncope, seizures
- Pruritus, conjunctival injection, lacrimation
- Pruritus, congestion, wheezing, clear rhinorrhea

**Upper airway**
- Hoarseness, stridor, epiglottitis or laryngeal edema, cough, complete obstruction

**Cardiovascular**
- Tachycardia, hypotension, arrhythmias, cardiac arrest

**Lower airway**
- Chest tightness, dyspnea, tachypnea, use of accessory muscles, cyanosis, bronchospasm, respiratory arrest

**Skin**
- Sensation of warmth, flushing, erythema, general pruritus, urticaria, angioedema

**Gastrointestinal**
- Nausea, vomiting, cramping, abdominal pain, diarrhea, suble biliary
Anaphylaxis – Mechanism

Type I (Anaphylaxis) Hypersensitivity

(a) First allergen exposure

[Diagram showing the mechanism of Type I (Anaphylaxis) hypersensitivity]

(b) Second allergen exposure

[Diagram showing the mechanism of Type I (Anaphylaxis) hypersensitivity]

β-Blockers - Frontline agents

α-Blockers - Hypertensive crisis, special circumstances

D_1a^-Agonist - Hypertensive crisis iv, ie. Fenoldopam

α_2^-Agonists - Useful, not frontline ie. Clonidine

Reserpine - Resistant hypertension, significant side effects, rarely used

Guanethidine - Resistant hypertension, significant side effects, rarely used

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>and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120–139</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥100</td>
</tr>
</tbody>
</table>

*Requires three measurements (repeat visits)
BP lowest in the morning → ↑ during the day
CV – USA Prevalence of Hypertension (>=140/90 mmHg)

- USA: 40-60 million HT
- ↓Na⁺ → ↓rise rate

Hypertension Is Largely Uncontrolled

- Whites (n=32.8 million): 31% undiagnosed, 17% acknowledged, 24% treated, 25% controlled
- African Americans (n=5.7 million): 27% undiagnosed, 17% acknowledged, 24% treated, 25% controlled
- Mexican Americans (n=1.3 million): 41% undiagnosed, 19% acknowledged, 15% treated, 25% controlled

Awareness, Treatment, Control of Hypertension in Whites, African Americans, and Hispanics
### CV - Antihypertensive Agents

1. Diuretics (1st of equals) — eg. hydrochlorothiazide
2. Renin / AgII (ACEI, ARBs) — eg. captopril, losartan
3. Beta-antagonists — eg. propranolol
4. Calcium-antagonists — eg. nifedipine, verapamil
5. Alpha-antagonists — eg. prazosin
6. Potassium sparing — eg. spironolactone
7. Vasodilators — eg. hydralazine, nitroprusside
8. Central acting alpha2-agonists: — eg. clonidine, α-methyl dopa
9. Inhibit/reduce NE release — eg. guanethidine, reserpine
10. Ganglionic blockers — eg. mecamylamine

### BP Daily Fluctuation

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Event</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>6AM</td>
<td>Gets up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Arrives at the company</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6PM</td>
<td>Leaves the company</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Dinner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6AM</td>
<td>Sleeps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Morning</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fluctuation Throughout a Day**

(Case: Male, 35 years of age)
Postural (Orthostatic) Hypotension

- Venous return falls
- Blood pressure falls
- Sympathetic activity increases
  - Constriction of great veins
  - Constriction of arteries (↑ TPR)
  - Increase in heart rate

BP (mmHg)

95 100 95

no reflex

reflex

BP (mmHg)

95 100 95

195 105

CV - Baroreceptor Reflex Arc

- oppose direct change in BP
- bidirectional, responds to ↑ or ↓ in BP
- not concerned with HR
- not concerned with pulse pressure

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Figure 1. Location and innervation of arterial baroreceptors
Congestive Heart Failure (CHF)

CO inadequate for body demand of oxygen (demand-supply)
2.5 million in USA, 50% mortality @ 5 year
350,000 new cases each year

Compensated heart failure:
- resting cardiac function, OK; stress or exercise, No

Congestive heart failure (CHF, uncompensated):
- resting cardiac function inadequate

CHF Hemodynamic Changes

Blood pressure is well maintained:
- ↑ sympathetic tone (tachycardia)
- ↓ parasympathetic tone
- activation of renin-angiotensin system
  - ↑ blood volume
  - ↑ vasopressin release

Consequences:
- ↓ force of contraction
- ↓ CO, ↑ TPR, ↓ stroke volume
- ↑ venous pressure
- ↓ tissue perfusion
- cardiac hypertrophy
- Na+ & water retention
- edema
CV - Angina Pectoris

- Chronic disease (3 million in USA)
- Intermittent attacks of chest pain, left shoulder and arm

Need to improve ratio
Coronary blood flow / cardiac work or Cardiac O2 supply / O2 demand

A. Typical (Stable, Effort) angina:
   - ↑ O₂ demand - fixed supply

B. Variant (Prinzmetal's) angina:
   - ↓ O₂ supply - unchanged demand
     - ie. at rest, coronary spasm (PGs?)

C. Unstable angina:
   - ↓ O₂ supply, fat buildup or clot

D. Microvascular angina (Syndrome X):
   - atherosclerosis in small coronary a.

Wild Mushrooms - Amanita

10,000 cases per year
Muscarine poisoning
5,000 mushroom species
100 “bad”, 10 “deadly”
Mainly atropine
Devil’s apple
Stink weed
Devil’s cherries

Mainly scopolamine & hyoscyamine
Thorn apple
Jimson weed

Deadly Nightshade
“Belladonna”
Approx 5,000 cases per yr

Hyperkalemia

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

[K+]

Hyperkalemia
Malignant Hyperthermia

- more likely with halothane
- 60% mortality
- $\uparrow$Ca** $\rightarrow$ $\uparrow$ body temp
- tachycardia
- dysrhythmia
- $\uparrow$HR, muscle rigidity

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

Gingival Hyperplasia

- Calcium blockers – especially nifedipine (10%)
- Phenytoin (Dilantin) – for seizures (40%)
- Cyclosporine – immunosuppressant (30%)
ACEI – Angioedema; Glossitis

- Angioedema (<1%)
- Dry mouth
- Glossitis (<5%)
- Oral ulceration
- Oral bleeding

Glossitis

Angioedema

Often occurs in the deep layers of the skin, usually near the eyes and mouth.

SNS - Exam Stress

Normal BP: 120 / 80 mmHg HR: 72 bpm
Before exam: 140 / 99 mmHg HR: 97 bpm
During exam: 179 / 149 mmHg HR: 110 bpm
End of exam: 111 / 74 mmHg HR: 76 bpm
ADHD PET Scan

Brain with ADHD has much less activity (red/white)
ADHD individuals do not have enough activity in their brain to focus on what they are doing or control their thoughts

Treatment aims to give a person with ADHD more "mental energy" so they can control their thoughts and actions

Antimuscarinic Toxicity

Belladonna (beautiful lady)

• mad as a hatter: - CNS, delirium
• red as a beet: - direct vasodilation
• blind as a bat: - cycloplegia
• hot as hell (a hare): - ↓sweat, thermoregulation
• dry as a bone: - decreased secretions