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β-Blockers: A systematic review

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ABSTRACT

β blockers are among the most prescribed drugs in the world. They are registered for a wide range of indications including hypertension, angina pectoris, arrhythmias, heart failure and as secondary prevention after myocardial infection (MI). The purpose of this article is to provide a brief outline of Drug Receptor Interaction, Signal transduction mechanisms and main groups of adrenergic receptors. Besides this it envisages the prevalent β Blockers in market & their side effects and mechanism of action of β blockers.

Keywords: β-blocker; Drug receptor; antagonists; agonist; adrenergic.

INTRODUCTION

β- Blockers were initially used to treat arrhythmias, but by the early 1970s they were also widely accepted for managing hypertension [1]. Their initial acceptance as one of the first-line classes of drugs for hypertension was based on their better side-effect profile compared with other antihypertensive drugs available at that time. In the 1980 and 1990 β-blockers were listed as preferred first-line antihypertensive drugs along with diuretics in national hypertension guidelines [2]. The British National Institute for Health and Clinical Excellence and the British Hypertension Society, in their 2004 guidelines, recommended beta-blockers as one of several first-line antihypertensive medications in young, nonblack patients [3]. More recently, the 2007 European Society of Hypertension and European Society of Cardiology reconsidered the role of beta-blockers, recommending them as an option in both initial and subsequent antihypertensive treatment strategies [4]. The current guidelines from the National Heart, Lung, and Blood Institute [5] which were published in 2003 were highly influenced by the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [6] and favor

diuretics as the first-line therapy. However, they indicate that beta-blockers are a suitable alternative, particularly when a compelling cardiac indication is present [7]. Beta-blockers reduce the workload on the heart and help it to beat more regularly.

2. Drug Receptor Interaction:

Receptors are macromolecules involved in chemical signaling between and within cells; they may be located on the cell surface membrane or within the cytoplasm. Activated receptors directly or indirectly regulate cellular biochemical processes (eg; Ion conductance, protein phosphorylation, DNA transcription, enzymatic activity).Molecules (eg: Drugs, Hormones and Neurotransmitters) that bind to a receptor are called ligands [8].

A ligand may activate or inactivate a receptor; activation may either increase or decrease a particular cell function. Each ligand may interact with multiple receptor subtypes. If any drugs are absolutely specific for one receptor or subtype, but most have relative selectivity. Selectivity is the degree to which a drug acts on a given site relative to other sites; selectivity relates largely to physicochemical binding of the drug to cellular receptors.

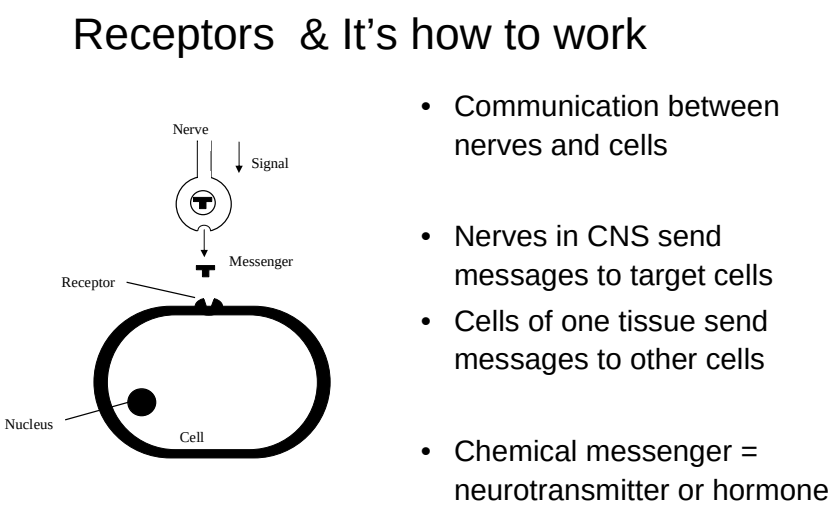


Figure1. Receptors and its mechanism

A drugs ability to affect a given receptor is related to the drugs affinity (Probability of the drug occupying a receptor at any given instant) and intrinsic efficacy (intrinsic-degree to which a ligand activates receptors and leads to cellular response). A drugs affinity and activity are determined by its chemical structure.

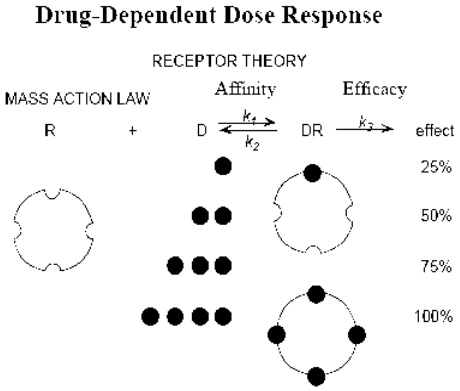


Figure2. Drug-Dependent Dose Response

Physiologic functions (eg; Contraction, secretion) are usually regulated by multiple receptor-mediated mechanisms and several steps (eg; receptor-coupling, multiple intracellular second interaction and ultimate tissue or organ response. Thus several dissimilar drug molecules can often be used to produce a desired response.

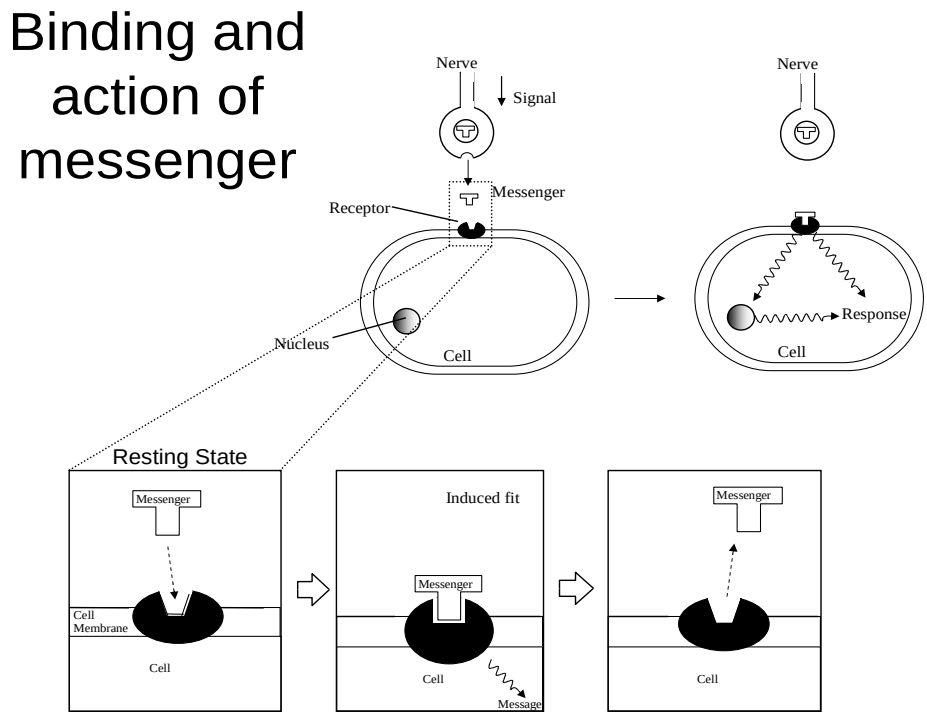


Figure3. Binding and Action of messenger

Ability to bind to a receptor is influenced by external factors as well as by intracellular regulatory mechanisms. Baseline receptor density and the efficiency of stimulus-response

mechanisms vary from tissue to tissue. Drugs aging genetic mutations and disorders can increase (up-regulate) or decrease (down-regulate) the number and binding affinity of receptors.

For example clonidine down-regulate α_2-receptor; rapid withdrawal of clonidine can cause hypertensive crisis. Chronic therapy with β- blockers up-regulates β-receptor density; thus severe hypertension or tachycardia can result from abrupt withdrawal. Receptor up-regulation and down-regulation affect adaptation to drugs (eg; Desensitization, tachyphylaxis, tolerance, acquired resistance, post withdrawal-Supersitivity).Ligands bind to precise molecular regions called recognition sites on receptor macromolecules.

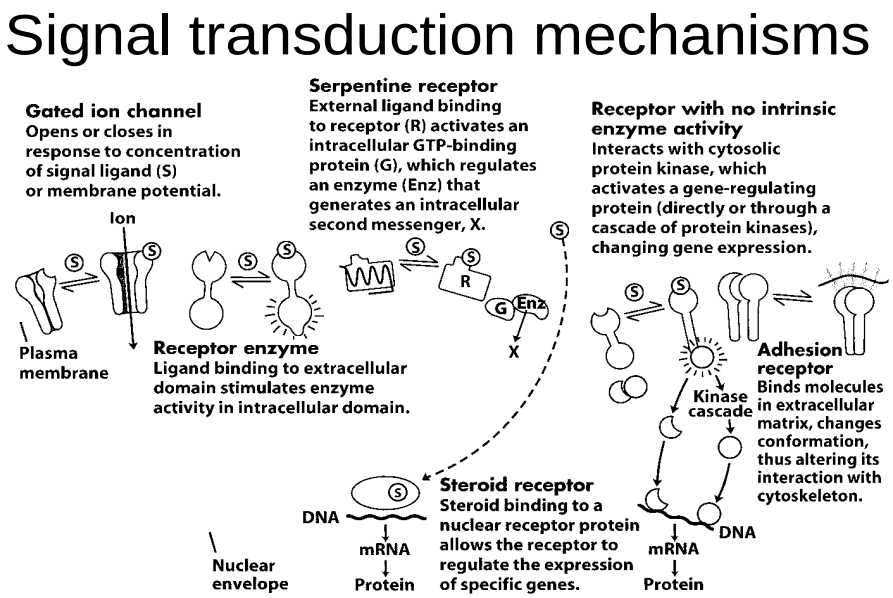


Figure4. Signal transduction mechanisms

The binding site for a drug may be the same as or different from that of an endogenous agonist (Hormone or neurotransmitter). Agonists that bind to an adjacent site or a different site on a receptor are sometimes called allosteric agonists. Nonspecific drug binding also occurs, at molecular site not designated as receptors (plasma proteins). Drug binding to such nonspecific sites prohibits the drug from binding to the receptor and thus inactivates the drug. Unbound drug is available to bind to receptors and thus have an effect.

Table1. Pharmacodynamics: Types of physiologic & drug-receptor proteins

Types	Cellular Location	Examples
Multisubunit Ion Channels	Cell Surface Transmembrane	Acetylcholine, GABA, Glutamate, Glycine
G-Protein Coupled Receptors	Cell Surface Transmembrane	α and β Adrenergic Receptor Protein, Eicosanoids
Protein Kinases	Cell Surface Transmembrane	Growth Factors, Insulin, Peptide Hormones
Transcription Factors	Cytoplasm	Steroid Hormones, Thyroid Hormones, Vitamin D

3. Classification of related agents of β-Blocker:

β-Blockers are drugs that slow the heart rate, decrease cardiac output, lessen the force with which the heart muscle contracts and reduce blood vessel contraction they do this by blocking β-adrenergic receptors in various parts of the body. This prevents adrenaline (epinephrine) from stimulating these receptors. They may be used to treat abnormal heart rhythms (arrhythmias) and prevent abnormally fast heart rate (tachycardia) or irregular rhythms such as premature ventricular beats. Since they reduce the demand of the heart muscle for oxygen they may be useful in treating angina (chest pain), which occurs when the oxygen demand of the heart exceeds the supply. They have become an important drug in improving survival after a person has had a heart attack. Beta-blockers are also used to treat high blood pressure and other heart conditions.

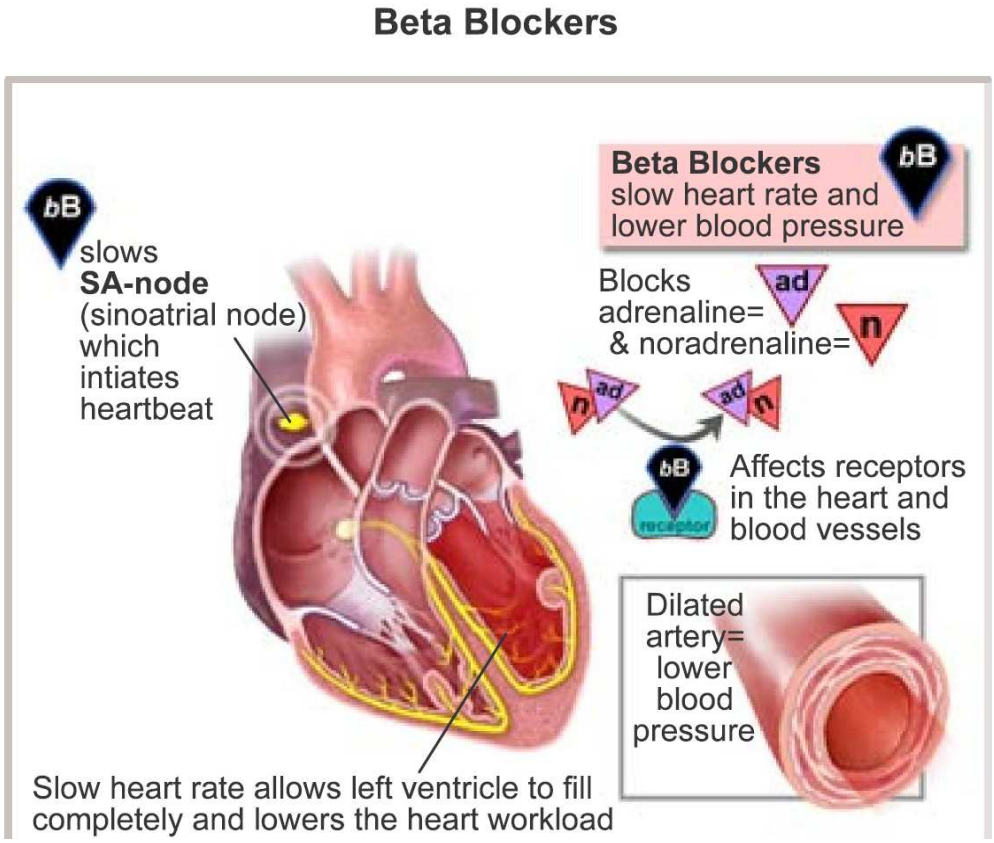


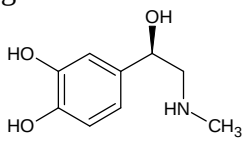
Figure5. General the mechanism of beta-blocker

Beta blockers block the action of endogenous catecholamines (epinephrine & nor-epinephrine), on beta-adrenergic receptors part of the sympathetic nervous system, which mediates the “fight or flight” response. There are three known types of beta receptor designated beta-1, beta-2 and beta-3 receptors. Beta-1- adrenergic receptors are located mainly in the heart and in the kidneys. Beta-2-adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle and skeletal muscle. Beta-3- adrenergic receptors are located in fat cells.

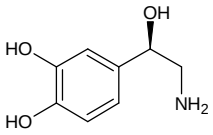
Table2. Beta-adrenergic Receptor: β-1, β-2 and β-3

Beta-1		**Beta-2**		**Beta-3**	
Agonists	***Antagonists***	***Agonists***	***Antagonists***	***Agonists***	***Antagonists***
Denopamine	Acebutolol	Metaproterenol	Butoxamine	Amibegron	SR59230A
Dobutamine	Atenolol	Bitolterol mesylate		Nebivolol	
Xamoterol	Betaxolol	Isoproterenol		Solabegron	
	Bisoprolol	Salbutamol		L-796,568	
	Celiprolol	Ritodrine		CL-316,243	
	Esmolol	Levalbuterol		LY-368,842	
	Metoprolol	Salmeterol		Ro40-2148	
	Nebivolol	Terbutaline			
		Clenbuterol			

There are two main groups of adrenergic receptors alpha & beta. Alpha receptors have the subtypes alpha-1 (Gq Coupled receptor) and alpha-2 (Gi Coupled receptor). Phenylephrine is a Selective agonist of the alpha receptor. Beta receptors have the subtypes beta-1, beta-2 and beta-3. All three are linked to Gs proteins (beta-2 also couples to Gi) which in turn are linked to adenylate cyclase. Agonist binding thus causes a rise in the intracellular concentration of the messenger cAMP. Downstream effectors of cAMP include cAMP-dependent protein kinase (PKA), which mediates some of the intracellular events following hormone binding. Isoprenaline is a selective agonist.



Adrenaline



Noradrenaline

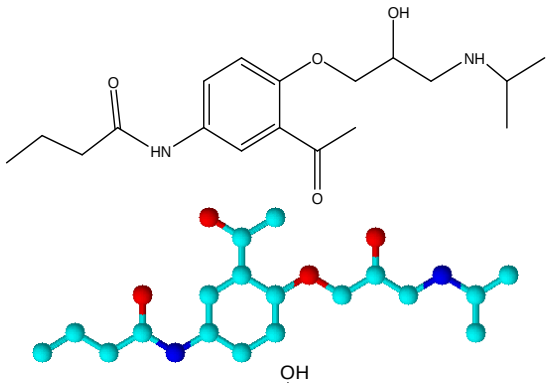
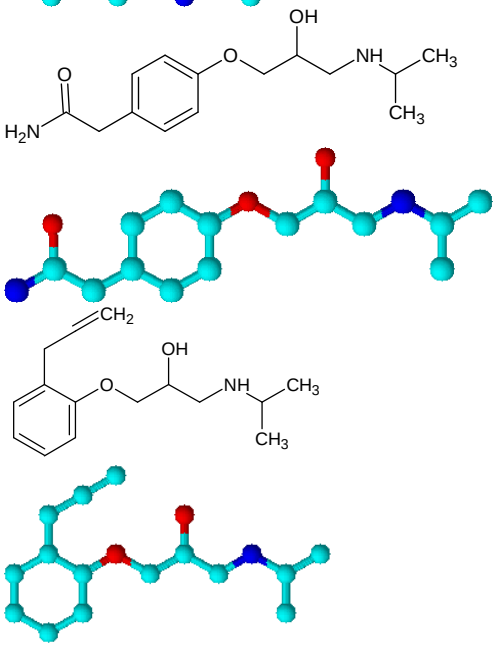
4. Mechanism of action of β blockers

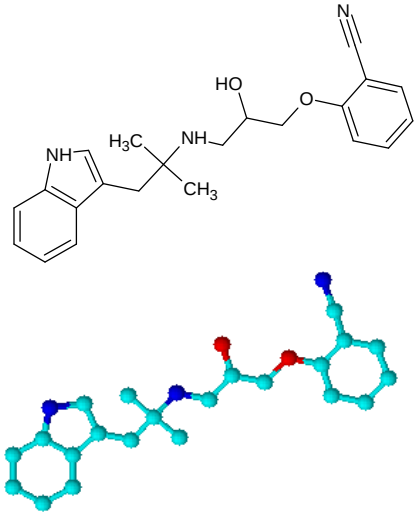
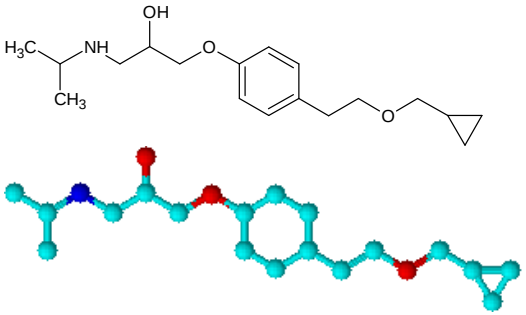
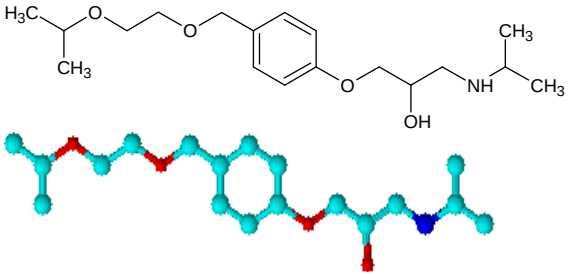
Beta-blockers effectively reduce blood pressure in both systolic-diastolic hypertension and isolated systolic hypertension [9-11]. It has been proposed that they may do so by:

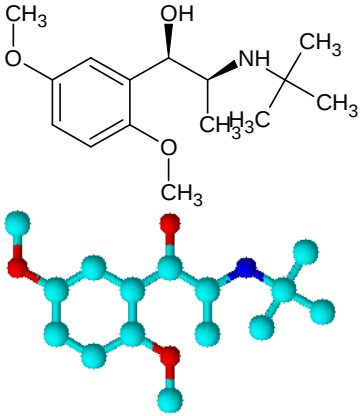
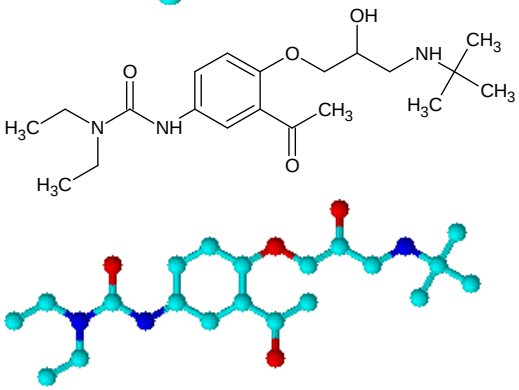
Reducing the heart rate and cardiac output: When catecholamines activate beta-1 receptors in the heart, the heart rate and myocardial contractility increase. By blocking beta-1 receptors, beta-blockers reduce the heart rate and myocardial contractility, thus lowering cardiac output and arterial blood pressure [12].

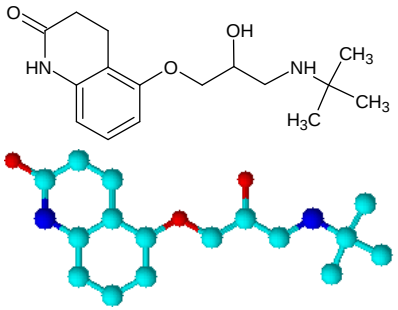
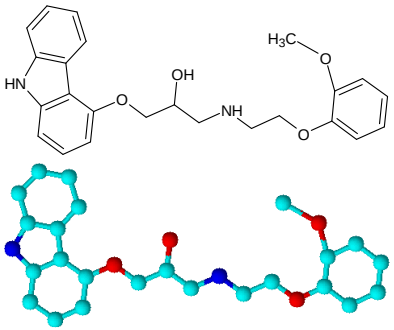
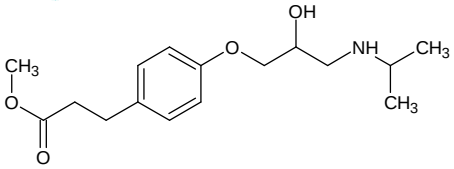
Inhibiting renin release: Activation of the renin-angiotensin system is another major pathway that can lead to elevated arterial blood pressure. Renin release is mediated through the sympathetic nervous system via beta-1 receptors on the juxtaglomerular cells of the kidney. β blockers can therefore lower blood pressure by inhibiting renin release [13].

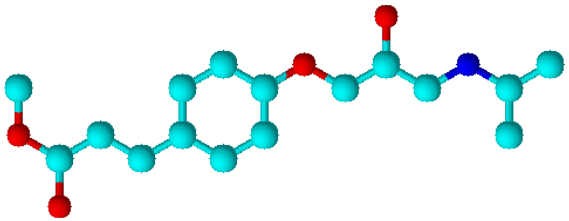
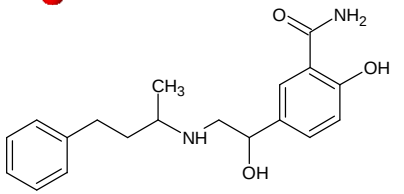
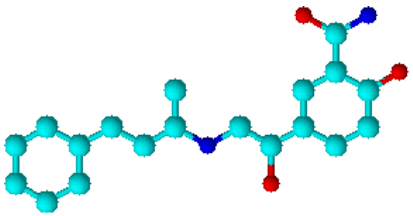
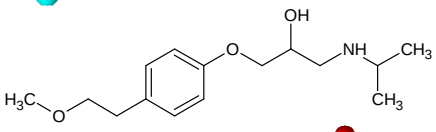
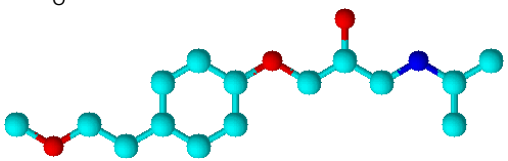
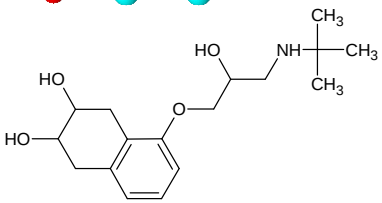
Table3. Prevalent β-Blockers in use & their side effects

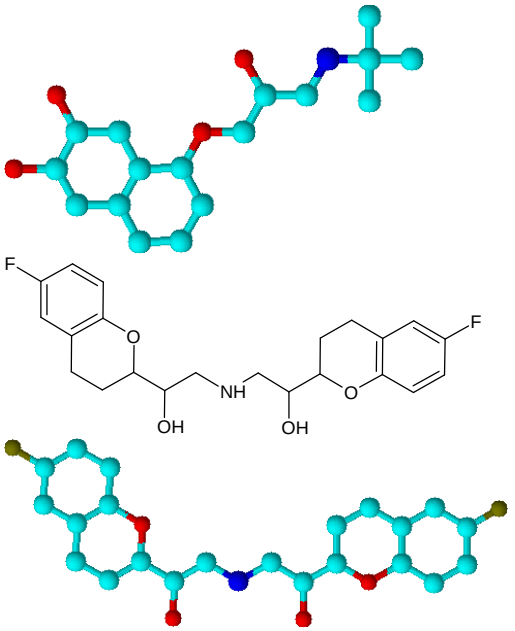
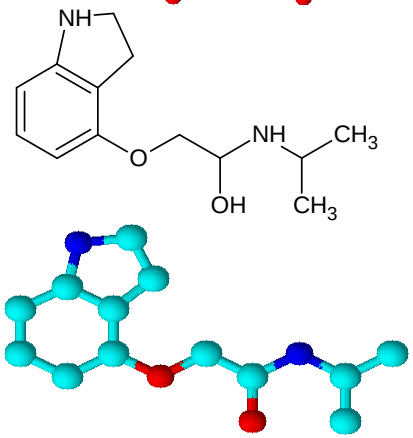
S.No.	Drugs	Trade Name	Applications	Structures	Side Effects
1.	Acebutolol	sectral	Used in the treatment of hypertension, arrhythmias, ventricular, atrial cardiac arrhythmia and acute myocardial infarction in high-risk patients, smith-magenis syndrome [15]		Side effects include abdominal cramps, diarrhea, dizziness, fatigue, depression, headache, nausea, impotence, slow heart rate, low blood pressure, numbness.
2.	Atenolol	Tenormin	Used in cardiovascular diseases and avoid various central nervous system side effects [16].		
3.	Alprenolol	Apllobal	A non-selective β- blocker as well as 5-HT_{1A} Receptor antagonist used in the treatment of angina pectoris [17].		

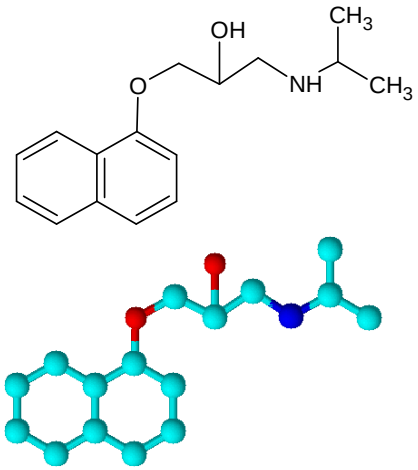
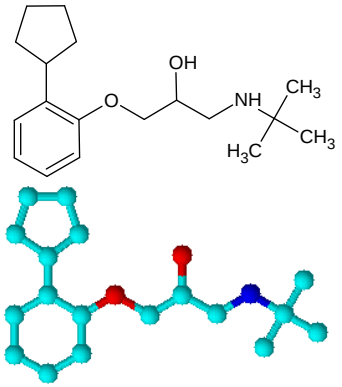
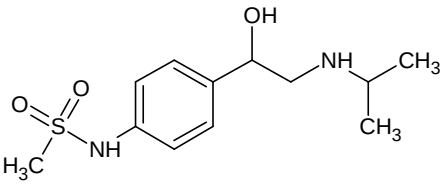
4.	Bucindolol		A non-selective β- blocker with additional weak alpha-blocking properties and some intrinsic sympathomimetic activity.		
5.	Betaxolol	Betoptic	A β-1-adrenergic blocker used in the treatment of hypertension and glaucoma.		Side effects include Transient ocular (temporary eye) discomfort, fatigue, insomnia, nausea, dizziness, lightheadedness, depression, slow heart rate, low blood pressure, cold extremities, and shortness of breath or wheezing.
6.	Bisoprolol	Zebeta	Used for cardiovascular diseases, high blood pressure, and heart pain.		Side effects are mild and transient.

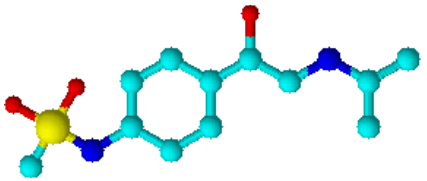
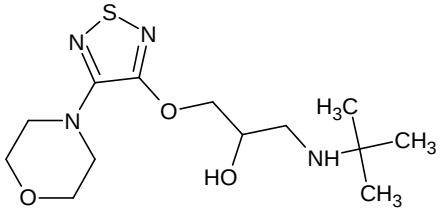
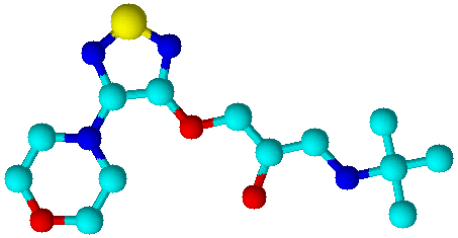
7.	Butaxamine	butoxamine	A β-2-selective beta blocker. Its primary in experimental situation in which blockade of beta-2-receptors is necessary the activity of the drug [18].		
8.	Celiprolol	Cardem	Used not only in high blood pressure but also in mild to moderate blood pressure, for Hypertension & angina pectoris.		Side effects include Headache, nausea, dizziness, abdominal discomfort, palpitations, Disturbances of the gut such as diarrhea, constipation, nausea, vomiting and muscle cramps.

9.	Carteolol	Ocupress	A non-selective β- blocker used to treat glaucoma. It's used alone or with other medication to treat high pressure inside the eye.		Side effects include Blurred vision; increased tear production; sensitivity to light; temporary burning or stinging.
10.	Carvedilol	Carloc	A non-selective β- blocker/α-1 blocker, used in the treatment of mild to moderate Congestive Heart Failure (CHF) [19].		
11.	Esmolol	Brevibloc	A cardio selective β-1-receptor blocker with rapid on set a very short duration of action and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages [20]. It decreases the force and rate of heart contractions by blocking beta-adrenergic receptors of sympathetic nervous system, which are found in the heart		Side effects include Slow or uneven heartbeats; nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes); anxiety, nervousness.

			and other organs of the body [21].		
12.	Labetalol	Normodyne	A mixed α/ β- adrenergic antagonist, which is used to treat high blood pressure [22]. It works by blocking these adrenergic receptors, which decreases peripheral vascular resistance without significantly altering heart rate or cardiac output. The β: α-antagonism of Labetalol is approximately 3:1 [23-24].	 	Some minor side effects like fatigue or weakness, dizziness, drowsiness,headache, nausea and stuffy nose, Some lesscommon labetalol side effects include, heartburn or indigestion, shortness of breath.
13.	Metoprolol	Lopressor	A β-1-receptor blocker, used in cardiovascular system, especially hypertension and angina pectoris (Chest pain), also used after heart attacks.	 	Side effects include swelling of the face, dry eyes and erectile dysfunction in men.
14.	Nadolol	Corgard	A non selective beta-blocker (β-1 & β-2 receptors) used in high blood pressure, migraine headaches and chest pain.		

15.	Nebivolol	Bystolic	A β-1- receptor blocker with nitric oxidepotentiating vasodilatory effect used in treatment of hypertension and, in Europe, also for left ventricular failure [25]. It is highly cardio selective under certain circumstances but has less evidence of survival benefit than other beta-blockers [26].		Side effects include Headache, Anxiety, Nausea, Fatigue, Constipation, Insomnia, Sweating, Dizziness, Chest pain, Difficulty in breathing
16.	Pindolol	Visken	A non-selective β-blocker with partial β-adrenergic receptor agonist activity. It possesses ISA (Intrinsic Sympathomimetic Activity) means pindolol particularly in high doses exerts effects like epinephrine or isoprenaline, but these effects are limited. It also functions as a 5-HT_{1A} receptor weak partial agonist/antagonist. Pindolol shows membrane stabilizing effects like quinidine possibly accounting for its antiarrhymic effects.		Side effects include Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest.

17.	Propranolol	Inderal	A non-selective beta-blocker mainly used in Hypertension. It's in generic form as Propranolol.HCl (hydrochloride salt of Propranolol).Its banned for sports activity (Olympics).		Side effects include swelling of the mouth, face, lips, or tongue); shortness of breath; slow or irregular heartbeat.
18.	Penbutolol	Levatol	Used in the treatment of high blood pressure. It is a noncardioselective beta-blocker and has intrinsic sympathomimetic activity. Penbutolol is a beta-adrenergic blocking agent.		Side effects include Constipation; depression; diarrhea; dizziness; drowsiness; fatigue; hallucinations; lightheadedness; nausea; sleeplessness; stomach cramps; tiredness; vision problems; vivid dreams; vomiting; weakness.
19.	Sotalol	Betapace	Used in rhythm disturbances (cardiac arrhythmias) of the heart, and to treat hypertension. Sotalol is a non-selective beta blocker. It is also a potassium channel blocker and is therefore a class III anti-arrhythmic agent.		Heartburn or indigestion, sour stomach, difficulty sleeping, lack of strength and leg or arm pain.

			Because of this dual-action, Sotalol prolongs both the PR interval and the QT interval.	
20.	Timolol	Timoptol	A non-selective beta-adrenergic receptor blocker. It's used to high blood pressure; prevent heart attacks and migraine headaches. It's ophthalmic from and used to treat open-angle, occasionally secondary glaucoma by reducing aqueous humour production through blockage of the beta receptors on the ciliary epithelium.	 

Inhibiting central nervous sympathetic outflow: Thereby inducing pre-synaptic blockade, which in turn reduces the release of catecholamines. Generating nitric oxide: Reducing peripheral vascular resistance [14].

CONCLUSION

β blockers are effective in long term secondary prevention after myocardial infection and provide life saving benefits in most of the subpopulations assessed. Beta-blockers have been found not to be effective for primary prevention of cardiovascular disease in patients with primary hypertension. The decision to withhold beta-blockers for diagnostic testing should be carefully considered on a case-by-case basis.

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