Adrenoceptor antagonist drugs
chapter 10

Overview

- The **adrenergic antagonists** (also called blockers or sympatholytic agents(
  - **bind to adrenoceptors** but do **not trigger** the **usual receptor-mediated** intracellular effect

- These drugs act by either **reversibly** or **irreversibly blocking** the **receptor**,
  - thus **preventing its activation** by **endogenous catecholamines**

- The adrenergic antagonists are classified according to the their **relative affinities for α or β receptors**.

Selective *vs.* Non-selective

Antagonist *vs.* Partial Agonist

Reversible *vs.* Irreversible

Alpha-adrenoceptor antagonist drugs

Introduction

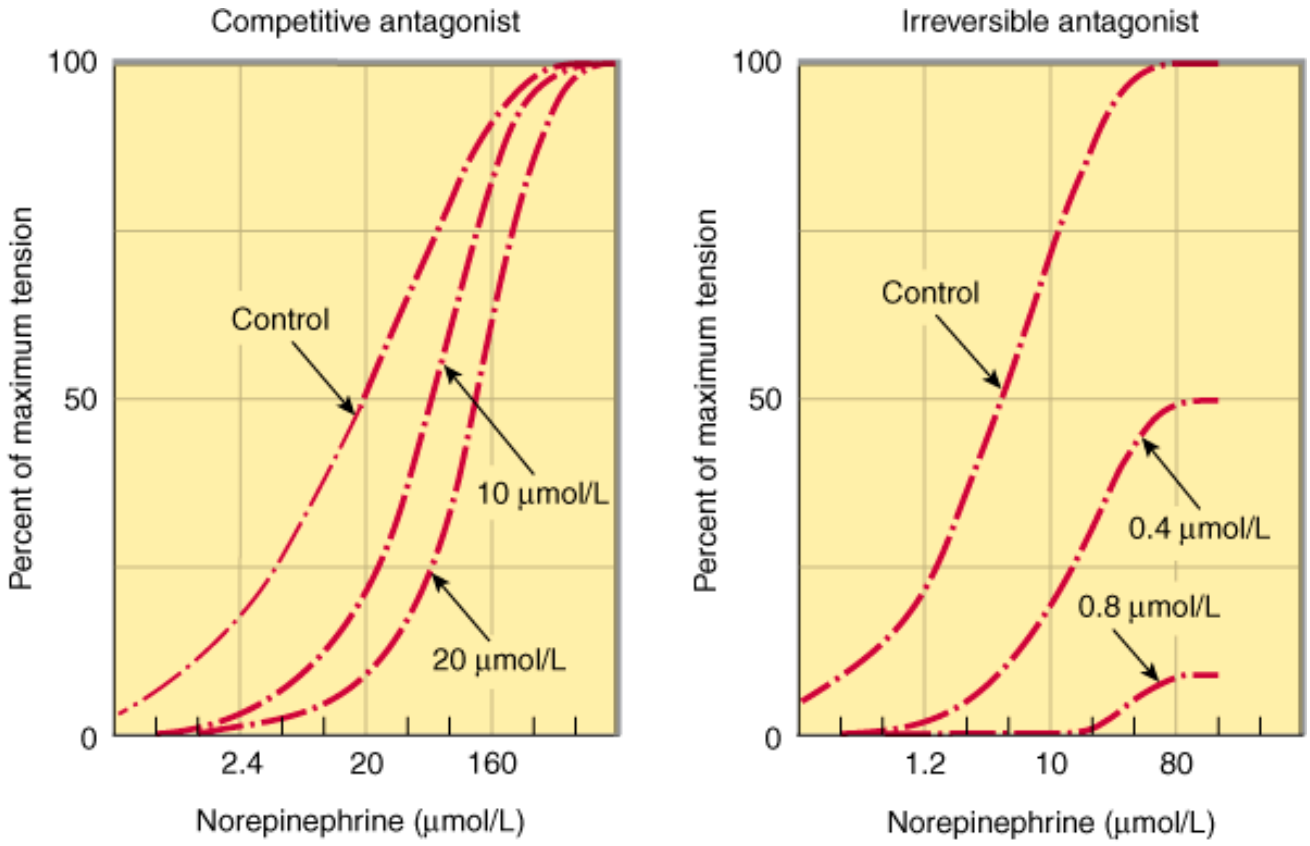
- The main groups of α-adrenoceptor antagonists are:
  - **Non-selective** **α**-receptor antagonists (e.g. ***phenoxybenzamine***, ***phentolamine***)
  - **α_1-selective** antagonists (e.g. ***prazosin***, ***doxazosin***, ***terazosin***)
  - **α_2-selective** antagonists (e.g. ***yohimbine***, ***tolazoline***)
  - Ergot derivatives (e.g. ***ergotamine***, ***dihydroergotamine***)

- Alpha-receptor antagonists may be **reversible** (e.g. ***phentolamine, prazosin)*** or **irreversible** ***(phenoxybenzamine)*** in their interaction with these receptors

- **Mixed antagonists** (***carvedilol,labetalol***)

- Selective β antagonists (***propranolol, metoprolol, Butoxamine***)

Reversible *vs.* Irreversible receptor blockade

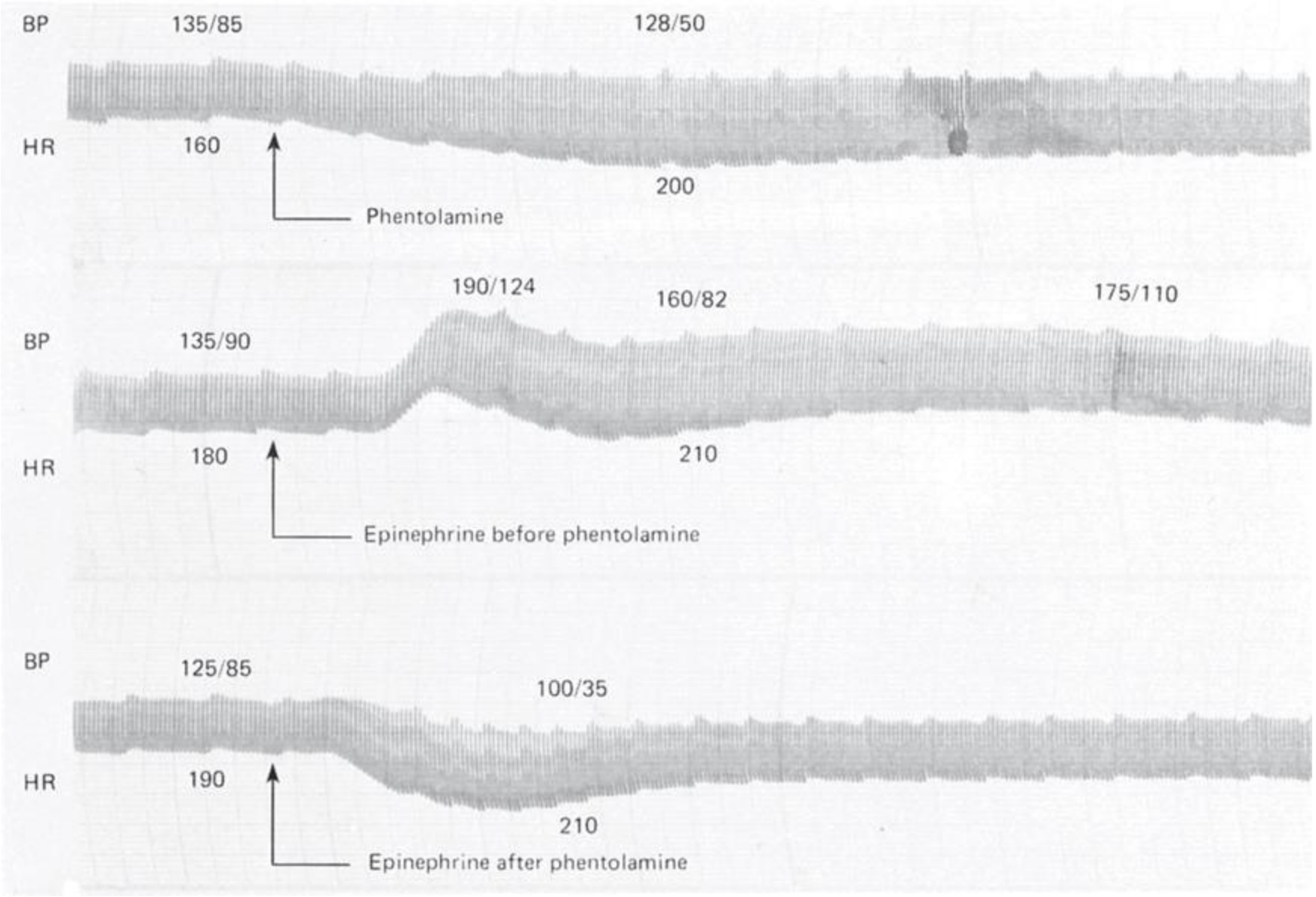


Pharmacologic effects/alpha antagonist

A. Cardiovascular effects:

- **Arteriolar and venous tone** are widely determined by α-receptors on vascular smooth muscle…increase in blood pressure
- So…..**α-receptor antagonists** will **cause lowering** of **peripheral vascular** resistance and

- **BUT:** in **the presence** of **agonists** with **both α and β_2** receptor effects (**eg, epinephrine**),
  - **blockade of α_1** receptor **selectively** may convert the **pressor to a depressor** response
  - "**epinephrine reversal**"


BP
135/85
128/50
HR
160
200
Phentolamine
190/124
160/82
175/110
BP
135/90
HR
180
210
Epinephrine before phentolamine
BP
125/85
100/35
HR
190
210
Epinephrine after phentolamine

α-adrenoceptor antagonist drugs

Pharmacologic effects

A. Cardiovascular effects:

- Alpha-receptor antagonists often cause **orthostatic hypotension** and **reflex tachycardia**

- **Orthostatic hypotension**
  - is due to **antagonism** of **sympathetic nervous** system stimulation of **α_1** receptors in **vascular smooth muscle**; (**contractio**n of **veins** is an important component of the **normal capacity to maintain blood pressure in the upright position since** it d**ecrease**s **venous pooling** in **the periphery**)

- **Tachycardia** may be **more marked** with agents that **block α_2-presynaptic** receptors (yohimbine) in the heart! **WHY??**

α-adrenoceptor antagonist drugs
Pharmacologic effects

B. Other effects

- **The eye: blockade of α_1 -**receptors in the eye elicits **miosis**

- **The nasal cavity:** blockade of α_1 -receptors **elicits nasal stuffiness**

- **The genitourinary tract:**
  - blockade of α_1 -receptors in the **base of the bladder** and the **prostate decreases resistance to the flow of urine**
  - ….**TX of BPH** (**benign prostatic hyperplasia**)

α-adrenoceptor antagonist drugs

Specific agents

1. **Phenoxybenzamine**

- Binds **covalently** to α-receptors (**mainly α_1**), causing **irreversible blockade** of long duration **(14–48 hours** or longer)

- It **also block :**
  - acetylcholine, histamine (H1) and 5-HT. receptors
  - (& block NET)

- Phenoxybenzamine is **absorbed** after **oral administration,** although bioavailability is low and its kinetic properties are not well known

α-adrenoceptor antagonist drugs

Specific agents

1. **Phenoxybenzamine** (Cont'd)

Effects (Cont'd):

- The pharmacologic actions of phenoxybenzamine are primarily related to antagonism of α-receptor–mediated events

- The most significant effect is **attenuation** of **catecholamine-induced vasoconstriction**

- While phenoxybenzamine causes relatively:
  - **little fall** in **blood pressure** in **normal supine** individuals,
  - **it reduces blood** pressure when **sympathetic tone** is **high,** eg, as a result of **upright posture**

α-adrenoceptor antagonist drugs

Specific agents

1. Phenoxybenzamine (Cont'd)

Effects (Cont'd):

- **Cardiac output** may be **increased** because of :
  - **reflex effect**s
  - **and** because of some **blockade** of **presynaptic α_2** receptors in **cardiac sympathetic nerves**

- Mainly used for **Tx of *pheochromocytoma***

α-adrenoceptor antagonist drugs
Clinical uses

❖ **Pheochromocytoma**

- Tumor of the adrenal medulla
- or sympathetic ganglion cells (symptoms)

- **Diagnosis** is confirmed on the basis of:
  - **elevated plasma** or **urinary levels** of **catecholamines** (biochemically),
  - **MRI**

- **Phenoxybenzamine** are useful in the **preoperative** management of patients with **pheochromocytoma**

α-adrenoceptor antagonist drugs
Clinical uses

❖ **Pheochromocytoma**

- Can also be very useful in the **chronic treatment** of **inoperable or metastatic** pheochromocytoma

- **Beta-receptor antagonist**s may be required **after α-receptor blockade** to:
  - **reverse** the **cardiac effects** of **excessive catecholamines**

- **Beta antagonists** should **never be used prior** to establishing **effective α-receptor** blockade,
  - since **unopposed β-receptor blockade** could theoretically **cause blood pressure elevation (increased vasoconstriction)**

α-adrenoceptor antagonist drugs
Specific agents

1. **Phenoxybenzamine** (Cont'd)

- **ADEs:**
  - Orthostatic hypotension and tachycardia (most important)
  - Nasal stuffiness
  - Inhibition of ejaculation
  - CNS: fatigue, sedation, & nausea

- It is **contraindicated** in patients with **decreased coronary perfusion**

α-adrenoceptor antagonist drugs
Specific agents

2. Phentolamine

- It is a potent **competitive α receptor antagonist**
- that has similar **affinities for α_1 and α_2 receptors**.
- Its action is **short-lasting (4-hours) (reversible)**
- **Effects:**
  - It reduces peripheral resistance through blockade of α_1 receptors and possibly α_2 receptors on vascular smooth muscle
  - It induces reflex tachycardia by:
    - the **baroreceptor reflex**
    - and by **blocking the presynaptic α_2 receptors** (leading to enhanced release of norepinephrine from sympathetic nerves)
  - It has minor inhibitory effects at serotonin receptors and agonist effects at muscarinic and H_1 and H_2 histamine receptors

α-adrenoceptor antagonist drugs
Specific agents

2. **Phentolamine** (Cont'd)

- **ADEs:** principal adverse effects are related **to cardiac stimulation:**
  - severe **tachycardia**,
  - **arrhythmias,**
  - and **myocardial ischemia**

- It is contraindicated in patients with **decreased coronary perfusion**

- Used for **Tx of pheochromocytoma** even if now not more available in the USA

α-adrenoceptor antagonist drugs

Specific agents

3. Prazosin, terazosin, doxazosin, & tamsulosin

- Are **selective** competitive **α_1 receptor antagonists**

- They **decrease** peripheral vascular **resistance** and lower arterial **blood pressure** by causing the relaxation of both arterial and venous smooth muscle, as well as smooth muscles in the prostate

- Associated with **less tachycardia** than occurs **with non-selective α-receptor antagonists**

α-adrenoceptor antagonist drugs
Specific agents

3. Prazosin, terazosin, doxazosin, & tamsulosin

- **Prazosin: :**
  - **extensively metabolized** in humans (**oral F~50%).**
  - Short **half-life ~3hr**

- **Terazosin**
  - also **approved** for use in men with **urinary symptoms** due to **benign prostatic hyperplasia** (BPH).
  - Better bioavailability,
  - intermediate **half-life ~12 hours**

- **Doxazosin**
  - efficacious in the treatment of **HTN**
  - and **BPH**
  - (**longer half-life ~22 hours**)

α-adrenoceptor antagonist drugs
Specific agents

3. Prazosin, terazosin, doxazosin, & tamsulosin

- **Tamsulosin** :
  - (quite **different structure),**
  - **highly bioavailable,**
  - half-life **of 9–15 hours,**
  - metabolized extensively in the liver

- N.B: Tamsulosin has higher **affinity for α_{1A} receptors**

- Has **greater potency** in i**nhibitin**g **contraction in *prostate*** smooth muscle versus ***vascular* smooth muscl**e compared with **other α_1-selective antagonists**
- **Particular effective in Tx of BPH** suggesting that α_{1A} receptor subtype may be the most important subtype mediating prostate smooth muscle contraction

α-adrenoceptor antagonist drugs

Specific agents

3. **Prazosin, terazosin, doxazosin, & tamsulosin** (Cont'd)

- **ADEs:**
  - dizziness,
  - a lack of energy,
  - nasal congestion,
  - headache,
  - drowsiness,
  - and orthostatic hypotension (although to **a lesser degree**, especially tamsulosin, than that observed with **phenoxybenzamine and phentolamine)**
- tamsulosin >>>> has relatively **minor effects on blood pressure at a low dose**.
- May be preferred in patients who have experienced orthostatic hypotension with other α_1-receptor antagonists

α-adrenoceptor antagonist drugs

Specific agents

4. Other α-adrenoceptor antagonists

- **Alfuzosin:**
  - is **an α_1-selective** quinazoline derivative
  - that is approved for use in benign prostatic hyperplasia (**BPH)**

- **Indoramin:**
  - is another **α_1**-selective antagonist that also has efficacy as an **antihypertensive**
- **Urapidil:**
  - is an **α_1 antagonist (its primary effect**)
  - that also has **weak α_2-agonist and 5-HT_{1A}-agonist** actions
  - and **weak antagonist action at β_1 receptors.**
  - It is used in Europe as an **antihypertensive** agent and for **benign prostatic hyperplasia.**

α-adrenoceptor antagonist drugs
Specific agents

4. Other α-adrenoceptor antagonists (Cont'd)

- **Ergot alkaloids/derivatives (e.g. ergotamine & dihydroergotamine):**
  - were the **first adrenergic receptor antagonists** to be discovered &
  - **they** cause **reversible α -receptor** blockade, probably via a **partial agonist** action

- **Yohimbine (indole alkaloid):**
  - is an **α_2-selective antagonist.**
  - It is **sometimes** used in the treatment of **orthostatic hypotension because** it promotes norepinephrine release through blockade of presynaptic α_2 receptors.
  - Yohimbine can **reverse the antihypertensive** effects of **an α_2-adrenoceptor agonist such as clonidine**

α-adrenoceptor antagonist drugs
Clinical uses

❖ **Hypertensive emergencies**

- The α-adrenoceptor antagonist drugs have **limited application** in the management of **hypertensive emergencies** *other drugs are generally preferable*

- **Labetalol** has been used in this setting

- α-adrenoceptor antagonists are most useful when **increased blood pressu**re reflects excess **circulating concentra**tions of agonists
  - eg, in **pheochromocytoma,**
  - **overdosage of sympathomimetic** drugs,
  - or **clonidine withdrawal**

α-adrenoceptor antagonist drugs
Clinical uses

❖ **Chronic Hypertension**

- Members of the **prazosin** family of **α_1-selective** antagonists are **efficacious** drugs
  - in the treatment **of mild to moderate** systemic **hypertension**

- They are generally well tolerated, but they are **not** usually r**ecommended as monotherapy** for hypertension
  - because **other classes** of antihypertensives are **more effective** in **preventing heart failure**

- The use of **α-adrenoceptor antagonists such as prazosin** has been found to be associated with either
  - **no changes in plasma lipids**
  - or **increased** concentrations of **HDL**, which could be a **favorable alteration**

α-adrenoceptor antagonist drugs

Clinical uses

❖ Peripheral vascular disease

- Individuals with **Raynaud's phenomenon** and other conditions involving **excessive reversible vasospasm** in the **peripheral circulation** do benefit from
  - **prazosin or**
  - **phenoxybenzamine**

α-adrenoceptor antagonist drugs
Clinical uses

❖ **Erectile dysfunction**

- A **combination** of **phentolamin**e + the nonspecific smooth **muscle relaxant papaverine**, when injected **directly** into **the penis**, may cause **erections** in men with **sexual dysfunction**

- **Long-ter**m administration may result in **fibrotic reactions**

- **Systemic absorption** may lead to **orthostatic hypotension**

α-adrenoceptor antagonist drugs

Applications of α_2-antagonists

- **Alpha$_2$ antagonists have relatively little clinical usefulness: (yohimbine & tolazoline)**
  - They have limited benefit in male erectile dysfunction
  - There has been **experimental interest** in the development of **highly selective α2 antagonists**
    - for treatment of **type 2 diabetes** (**α_2 receptors** inhibit **insulin secretion),**
    - for treatment of psychiatric depression
    - or to use in **Raynaud's phenomenon** to **inhibit smooth muscle contraction**

β-adrenoceptor antagonist drugs

Introduction

- All the **"β–blockers"**, share the common feature of antagonizing the effects of catecholamines at β-adrenoceptors in a **competitive manner ,** Differ in their:
  - Relative **affinities for β_1 and β_2** receptors,
  - **Intrinsic sympathomimetic** activity,
  - **CNS** effect, and
  - **Pharmacokinetics**

- **None** of the clinically available β-receptor antagonists are **absolute**ly **specific for β_1 receptors**. Their **selectivity is dose-dependent**

- **There are no clinically useful β_2 antagonists**

- The names of all β-blockers end in "-olol" except for labetalol and carvedilol

TABLE 10–2 Properties of several beta-receptor-blocking drugs.

	Selectivity	Partial Agonist Activity	Local Anesthetic Action	Lipid Solubility	Elimination Half-life	Approximate Bioavailability
Acebutolol	β_1	Yes	Yes	Low	3–4 hours	50
Atenolol	β_1	No	No	Low	6–9 hours	40
Betaxolol	β_1	No	Slight	Low	14–22 hours	90
Bisoprolol	β_1	No	No	Low	9–12 hours	80
Carteolol	None	Yes	No	Low	6 hours	85
Carvedilol[1]	None	No	No	Moderate	7–10 hours	25–35
Celiprolol	β_1	Yes	No	Low	4–5 hours	70
Esmolol	β_1	No	No	Low	10 minutes	0
Labetalol[1]	None	Yes	Yes	Low	5 hours	30
Metoprolol	β_1	No	Yes	Moderate	3–4 hours	50
Nadolol	None	No	No	Low	14–24 hours	33
Nebivolol	β_1	?[2]	No	Low	11–30 hours	NF[3]
Penbutolol	None	Yes	No	High	5 hours	>90
Pindolol	None	Yes	Yes	Moderate	3–4 hours	90
Propranolol	None	No	Yes	High	3.5–6 hours	30[4]
Sotalol	None	No	No	Low	12 hours	90
Timolol	None	No	No	Moderate	4–5 hours	50

[1]Carvedilol and labetalol also cause α_1-adrenoceptor blockade.

[2]Not determined.

[3]Not found.

[4]Bioavailability is dose-dependent.

Pharmacokinetic Properties of the Beta-Receptor Antagonists

- **Absorption: well absorbed** after **oral** administration **& peak** concentrations **occur 1–3 hours** after ingestion

- **Bioavailability:**
  - **propranolol** (the **prototype of β–blockers**) undergoes **extensive hepatic first-pass** metabolism.
  - Its bioavailability **(F~0.3**) is **dose-dependent** (suggest that the **hepatic extracti**on become **saturated**)
  - The first-pass effect varies among individuals…….there is **great individual variability** in the plasma concentrations achieved after **oral propranolol** (approximately **twentyfold)** which contributes to **the wide range of doses** in **terms of clinical efficacy**

- Exception of betaxolol, penbutolol, pindolol, and sotalol

Pharmacokinetic Properties of the Beta-Receptor Antagonists (Cont'd)

- **Distribution**: the β–adrenergic antagonists are rapidly distributed and have large volumes of distribution
  - **Propranolol** and **penbutolol** are **quite lipophilic** and readily **cross** the blood-brain barrier (**BBB)**

- **Clearance: most β–adrenergic** antagonists have elemination half-lives in the range of **3–10 hours….BUT!!!!**
  - **Esmolol** contains an **ester** linkage……**rapidly hydrolyzed** by **esterases in erythrocytes**. **$T_{1/2}$~10 min**
  - **Nadolol is excreted unchanged** in the urine and has the longest half-life (**24 hours**).
    - Its **half-life** may be **prolonged in** the presence **of renal failure**

Pharmacokinetic Properties of the Beta-Receptor Antagonists (Cont'd)

- **Propranolol and metoprolol** are **extensively metabolized** in the **liver,** with little unchanged drug appearing in the urine
- The e**limination** of drugs such as **propranolol** may be **prolonged in the presence of:**
  - **liver disease,**
  - **diminished hepatic blood flow, or**
  - **hepatic enzyme inhibition**
  - **The cytochrome P450 2D6 (CYP2D6) genotype** is a major determinant of **interindividual differences** in **metoprolol plasma clearance**:
- Poor metabolizers exhibit three-fold to ten-fold higher plasma concentrations than extensive metabolizers

Pharmacologic effects
Cardiovascular effects

- The **major therapeutic effects** of β-receptor antagonists are **on** the **CVS**….**decrease BP**
- It is important to distinguish these effects in normal subjects from those in subjects with cardiovascular disease such as HTN or MI
- These drugs **do *not* usually** cause **hypotension** in **healthy individuals** with **normal blood pressure** **???**
  - When **tonic stimulation** of **β-receptors is low**, the **effect** of **β-receptor antagonists** is correspondingly **modest**

- However, when the **sympathetic nervous system** is **activated**, as **during exercise or stress**,
  - β-receptor antagonists (**BB**) **attenuate** the **expected rise** in **heart rate**

PHARMACOLOGIC EFFECTS
CARDIOVASCULAR EFFECTS

- β-receptor antagonists have both:
  - **negative inotropic**, c**hronotro**pic and **dromotropic** effects **on the heart**.
  - **>>>>>>>> Cardiac output, work, and oxygen consumption** are **decreased** by **blockade of β_1** receptor

- In **the vascular system**,
  - **β-receptor blockade** opposes **β_2-mediated vasodilation**
  - …..This may **acutely** lead to a **rise in peripheral resistance**
  - from **unopposed α-receptor-mediated effects**

- **Nonselective and β_1-blocking** drugs
  - a**ntagoniz**e the **release of renin** caused by the **sympathetic nervous system**

β-adrenoceptor antagonist drugs

Pharmacologic effects

A. Cardiovascular effects

- **No postural hypotension** occurs, because the **α_1-adrenergic receptors** that control vascular resistance are **unaffected**

- Overall, the **acute effects** of these drugs may include a **rise in peripheral resistance**.

- However, with l**ong-term** use of β- receptor antagonists,
  - **total peripheral resistance** returns to **initial values** or **decreases in patients with hypertension**

Pharmacologic effects
Respiratory system

- **Blockade** of the **β_2 receptors** in bronchial smooth muscle may lead to
  - **an increase** in **airway resistance**, **particularly** in patients with **asthma**

- **β_1-receptor antagonists** (e.g. metoprolol & atenolol) may have some **advantage over nonselective** antagonists when blockade of **β_1 receptors** in the **heart** is desired and **β_2-receptor blockade** is **undesirable**

- **None** of the **β_1-selective antagonist** is sufficiently **specific** to *completely* avoid interactions with β_2 adrenoceptors…….

- Should generally be **avoided** in patients **with asthma** or **used with caution** in patients with **COPD**

Pharmacologic effects
Metabolic and endocrine effect

- Drugs such as **propranolol inhibit sympathetic nervous** system stimulation **of lipolysis**

- **β_2-receptor blockade** lead to **decreased glycogenolysis** in the human liver and **decreased glucose release**

  - Therefore, **β-blockers** should be used with **caution** in type I diabetic patients……**much safer** in those **type 2 diabetic patients** who do not have hypoglycemic episodes

  - Selective **β_1-blockers** may be **less prone** to **inhibit** r**ecovery** from **hypoglycemia**

Pharmacologic effects
Metabolic and endocrine effect

- The **chronic** use of **β-blockers** has been associated with
  - **increased** plasma concentrations of **VLDL** and d**ecreased** levels of **HDL** cholesterol

- **Decline** in the **HDL/LDL ratio**
  - Both of these changes are potentially unfavorable in terms of risk of cardiovascular disease (may increase the risk of coronary artery diseases)
- **These changes occur with both selective** and **nonselective blockers**……less likely to occur with blockers possessing intrinsic sympathomimetic activity (partial agonists)

Pharmacologic effects
Effects not related to beta-blockade

- **Local anesthetic action**, also known as "**membrane-stabilizing**" action, is a prominent effect of several β-blockers (e.g. **acebutolol**, l**abetalol**, **metoprolo**l, & **penbutolol)**
  - This **action is the result** of **typical local anesthetic blockade of sodium channels**
  - **This effect** is **not important** after **systemic** administration of these drugs, since the **concentration in plasma** usually achieved by these routes is **too low** for **the anesthetic** effects to be evident

- **Sotalol** is a **nonselective β-receptor** antagonist that lacks local anesthetic action but has marked **antiarrhythmic** effects, reflecting **potassium channel blockade**

Nonselective β-adrenergic antagonists

- Propranolol, Timolol, Nadolol, Levobunolol , & Carteolol

- **Propranolol:**
  - The prototypical β-blocking drug and **blocks** both **β_1 and β_2 receptors**

  - **Sustained release (SR)** preparations for o**nce-a-day** dosing are available
  - Propranolol may block some serotonin receptors in the brain, the clinical significance is unclear

Nonselective β-adrenergic antagonists

- **Timolol**
  - It **reduces** the **production** of **aqueous humor** in the eye
    - Used topically in the **treatment** of **chronic open-angle glaucoma** (as well as levobunolol) and,
  - o**ccasionally** for **treatment of HTN**

- **Nadolol**
  - A l**ong-acting** antagonist (half-life of **12-24hrs**)
  - Nadolol is **incompletely** a**bsorbed** from **the gut (hydrophilic)**; its b**ioavailability** is **about 35%**
  - The low lipid solubility of nadolol may result in lower concentrations of the drug in the brain compared with more lipid-soluble antagonists

β_1-adrenergic antagonists

- **Metoprolol,** Acebutolol, Atenolol, **Esmolo**l, Bisoprolol, & **Nebivolol**

- Drugs that preferentially **block β_1** receptors have been developed to
  - **eliminate** the **unwanted bronchoconstrictor** effect (**β_2 effect**) of propranolol seen among asthmatic patients

- **Preferable** in p**atients** with **diabetes** or **peripheral vascular disease**,
  - since **β_2** receptors are probably important in liver (**recovery from hypoglycemi**a) and blood vessels (**vasodilation**)

β_1-adrenergic antagonists

- **Nebivolol** is the **most highly selective β_1-adrenergic receptor blocker**,
  - and it has the a**dditional** quality of **eliciting vasodilation**?
  - .....May be due **to stimulation** of the **endothelial nitric oxide pathway**

- **Esmolol: ultra-short–acting** & **β_1-selective** antagonist
  - Administered **intravenously (i.v.)** and is used
  - when **β-blockade** of **short duration is desired** or in critically ill patients
  - It is useful in controlling:
    - **arrhythmias**,
    - **perioperative hypertension**,
    - and **myocardial ischemia** in **acutely ill** patients

Partial β-adrenergic agonists

- Pindolol, Acebutolol, Carteolol, Bopindolol, Oxprenolol, Celiprolol, & Penbutolol

- They have the ability to **weakly stimulate** both **β_1 and β_2** receptors and are said to have **intrinsic sympathomimetic activity**

  - These **partial agonists** may be **less likely** to cause **bradycardia**
  - They **minimize** the **disturbances** of **lipid** and **carbohydrate** metabolism that are seen with other β-blockers

Antagonists of both α- and β-adrenoceptors

- Labetalol, Carvedilol, Cedroxalol, & Bucindolol

- These are **reversible β-blockers** with concurrent **α_1-blocking** actions…….produce peripheral **vasodilation**, thereby **reducing blood pressure**
  - They **contrast** the **other β-blockers** that **produce peripheral vasoconstriction**……..useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable

- Do **not alter** serum **lipid or blood glucose** levels

- **Carvedilol** also
  - d**ecreases lipid peroxidation** a
  - nd **vascular wall thickening,** effects
  - that have **benefit i**n **heart failure**

Therapeutic uses of Beta-Receptor–Blocking Drugs

1. Cardiovascular applications

A. Hypertension

- Beta-blockers have proved to be effective and well tolerated in hypertension. They are often used with either a diuretic or a vasodilator
- In spite of the **short half-life** of many antagonists, these drugs may be administered **once or twice** daily and **still have an adequate therapeutic effect**

- There is **some evidence** that drugs in **this class** may be **less effective** in the **elderly** and in **individuals of African ancestry**

Therapeutic uses of Beta-Receptor–Blocking Drugs

B. Ischemic heart disease

- Beta-adrenoceptor blockers **reduce** the **frequency** of **anginal episodes** and **improve exercise** tolerance in many **patients with angina**

- These actions relate to the **blockade of cardiac β-receptors**,
  - resulting in **decreased cardiac work** and **reduction in oxygen demand**
- Slowing and regularization of the heart rate may contribute to clinical benefits
- **Multiple large-scale prospective studies** indicate that :
  - the **long-term use** of **timolol, propranolol,** or **metoprolol** in patients **who have had** a **myocardial infarction prolongs survival**

Therapeutic uses of Beta-Receptor–Blocking Drugs

C. Cardiac arrhythmias

- **Beta antagonists** are often effective in the t**reatment** of both s**upraventricula**r and v**entricular arrhythmias**

- It has been **suggested** that the **improved** s**urvival** following **myocardial infarction** in patients using **β antagonists** is due to **suppression of arrhythmias**, but this has **not been proved**

- By **increasing** the **atrioventricula**r **nodal refractory period**, antagonists **slow** v**entricular response rates** in **atrial flutter** and **fibrillation**
- These drugs can also **reduce ventricular ectopic be**ats, **particularly** if the ectopic activity **has been precipitated** by **catecholamines**

- **Sotalol has antiarrhythmic effects**

Therapeutic uses of Beta-Receptor–Blocking Drugs

D. Heart failure

- It is a **common clinical observation** that **acute administration** of **β-receptor antagonists** can **worsen markedly** or **even precipitate congestive heart failure** in compensated p**atients** with **multiple forms of heart disease,** such as **ischemic or congestive cardiomyopathy**

- Three antagonists — **metoprolol, bisoprolol, and carvedilol** —
  - are effective in **reducing long-term mortality** in selected patients with **chronic heart failure**

Non-cardiovascular applications

A. Glaucoma:

- **Topical** administration of **beta-blockers reduces intraocular pressure**
  - The mechanism involve **reduced production** of **aqueous humor** by the **ciliary body**, which is **physiologically** **by cAMP**

- Timolol, betaxolol, carteolol, levobunolol, and metipranolol are
  - **FDA approved** for the treatment of ***open angle glaucoma*** **(lack local anasthetic properties)**

- However, sufficient **timolol** may be **absorbed** from **the eye** to cause **serious ADEs** on the **heart** and a**irways** in ***susceptible individuals***

PHARMACOLOGIC EFFECTS ON THE EYE

- Two major types of glaucoma are recognized: o**pen-angle** and **closed-angle (or narrow-angle**)

- The **closed-angl**e form is associated with a shallow anterior chamber, in which a **dilated iris** can **occlude** the **outflow** drainage pathway at the **angle** between **the cornea** and the **ciliary body**

- The o**pen-angle** form of glaucoma is a **chronic condition,** and treatment is largely **pharmacologic**

- **Five general groups of drugs**—cholinomimetics, α-agonists, β-blockers, prostaglandin F2α analogs, and diuretics

TABLE 10–3 Drugs used in open-angle glaucoma.

	Mechanism	Methods of Administration
Cholinomimetics		
Pilocarpine, carbachol, physostigmine, echothiophate, demecarium	Ciliary muscle contraction, opening of trabecular meshwork; increased outflow	Topical drops or gel; plastic film slow-release insert
Alpha agonists		
Nonselective	Increased outflow	Topical drops
Epinephrine, dipivefrin		
Alpha$_2$-selective	Decreased aqueous secretion	
Apraclonidine		Topical, postlaser only
Brimonidine		Topical
Beta-blockers		
Timolol, betaxolol, carteolol, levobunolol, metipranolol	Decreased aqueous secretion from the ciliary epithelium	Topical drops
Diuretics		
Dorzolamide, brinzolamide	Decreased aqueous secretion due to lack of HCO_3^-	Topical
Acetazolamide, dichlorphenamide, methazolamide		Oral
Prostaglandins		
Latanoprost, bimatoprost, travoprost, unoprostone	Increased outflow	Topical

Therapeutic uses of Beta-Receptor–Blocking Drugs

B. Hyperthyroidsim

- **Many** of the **signs and symptoms** of **hyperthyroidism** are **reminiscent** of the **manifestations** of **increased sympathetic** nervous system **activity**

- Excess **thyroid hormone** increases the **expression of β-receptors** in the **heart**
- The beneficial effects presumably relate to:
  - **blockade** of a**drenoceptors**
  - and perhaps in part to the **inhibition** of **peripheral conversion** of **thyroxine (T3)** to **triiodothyronine(T4)**

- **Propranolol** has been **used extensively** in patients with **thyroid storm** (**severe hyperthyroidism**)

Therapeutic uses of Beta-Receptor Blocking Drugs

C. Other uses

1. **Propranolol** reduces the frequency and intensity **of migraine headache** when **used prophylactically**
   - Other β-receptor antagonists include metoprolol and probably also atenolol, timolol, and nadolol
   - The mechanism may depend on **the blockade** of **catecholamine-induced vasodilation** in the **brain vasculature**

2. Since **sympathetic activity** may **enhance** skeletal muscle **tremor**, it is not surprising that **β-antagonists (propranolol)** can **reduce certain tremors**

C. Other uses

- The **somatic manifestations** of **anxiety** may respond dramatically to **low doses** of **propranolol**, particularly when taken **prophylactically**
- Benefit has been found in musicians with performance anxiety

3. **Propranolol** may contribute to the **symptomatic** treatment of **alcohol withdrawal** in **some patient**s

4. **Beta-receptor antagonists** have been found to **diminish portal vein pressure** in patients with **cirrhosis**
   - Propranolol and nadolol are **efficacious** in the **primary** p**revention** of b**leeding** in patients with **portal** hyp**ertension** caused by **cirrhosis of the liver**

Choice of β-adrenoceptor antagonist drug

- The various β-receptor antagonists that are used for the treatment of HTN and angina appear to have similar efficacies
- Selection of the most appropriate drug for an individual patient should be based on **PK and PD differences** among the drugs, **cos**t, and whether there are **concurrent medical problems**
- For example, **only antagonists** known to be effective in **stable heart failure** or in **prophylactic therapy after myocardial infarction** should be used **for those indications**

Adverse effects of β-adrenoceptor antagonist drug

- **Bradycardia** (most common): normal response to β-adrenoceptor blockade

- **Bronchoconstriction:** β_2 receptor blockade associated with the use of non-selective β-blockers (e.g. propranolol)

- **Hypoglycemia** in type I diabetic patients who are subject to frequent hypoglycemic episodes

- **Coolness of hands & feet in winter:** are presumably due to a loss of β-receptor-mediated vasodilatation in cutaneous vessels
- **CNS effects:** include **fatigue**, **sleep disturbances** (including i**nsomnia and nightmares**), and **depression**

Adverse effects of β-adrenoceptor antagonist drug

- **Cardiac arrhythmias**
- **Long-term** treatment with a **β antagonist** leads to **up-regulation** of the **β-receptor**

- Tx. with β-blockers *must* ***never be stopped quickly***
  - because of the **risk of precipitating cardiac arrhythmias**, which may be severe
  - On suspension of therapy, the increased receptors can **worsen angina** or **hypertensio**n

- β-blockers must be **tapered off gradually**

Adverse effects of β-adrenoceptor antagonist drug

- **Congestive heart failure in susceptible patients**:
  - β-receptor blockade **may cause or exacerbate** heart failure in patients with **compensated heart failure** (beta-receptor blockade **depresses myocardial contractility** and e**xcitabi**lity; **decrease cardiac output**)
  - **Caution** must be exercised **in starting** a **β-receptor antagonist even though long-term** use of these drugs in these patients **may prolong life**
  - A **life-threatening adverse cardiac effect** may be overcome directly with **isoproterenol** or with **glucagon**

Drug interactions

- **Pharmacodynamic interactions:**
- **Beta blockers** may **interact** with the **calcium antagonist**
  - …….severe hypotension,
  - bradycardia,
  - heart failure,
  - and cardiac conduction abnormalities have all been described
- These adverse effects may even arise in susceptible patients taking a **topical (ophthalmic) blocker** and **oral verapamil**

Table 9–3 Distribution of Adrenoceptor Subtypes

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS adrenoceptors	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibition of transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibition of lipolysis
β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Fat cells	Activates lipolysis

Subclass	Effects	Clinical Applications	Toxicities, Interactions
α_1 Agonists			
Midodrine	Vascular smooth muscle contraction increasing blood pressure (BP)	Orthostatic hypotension	Produces supine hypertension, piloerection (goose bumps), and urinary retention
Phenylephrine	IV for short-term maintenance of BP in acute hypotension and intranasally to produce local vasoconstriction as a decongestant		
α_2 Agonists			
Clonidine	Vasoconstriction is masked by central sympatholytic effect, which lowers BP	Hypertension	produces dry mouth and sedation
Methyldopa	Also used as central sympatholytics		
guanfacine			
guanabenz			
Dexmedetomidine	Prominent sedative effects and used in anesthesia		
Tizanidine	Used as a muscle relaxant		
Apraclonidine	Used in glaucoma to reduce intraocular pressure		
brimonidine			

Subclass	Effects	Clinical Applications	Toxicities, Interactions
β_1 Agonists			
Dobutamine[1]	Positive inotropic effect	Primarily used in acute heart failure to increase cardiac output	
β_2 Agonists			
Albuterol	Bronchial smooth muscle dilation	Asthma	Tremor, tachycardia
Indirect-acting phenylisopropylamines			
Amphetamine, metamphetamine	Displaces stores of catecholamines	Anorexiant, ADHD, narcolepsy	Insomnia, hypertension
Ephedrine		Narcolepsy, postural hypotension	Lower addiction liability
Tyramine		None, found in fermented food	Hypertension, arrhythmias
Cocaine	Block NET & **DAT**	Local anasthetic	High addiction liability, HT, arrhythmias, seizures

Subclass	Mechanism of Action	Clinical Applications	Toxicities, Interactions
Alpha-adrenoceptor antagonists			
Phenoxybenzamine	Irreversibly blocks α receptors	Pheochromocytoma, Raynaud's phenomenon	Orthostatic hypotension, reflex tachycardia
Phentolamine	Competitively blocks α receptors	Pheochromocytoma, antidote to over dose of α agonist	
Prazosin	Block α_1, but not α_2	Hypertension, benign prostatic hyperplasia BPH	May cause orthostatic hypotension (especially with first dose)
Doxazosin			
Terazosin			
Tamsulosin	Tamsulosin is slightly selective for $\boldsymbol{\alpha_{1A}}$	Benign prostatic hyperplasia	Orthostatic hypotension less common
Yohimbine	Blocks α_2 (increased central sympa. activity and NE release)	Male erectile dysfunction, hypotension	May cause anxiety, excess pressor effect if NET is blocked
Labetalol	α and β blockade	Hypertension (emergencies)	Less tachycardia than other agents

Subclass	Mechanism of Action	Clinical Applications	Toxicities, Interactions
Beta-adrenoceptor antagonists			
Propranolol Nadolol Timolol	Block β_1 and β_2 receptors	Hypertension, angina pectoris, arrhythmias, migraine, hyperthyroidism	Bradycardia, worsened asthma, fatigue, vivid dreams, cold hands
Metoprolol Atenolol	Block $\beta_1 > \beta_2$	Shown to reduce mortality in heart failure	Bradycardia, fatigue, vivid dreams, cold hands
Alprenolol Betaxolol		***ALL:*** Angina pectoris, hypertension, arrhythmias	
Nebivolol Esmolol		Hypertensive emergencies, arrhythmias, thyrotoxicosis	Bradycardia
Butoxamine[1]	Blocks $\beta_2 > \beta_1$	No clinical indication	Bronchospasm
Pindolol Acebutolol Carteolol Bopindolol[1] Oxprenolol[1] Celiprolol[1] Penbutolol	Partial agonist (with intrinsic sympatho-mimetic effect)	Hypertension, arrhythmias, migraine, may avoid worsening of bradycardia (possibly safer in asthma)	Fatigue, vivid dreams, cold hands

Subclass	Mechanism of Action	Clinical Applications	Toxicities, Interactions
Beta-adrenoceptor antagonists			
Carvedilol	α and β blockade	Heart failure	Fatigue
Medroxalol[1]			
Bucindolol[1]			
Tyrosine hydroxylase inhibitor			
Metyrosine	Blocks tyrosine hydroxylase	Pheochromocytoma	Extrapyramidal symptoms, orthostatic hypotension