Adrenergic Antagonists (adrenergic blockers or sympatholytics):

Adrenergic-receptor antagonists block the effects of sympathetic stimulation and adrenergic agonists mediated through α and β receptors.

α-Adrenergic Blocking Agents: Drugs that block α1-adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α1-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This lowered blood pressure induces reflex tachycardia.

I. Non-selective (α1 and α2) blockers:

Phenoxybenzamine: binds covalently to α-receptors and causes irreversible noncompetitive blockade. It has a long duration of action because of irreversible blockade of α-receptors. Phenoxybenzamine is used in the treatment of sweating and hypertension associated with pheochromocytoma,(a catecholamine-secreting tumor of cells derived from the adrenal medulla).

Phentolamine: produces a competitive block of α1 and α2 receptors. It has a short duration of action. It is used for the diagnosis and short-term management of pheochromocytoma. It is also used locally to prevent dermal necrosis following extravasation of norepinephrine. Phentolamine is useful to treat hypertensive crisis due to abrupt withdrawal of clonidine or ingestion of tyramine containing foods in patients taking monoamine oxidase inhibitors. phentolamine mesylate is used in dentistry as an agent to reverse the action of soft tissue anesthesia.

II. Selective α1-Blockers:

Prazosin, terazosin, and doxazosin: are selective competitive blockers of the α1 receptor. These agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle. They are useful in the treatment of hypertension. The first dose of these drugs may produce an exaggerated orthostatic hypotensive response that can result in syncope (fainting). This action, termed a "first-dose" effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime.

Tamsulosin, ***alfuzosin***, and ***silodosin:*** are indicated for the treatment of benign prostatic hyperplasia. Tamsulosin, alfuzosin, and silodosin have less pronounced effects on blood pressure because they are less selective for α1B receptors found in the blood vessels and more selective for α1A receptors in the prostate and bladder. Blockade of the α1A receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

III. Selective α2-Blockers:

***Yohimbine*:** works at the level of the CNS to increase sympathetic outflow to the periphery. It is found as a component of the bark of the yohimbe tree and has been used as a sexual stimulant and in the treatment of erectile dysfunction. Its use in the treatment of these disorders is not recommended due to lack of demonstrated efficacy.

β-Adrenergic Blocking Agents: Clinically all of the available β-blockers are competitive antagonists. Although all β-blockers lower blood pressure, they do not induce postural hypotension, because the α-adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. β-Blockers are effective in treating systemic as well as portal hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma. They are also used for the prophylaxis of migraine headaches. [Note: The names of all β-blockers end in "-olol" except for labetalol and carvedilol.]

I. Nonselective β antagonist: act at both β1 and β2 receptors

Propranolol: is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors. After oral administration, propranolol is almost completely absorbed. It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation. The drug readily crosses the blood–brain barrier due to its high lipophilicity.

Action:

*CVS: Propranolol diminishes cardiac output, having both negative inotropic and chronotropic effects. It directly depresses sinoatrial and atrioventricular nodal activity. Cardiac output, workload, and oxygen consumption are decreased by blockade of β1 receptors, and these effects are useful in the treatment of angina. The β-blockers are effective in attenuating supraventricular cardiac arrhythmias.

*Peripheral vasoconstriction: Nonselective blockade of β receptors prevents β2-mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance.

The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery.

In patients with hypertension, total peripheral resistance returns to normal or decreases with long-term use of propranolol as a result of down regulation of the β receptors. There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

*Bronchoconstriction: Blocking β2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle. This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or

asthma. Therefore, β-blockers, particularly nonselective ones, are contraindicated in patients with asthma and should be avoided in COPD.

*Disturbances in glucose metabolism: β-Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if propranolol is given to a diabetic patient receiving insulin, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after insulin injection. β-Blockers also attenuate the normal physiologic response to hypoglycemia. [Note: Diaphoresis with hypoglycemia still occurs, as this is mediated through the neurotransmitter acetylcholine.]

***Important notes for dentists:

-Nonselective β-blockers prevent vasodilatory effects of epinephrine on β2 receptors, leaving α receptor stimulation unopposed. This may lead to increased peripheral resistance and increased blood pressure.

-Nonselective β-blockers such as propranolol may prevent the rescue effects of epinephrine in anaphylaxis.

-Treatment with β-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can precipitate worsened angina or hypertension through action of endogenous catecholamines on the upregulated β receptors.

Nadolol and ***timolol***: Nadolol and timolol also block β1- and β2-adrenoceptors. *Nadolol* has a very long duration of action.

Timolol reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma. Unlike the cholinergic drugs, this agent neither affects the ability of the eye to focus for near vision nor changes pupil size.

II. selective β1 antagonists:

Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol:

Blockade of the β1 receptors minimize the unwanted bronchoconstriction (β2 effect) seen with use of nonselective agents in asthma patients. They are

cardioselective β-blockers that antagonize β1 receptors at doses 50- to 100-fold less than those required to block β2 receptors. This cardioselectivity is most pronounced at low doses and is lost at high doses. [Note: Because β1 selectivity of these agents is lost at high doses, they may antagonize β2 receptors.]
In contrast to propranolol, the cardioselective β-blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism.
The cardioselective β-blockers are useful in hypertensive patients with impaired pulmonary function.
These agents are also first-line therapy for chronic stable angina. Bisoprolol and the extended-release formulation of metoprolol are indicated for the management of chronic heart failure.

Acebutolol (β1-selective antagonist) and ***pindolol*** (nonselective β-blocker): are not pure antagonists. These drugs can also weakly stimulate both β1 and β2 receptors and are said to have. These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine.

***Note: **There are no clinically useful β2 selective antagonists.**

III. *Labetalol* and *carvedilol*: antagonists of both α- and β-adrenoceptors:

They are nonselective β-blockers with concurrent α1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other β- blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. Carvedilol also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.
Labetalol is used as an alternative to methyldopa in the treatment of pregnancy-induced hypertension.