Cardiovascular system

A. Positive inotropic drugs

Drug classifications:

- *Cardiac glycosides* - *Digoxin , Digitoxin*
- *Phosphodiesterase inhibitors* - *Enoximone , milrinone*
- *Inotropic sympathomimetics* - *dobutamine , dopamine , dopexamine*

Mechanism of Action :

- ***Cardiac glycosides***
  Digoxin increase the force of myocardial contraction and reduce conductivity within the atrioventricular (AV) node.
- ***Phosphodiesterase inhibitors***
  Enoximone and milrinone are selective phosphodiesterase inhibitors which exert most of their effect on the myocardium.
- ***Inotropic sympathomimetics***
  -Dobutamine and dopamine act on beta receptors in cardiac muscle, and increase contractility with little effect on rate.
  - Dopexamine acts on beta receptors in cardiac muscle to produce its positive inotropic effect; and on peripheral dopamine receptors to increase renal perfusion; it is reported not to induce vasoconstriction.

Clinical Use :

- In patients with heart failure who are in sinus rhythm, a satisfactory plasma digoxin concentration can be achieved over a period of about a week.
- Cardiac glycosides are most useful in the treatment of supraventricular tachycardias, especially for controlling ventricular response in persistent atrial fibrillation.
- Digoxin is now rarely used for rapid control of heart rate even with intravenous administration, response may take many hours; persistence of tachycardia is therefore not an indication for exceeding the recommended dose.
- The intramuscular route is not recommended.
- Sustained haemodynamic benefit has been observed after administration of
- phosphodiesterase inhibitors.
- The use of sympathomimetic inotropes in inotropic support and vasodilator in exacerbations of chronic heart failure and in heart failure associated with cardiac surgery cardiogenic shock in infarction.

Digoxin dosing

- Digoxin has a long half-life and maintenance doses need to be given only once daily (although higher doses may be divided to avoid nausea).
- Digitoxin also has a long half-life and maintenance doses need to be given only once daily or on alternate days.
- Renal function is the most important determinant of digoxin dosage, whereas elimination of digitoxin depends on metabolism by the liver.

Digitalisation

- Rapid digitalisation, for atrial fibrillation or flutter, by mouth, 0.75–1.5 mg over 24 hours in divided doses . Maintenance, for atrial fibrillation or flutter, by mouth, according to renal function and initial loading dose; usual range 125–250 micrograms Daily .
- **Slow digitalisation** , for heart failure (for patients in sinus rhythm), by mouth, 62.5–125 micrograms once daily .
- Emergency loading dose, for atrial fibrillation or flutter, by intravenous infusion (but rarely necessary), 0.75–1 mg over at least 2 hours , then maintenance dose by mouth on the following day.

Cautions and contraindications

- Cardiac glycosides should be used with special care in the elderly who may be particularly susceptible to digitalis toxicity.
- Hypokalaemia predisposes the patient to digitalis toxicity; it is managed by giving apotassium sparing diuretic or, if necessary, potassium supplementation.
- monitor blood pressure with phosphodiesterase inhibitors heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count, hepatic enzymes; avoid extravasation .
- The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

Side-effect:

- Unwanted effects depend both on the concentration of the cardiac glycoside in the plasma and on the sensitivity of the conducting system or of the myocardium, which is often increased in heart disease.
- It can sometimes be difficult to distinguish between toxic effects and clinical deterioration because symptoms of both are similar. Also, the plasma concentration alone cannot indicate toxicity reliably but the likelihood of toxicity increases progressively through the range 1.5 to 3 micrograms/ litre for digoxin.
- Regular monitoring of plasma-digoxin concentration during maintenance treatment is not necessary unless problems are suspected.
- Toxicity can often be managed by discontinuing digoxin; serious manifestations require urgent specialist management.
- Digoxin-specific antibody fragments are available for reversal of life-threatening over dosage

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B. Anti-arrhythmic drugs

Drug classification

- *Class I: membrane stabilising drugs (e.g.lidocaine,flecainide)*
- *Class II: beta-blockers*
- *Class III: amiodarone and sotalol (also Class II)*
- *Class IV: calcium-channel blockers (includes verapamil but not dihydropyridines).*

Mechanism of action

- They can also be classified according to their effects on the electrical behaviour of myocardial cells during activity.

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❖ Anti-arrhythmic drugs can be classified clinically into:

- those that act on supraventricular arrhythmias (e.g. verapamil)
- those that act on both supraventricular and ventricular arrhythmias (e.g. disopyramide), and
- those that act on ventricular arrhythmias (e.g. lidocaine (lignocaine)).

Clinical uses;

1. Supraventricular arrhythmias

- Adenosine is usually the treatment of choice for terminating paroxysmal supraventricular tachycardia
- Unlike verapamil,adenosine can be used after a beta-blocker. Verapamilmay be preferable to adenosine in asthma
- cardiac glycoside (such as digoxin, slows the ventricular response in cases of atrial fibrillation and atrial flutter Verapamil is usually effective for supraventricular tachycardias
- Beta-blocker such as esmolol or propranolol, can achieve rapid control of the ventricular rate.

2. Supraventricular and ventricular arrhythmias

- Amiodarone is used in the treatment of arrhythmias particularly when other drugs are ineffective or contraindicated. It may be used for paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. It may also be used for tachyarrhythmias associated with Wolff- Parkinson-White syndrome.
- Disopyramide may be given by intravenous injection to control arrhythmias after myocardial infarction
- Flecainide belongs to the same general class as lidocaine and may be of value for serious symptomatic ventricular arrhythmias. It may also be indicated for junctional re-entry tachycardias and for paroxysmal atrial fibrillation.
- Propafenone is used for the prophylaxis and treatment of ventricular arrhythmias and also for some supraventricular arrhythmias

3. Ventricular arrhythmias

- Lidocaine (lignocaine) is relatively safe and should be considered first for emergency use.
- Moracizine for the prophylaxis and treatment of serious and life-threatening ventricular arrhythmias.
- Mexiletine for treatment of life-threatening ventricular arrhythmias.

Caution and Contraindications

- The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Therefore special care should be taken if two or more are used, especially if myocardial function is impaired.
- Hypokalaemia enhances the arrhythmogenic (pro-arrhythmic) effect of many drugs.
- Cardiac glycosides are contra-indicated in supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome).
- some supraventricular arrhythmias in childhood can be accelerated by verapamil with dangerous consequences. It is also contra-indicated in atrial fibrillation with preexcitation
- (e.g. Wolff-Parkinson-White syndrome)

Side effect

- Bradycardia
- Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism may occur ,amiodarone develop corneal Micro deposits.

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C. *Antihypertensive drugs*

1. *Diuretics*

Drug classifications:

Thiazides and related diuretics : *hydrochlorothiazide, bendroflumethiazide chlortalidone , Xipamide , indapamide ,hydroflumethiazide , benzthiazide, clopamide, cyclopenthiazide, Metolazone*

Loop diuretics :*Furosemide (frusemide), bumetanide, torasemide*

Potassium-sparing diuretics and aldosterone antagonists:*Amiloride,triamterene, Spironolactone, Eplerenone*

Osmotic diuretics: *Mannitol*

Carbonic anhydrase inhibitors: *Acetazolamide*

Mechanism of action:

1. Thiazides and related diuretics:

Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule.

2. Loop diuretics:

Loop diuretics inhibit reabsorption from the ascending limb of the loop of Henle´ in the renal tubule and are powerful diuretics.

3. Potassium-sparing diuretics and aldosterone antagonists:

Amiloride and triamterene on their own are weak diuretics. They cause retention of potassium and are therefore given with thiazide or loop diuretics.

Spironolactone antagonising aldosterone; it is a potassium-sparing diuretic.

***4 .Osmotic diuretics*:** osmotic gradient inside tubular lumen

Carbonic anhydrase inhibitors

Clinical uses:

1. Thiazides and related diuretics:

- Thiazides are used to relieve oedema due to chronic heart failure and, in lower doses, to reduce blood pressure.
- Bendroflumethiazide (bendrofluazide) is widely used for mild or moderate heart failure and for hypertension— alone in the treatment of mild hypertension or with other drugs in more severe hypertension.
- Chlortalidone (chlorthalidone), a thiazide-related compound, has a longer duration of action than the thiazide and may be given on alternate days to control oedema.
- Metolazone is particularly effective when combined with a loop diuretic.
- Indapamide is claimed to lower blood pressure with less metabolic disturbance, particularly less aggravation of diabetes mellitus.
- Potassium supplements or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension.

2. *Loop diuretics:*

- Loop diuretics are used in pulmonary oedema due to left ventricular failure and in patients with chronic heart failure.
- Combination with thiazide diuretic therapy may be effective in patients with oedema resistant to treatment with one diuretic.
- Loop diuretics are used in pulmonary oedema due to left ventricular failure; intravenous administration produces relief of breathlessness and reduces pre-load sooner than would be expected from the time of onset of diuresis. Loop diuretics are also used in patients with chronic heart failure.
- Diuretic-resistant oedema (except lymphoedema and oedema due to peripheral venous stasis or calcium-channel blockers) can be treated with a loop diuretic combined with metolazone.
- Torasemide has properties similar to those of furosemide and bumetanide, and is indicated for oedema and for hypertension.

3. *Potassium-sparing diuretics and aldosterone antagonists*

- Spironolactone, a potassium-sparing diuretic , is chosen for oedema arising from cirrhosis of the liver.
- Spironolactone is also used in primary hyperaldosteronism (Conn's syndrome).
- Eplerenone is licensed for use as an adjunct in left ventricular dysfunction with evidence of heart failure after a myocardial infarction.

4. *Osmotic diuretics*

Mannitol is an osmotic diuretic that can be used to treat cerebral oedema and raised intra-ocular pressure.

5. *Carbonic anhydrase inhibitors*

The carbonic anhydrase inhibitor acetazolamide is a weak diuretic and is little used for its diuretic effect. It is used for prophylaxis against mountain sickness . Acetazolamide and eye drops of dorzolamide and brinzolamide inhibit the formation of aqueous humour and are used in glaucoma .

Cautions and contraindications

- Vigorous diuresis, particularly with loop diuretics, may induce acute hypotension; rapid reduction of plasma volume should be avoided.
- Elderly Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).
- Thiazides and related diuretics can exacerbate diabetes, gout, and systemic lupus erythematosus. Electrolytes should be monitored, particularly with high doses, long-term use, or in renal impairment. Thiazides and related diuretics should also be used with caution in nephrotic syndrome, hyperaldosteronism, malnourishment, hepatic impairment.

- Potassium supplements must not be given with potassium- sparing diuretics. Administration of a potassium sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

Side-effect:

- ***Potassium loss*** Hypokalaemia may occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent of a loop diuretic.
- Furosemide (frusemide) and bumetanide are similar in Activity . The diuresis associated with these drugs is dose related. In patients with impaired renal function very large doses may occasionally be needed; in such doses both drugs can cause deafness and bumetanide can cause myalgia.
- Side-effects of thiazides and related diuretics include mild gastro-intestinal disturbances, postural hypotension, altered plasma lipid concentrations, metabolic and electrolyte disturbances including hypokalaemia , hyponatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, hypochloraemic alkalosis, hyperuricaemia, and gout.

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2. *Angiotensin-converting enzyme inhibitors*

Drug classifications

CAPTOPRIL , ENALAPRIL , FOSINOPRIL , LISINOPRIL , IMIDAPRIL , CILAZAPRIL , PERINDOPRIL, QUINAPRIL , MOEXIPRIL , RAMIPRIL ,, TRANDOLAPRIL

Mechanism of Action

- Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II.

Clinical Use

- *Heart failure* :ACE inhibitors are used in all grades of heart failure, usually combined with a beta-blocker.. However, a low dose of spironolactone may be beneficial in severe heart failure .
- *Hypertension*:An ACE inhibitor may be the most appropriate initial drug for hypertension in younger Caucasian patients; Afro-Caribbean patients, thoseaged over 55 years, and those with primary aldosteronism respond less well . ACE inhibitors are particularly indicated for hypertension in patients with type 1 diabetics with nephropathy.
- *Diabetic nephropathy*: For comment on the role of ACE inhibitors in the management of diabetic nephropathy
- *Prophylaxis of cardiovascular events*: ACE inhibitors are used in the early and long-term management of patients who have had a myocardial infarction,. ACE inhibitors may also have a role in preventing cardiovascular events.
- *Combination products* :Products incorporating an ACE inhibitor with a thiazide diuretic or a calcium channel blocker are available for the management of hypertension. Use of these combination products should be reserved for patients whose blood pressure has not responded adequately to a single antihypertensive drug and who have been stabilised on the individual components of the combination in the same proportions.
- *Initiation under specialist supervision*: ACE inhibitors should be initiated under specialist supervision and with careful clinical monitoring in those with severe heart failure or in those:

➢ receiving multiple or high-dose diuretic therapy (e.g.more than 80 mg of furosemide daily or its equivalent);
➢ with hypovolaemia;
➢ with hyponatraemia (plasma-sodium concentration below 130 mmol/litre);
➢ with hypotension (systolic blood pressure below 90 mmHg);
➢ with unstable heart failure;
➢ receiving high-dose vasodilator therapy;
➢ known renovascular disease.

Renal effects

- Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment.
- Hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced
- Although ACE inhibitors now have a specialised role in some forms of renal disease, including chronic kidney disease,

- they occasionally cause impairment of renal function which may progress and become severe in other circumstances (at particular risk are the elderly)..
- Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia.
- In patients with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are therefore not recommended in patients known to have these forms of critical renovascular disease.
- ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in patients with severe unilateral renal artery stenosis and a normal contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney. ACE inhibitors are therefore best avoided in patients with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If ACE inhibitors are used, they should be initiated only under specialist supervision and renal function should be monitored regularly.
- ACE inhibitors should also be used with particular caution in patients who may have undiagnosed and clinically silent renovascular disease. This includes patients with peripheral vascular disease or those with severe generalised atherosclerosis.

Cautions and Contra-indications

- ACE inhibitors need to be initiated with care in patients receiving diuretics ,first doses can cause hypotension especially in patients taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated or with heart failure.
- They should also be used with caution in peripheral vascular disease or generalized atherosclerosis owing to risk of clinically silent renovascular disease;
- The risk of agranulocytosis is possibly increased in collagen vascular disease (blood counts recommended).
- ACE inhibitors should be used with care in patients with severe or symptomatic aortic stenosis (risk of hypotension) and in hypertrophic cardiomyopathy.
- They should also be used with care (or avoided) in those with a history of idiopathic or hereditary angioedema.
- ACE inhibitors should be used with caution in breast-feeding
- To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulphate; they should also be withheld before desensitisation with wasp or bee venom.
- ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. the first dose should preferably be given at bedtime.
- If the dose of diuretic is greater than 80 mg furosemide or equivalent, the ACE inhibitor should be initiated under close supervision and in some patients the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilised.
- ACE inhibitors are contra-indicated in patients with hypersensitivity to ACE inhibitors
- ACE inhibitors should not be used in pregnancy .

Side-effects

- ACE inhibitors can cause profound hypotension , renal impairment and a persistent dry cough.
- They can also cause angioedema , rash (which may be associated with pruritus and urticaria), pancreatitis, and upper respiratory-tract symptoms such as sinusitis, rhinitis, and sore throat.
- Gastro-intestinal effects reported with ACE inhibitors include nausea, vomiting, dyspepsia, diarrhoea, constipation, and abdominal pain.
- Altered liver function tests, cholestatic jaundice, and hepatitis have been reported.
- Hyperkalaemia, Potassium supplements and potassium sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia .
- hypoglycaemia,
- blood disorders including thrombocytopenia, leucopenia, neutropenia, and haemolytic anaemia have also been reported.
- Other reported side-effects include headache, dizziness, fatigue, malaise, taste disturbance, paraesthesia, bronchospasm, fever, serositis, vasculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leucocytosis, and photosensitivity.

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3. *Angiotensin-II receptor antagonists*

Drug classifications

Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan

Mechanism of Action

- angiotensin-II receptor antagonists with many properties similar to those of the ACE inhibitors.

Clinical Use

- An angiotensin-II receptor antagonist may be used as an alternative to an ACE inhibitor in the management of heart failure or diabetic nephropathy.
- unlike ACE inhibitors, they do not inhibit the breakdown of bradykinin and other kinins, and thus are unlikely to cause the persistent dry cough which commonly complicates ACE inhibitor therapy. They are therefore a useful alternative for patients who have to discontinue an ACE inhibitor because of persistent cough.

Cautions and Contra-indications

- Angiotensin-II receptor antagonists should be used with caution in renal artery stenosis .
- Monitoring of plasma-potassium concentration is advised, particularly in the elderly and in patients with renal impairment; lower initial doses may be appropriate in these patients.
- Angiotensin-II receptor antagonists should be used with caution in aortic or mitral valve stenosis and in hypertrophic cardiomyopathy. Those with primary aldosteronism, and Afro-Caribbean patients (particularly those with left ventricular hypertrophy), may not benefit from an angiotensin-II receptor antagonist.
- Angiotensin-II receptor antagonists, like the ACE inhibitors, should also be avoided in pregnancy and breast-feeding

Side-effects

- Side-effects are usually mild. Symptomatic hypotension including dizziness may occur, particularly in patients with intravascular volume depletion(e.g. those taking high-dose diuretics).
- Hyperkalaemia occurs occasionally; angioedema has also been reported with some angiotensin-II receptor antagonists.

Renin inhibitors

Aliskiren

Renin inhibitors inhibit renin directly; renin converts angiotensinogen to angiotensin I. Aliskiren is licensed for the treatment of hypertension, either alone or in combination with other antihypertensives.

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4. Beta-adrenoceptor blocking drugs

Drug classifications

- ***water-soluble***: Atenolol, celiprolol, nadolol, and sotalol; they are less likely to enter the brain, and may therefore cause less sleep disturbance and nightmares. Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.

- ***lipid –soluble***: Beta-blockers are with a relatively short duration of action have to be given two or three times daily.

- ***intrinsic sympathomimetic activity***: Oxprenolol, pindolol, acebutolol, and celiprolol have they tend to cause less bradycardia than the other beta-blockers and may also cause less coldness of the extremities . Intrinsic sympathomimetic activity (ISA, partial agonist activity) represents the capacity of beta-blockers to stimulate as well as to block adrenergic receptors.

- ***intrinsically longer duration***: of action , atenolol, bisoprolol, carvedilol, celiprolol, and nadolol , need to be given only once daily.

- ***relatively cardioselective***: Atenolol, bisoprolol, metoprolol, nebivolol, and (to a lesser extent) acebutolol, , but they are not cardiospecific

Mechanism of Action

- ***Beta-adrenoceptor blocking drugs (beta-blockers):*** block the beta-adrenoceptors in the heart, peripheral vasculature, bronchi, pancreas, and liver.
- Beta-blockers slow the heart and can depress the myocardium;
- ***Sotalol*** may prolong the QT interval, and it occasionally causes life-threatening ventricular arrhythmias. (important: particular care is required to avoid hypokalaemia in patients taking sotalol)
- ***Labetalol, celiprolol, carvedilol***, ***and nebivolol*** :are beta-blockers that have, in addition, an arteriolar vasodilating action, by diverse mechanisms, and thus lower peripheral resistance.
- The mode of action of beta-blockers in hypertension is not understood, but they reduce cardiac output, alter baroceptor reflex sensitivity, and block peripheral adrenoceptors. Some beta-blockers depress plasma rennin secretion. It is possible that a central effect may also partly explain their mode of action.

Clinical Use

- Many beta-blockers are now available and in general they are all equally effective. There are, however, differences between them which may affect choice in treating particular diseases or individual patients...
- ***Hypertension-.*** Beta-blockers are effective for reducing blood pressure but other antihypertensives are usually more effective for reducing the incidence of stroke, myocardial infarction, and cardiovascular mortality, especially in the elderly. Beta-blockers can be used to control the pulse rate in patients with phaeochromocytoma . However, they should never be used alone as beta-blockade without concurrent alpha-blockade may lead to a hypertensive crisis.
- ***Angina*** By reducing cardiac work beta-blockers improve exercise tolerance and relieve symptoms in patients with angina.. Sudden withdrawal may cause an exacerbation of angina

and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped. There is a risk of precipitating heart failure when beta-blockers and verapamil are used together in established ischaemic heart disease .

- ***Myocardial infarction*** some beta-blockers can reduce the recurrence rate of myocardial infarction. Atenolol and metoprolol may reduce early mortality after intravenous and subsequent oral administration in the acute phase, while acebutolol, metoprolol, propranolol, and timolol have protective value when started in the early convalescent phase. Sudden cessation of a betablocker can cause a rebound worsening of myocardial ischaemia.
- ***Arrhythmias*** Beta-blockers act as anti-arrhythmic drugs can be used in conjunction with digoxin to control the ventricular response in atrial fibrillation, especially in patients with thyrotoxicosis. Beta-blockers are also useful in the management of supraventricular tachycardias, and are used to control those following myocardial infarction . Esmolol is a relatively cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of supraventricular arrhythmias, sinus tachycardia, or hypertension, acute myocardial infarction. Sotalol, a non-cardioselective beta-blocker with additional class III anti-arrhythmic activity, is used for prophylaxis in paroxysmal supraventricular arrhythmias. It also suppresses ventricular ectopic beats and non-sustained ventricular tachycardia.
- ***Heart failure*** Beta-blockers may produce benefit in heart failure by blocking sympathetic activity. Bisoprolol and carvedilol reduce mortality in any grade of stable heart failure; nebivolol is licensed for stable mild to moderate heart failure in patients over 70 years..
- ***Thyrotoxicosis.*** Administration of propranolol can reverse clinical symptoms of thyrotoxicosis within 4 days. Routine tests of increased thyroid function remain unaltered. The thyroid gland is rendered less vascular thus making surgery easier
- ***Other uses*** Beta-blockers have been used to alleviate some symptoms of anxiety; probably patients with palpitation, tremor, and tachycardia respond best . Beta-blockers are also used in the prophylaxis of migraine . Betaxolol, carteolol, levobunolol, metipranolol and timolol are used topically in glaucoma .
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<u>Cautions and Contra-indications</u>

- Avoid abrupt withdrawal especially in ischaemic heart disease; first degree AV block; they are contra-indicated in patients with second- or third-degree heart block. Beta-blockers should also be avoided in patients with worsening unstable heart failure; care is required when initiating a beta-blocker in those with stable heart failure.
- portal hypertension (risk of deterioration in liver function);
- Diabetes; Beta-blockers are not contra-indicated in diabetes; however, they can lead to a small deterioration of glucose tolerance and interfere with metabolic and autonomic responses to hypoglycaemia.
- History of obstructive airways disease (introduce cautiously and monitor lung function).
- myasthenia gravis; psoriasis;
- symptoms of hypoglycaemia and thyrotoxicosis may be masked .
- History of hypersensitivity— may increase sensitivity to allergens and result in more serious hypersensitivity response, also may reduce response to adrenaline (epinephrine)
- Reduce dose of oral propranolol in hepatic impairment; renal impairment ; pregnancy ; breast-feeding ; interactions: mainly: verapamil interaction,
- Asthma , Bronchospasm ,beta-blockers, including those considered to be cardioselective, should not be given to patients with a history of asthma or bronchospasm. However, in rare situations where there is no alternative a cardioselective beta-blocker is given to these patients with extreme caution and under specialist supervision

- uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third- degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; phaeochromocytoma .
- Beta blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

Side-effects

- gastro-intestinal disturbances;
- bradycardia, heart failure, hypotension, conduction disorders,
- peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud's phenomenon); . Beta-blockers associated with fatigue, coldness of the extremities (may be less common with those with ISA, see above), and sleep disturbances with nightmares (may be less common with the water-soluble beta blockers).
- bronchospasm , dyspnoea;
- headache, fatigue, sleep disturbances, paraesthesia, dizziness, vertigo, psychoses;
- sexual dysfunction; purpura, thrombocytopenia; visual disturbances; exacerbation of psoriasis, alopecia; rarely rashes and dry eyes (reversible on withdrawal).

5. *Vasodilator antihypertensive drugs*

Drug classifications:

- ***Arteriodilatores*** Hydralazine , Minoxidil
- ***Veno- Arteriodilatores*** Sodium nitroprusside , Diazoxide
  Others- Ambrisentan, bosentan, epoprostenol , iloprost, sildenafil, and sitaxentan

Mechanism of action

- Direct relaxation to the vascular smooth muscles

Clinical uses:

- Vasodilators have a potent hypotensive effect, especially when used in combination with a beta-blocker and a thiazide.
- Diazoxide has been used by intravenous injection in hypertensive emergencies.
- Hydralazine is given by mouth as an adjunct to other antihypertensives for the treatment of resistant hypertension but is rarely used.
- Sodium nitroprusside is given by intravenous infusion to control severe hypertensive crises on the rare occasions when parenteral treatment is necessary.
- Minoxidil should be reserved for the treatment of severe hypertension resistant to other drugs.
- Ambrisentan, bosentan, epoprostenol , iloprost, sildenafil, and sitaxentan are licensed for the treatment of some types of pulmonary hypertension.

Caution and Contraindications:

- A warning on the hazards of a very rapid fall in blood pressure.

Side effect :

- Hydralazine alone causes tachycardia and fluid retention. The incidence of sideeffects is lower if the dose is kept below 100 mg daily, but systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis, or any other unexplained ill health.
- Vasodilatation is accompanied by increased cardiac output and tachycardia and the patients develop fluid retention. For this reason the addition of a beta-blocker and a diuretic (usually furosemide, in high dosage) are mandatory.
- Hypertrichosis is troublesome and renders this drug unsuitable for women.

6. Centrally acting antihypertensive drugs

Drug classifications

Methyldopa Moxonidine Clonidine

Mechanism of action

- Methyldopa is a centrally acting antihypertensive

Clinical uses

- Methyldopa may be used for the management of hypertension in pregnancy.
- Moxonidine, a centrally acting drug, is licensed for mild to moderate essential hypertension. It may have a role when thiazides, calcium-channel blockers, ACE inhibitors, and beta-blockers are not appropriate or have failed to control blood pressure.

Caution and Contraindications

- with Methyldopa , monitor blood counts and liver-function before treatment . positive direct Coombs' test in up to 20% of patients (may affect blood cross-matching).
- Avoid abrupt withdrawal of Moxonidine or Clonidine (if concomitant treatment with beta-blocker.

Side effect :

- Side-effects are minimised if the daily dose is kept below 1 g.
- Clonidine has the disadvantage that sudden withdrawal may cause a hypertensive crisis

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7. Alpha-adrenoceptor blocking drugs

Drug classifications *Prazosin , Doxazosin, Alfuzosin tamsulosin indoramin, terazosin*

Mechanism of action:

- Prazosin has post-synaptic alpha-blocking and vasodilator properties and rarely causes tachycardia.

Clinical uses:

- Alpha-blockers can be used with other antihypertensive drugs in the treatment of resistant hypertension .
- ***Prostatic hyperplasia*** Alfuzosin, doxazosin, indoramin, prazosin, tamsulosin, and terazosin are indicated for benign prostatic hyperplasia.

Caution and Contraindications

- It may reduce blood pressure rapidly after the first dose and should be introduced with caution.

Side effect

- gastro-intestinal disturbances; postural hypotension, oedema.

8. Adrenergic neurone blocking drugs

Guanethidine

- Adrenergic neurone blocking drugs prevent the release of noradrenaline from postganglionic adrenergic neurones. These drugs do not control supine blood pressure and may cause postural hypotension. For this reason they have largely fallen from use, but may be necessary
- with other therapy in resistant hypertension. Guanethidine, which also depletes the nerve endings of noradrenaline, is licensed for rapid control of blood pressure.

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9. Calcium-channel blockers

Drug classifications

- Dihydropyridine calcium-channel blockers (nifedipine - Short-acting , felodipine, isradipine, lacidipine, lercanidipine, nicardipine, , amlodipine and nimodipine -long - acting).
- Non– dihydropyridines calcium-channel blockers (Verapamil and diltiazem).

Mechanism of action

- Calcium-channel blockers (less correctly called 'calcium- antagonists') interfere with the inward displacement of calcium ions through the slow channels of active cell membranes.
- They influence the myocardial cells, the cells within the specialised conducting system of the heart, and the cells of vascular smooth muscle. Thus, myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed, and coronary or systemic vascular tone may be diminished.

Clinical uses

- Verapamil is used for the treatment of angina , hypertension and arrhythmias. It is a highly negatively inotropic and it reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should not be used with beta-blockers.
- Nifedipine relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It has more influence on vessels and less on the myocardium and has no anti-arrhythmic activity.
- Short-acting formulations of nifedipine are not recommended for angina or long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia.

- Diltiazem is effective in most forms of angina; the longer-acting formulation is also used for hypertension. It may be used in patients for whom beta-blockers are contra-indicated or ineffective. It has a less negative inotropic effect than verapamil and significant myocardial depression occurs rarely. Nevertheless because of the risk of bradycardia it should be used with caution in association with beta-blockers.
- Nicardipine has similar effects to those of nifedipine and may produce less reduction of myocardial contractility. Amlodipine and felodipine also resemble nifedipine and nicardipine in their effects and do not reduce myocardial contractility and they do not produce clinical deterioration in heart failure.
- Nifedipine, nicardipine, amlodipine, and felodipine are used for the treatment of angina or hypertension. All are valuable in forms of angina associated with coronary vasospasm.
- Isradipine, lacidipine, and lercanidipine have similar effects to those of nifedipine and nicardipine; they are indicated for hypertension only.
- Nimodipine is related to nifedipine but the smooth muscle relaxant effect preferentially acts on cerebral arteries. Its use is confined to prevention and treatment of vascular spasm following aneurysmal subarachnoid haemorrhage.

- ***Unstable angina*** Calcium-channel blockers do not reduce the risk of myocardial infarction in unstable angina. The use of diltiazem or verapamil should be reserved for patients resistant to treatment with beta-blockers .

Caution and contraindications

- There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of angina.

Side effect

- Constipation is the most common side-effect of Verapamil
- Verapamil and diltiazem should usually be avoided in heart failure because they may further depress cardiac function and cause clinically significant deterioration.
- Side-effects associated with vasodilatation of dihydropyridines such as flushing and headache (which become less obtrusive after a few days), and ankle swelling (which may respond only partially to diuretics) are common.

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D. Antianginal Nitrates

Drug classifications:

- Glyceryl trinitrate

Mechanism of action

- potent coronary vasodilators,
- their principal benefit follows from a reduction in venous return which reduces left ventricular work.

Clinical uses

- Nitrates have a useful role in angina.
- Sublingual glyceryl trinitrate is one of the most effective drugs for providing rapid symptomatic relief of angina, but its effect lasts only for 20 to 30 minutes; the 300-microgram tablet is often appropriate when glyceryl trinitrate is first used. The aerosol spray provides an alternative method of rapid relief of symptoms for those who find difficulty in dissolving sublingual preparations. Duration of action may be prolonged by modified-release and transdermal preparations (but tolerance may develop)

- Isosorbide dinitrate is active sublingually and is a more stable preparation for those who only require nitrates infrequently. It is also effective by mouth for prophylaxis; although the effect is slower in onset, it may persist for several hours. Duration of action of up to 12 hours is claimed for modified-release preparations.
- The activity of isosorbide dinitrate may depend on the production of active metabolites, the most important of which is isosorbide mononitrate. Isosorbide mononitrate itself is also licensed for angina prophylaxis; modified-release formulations (for once daily administration) are available.
- Glyceryl trinitrate or isosorbide dinitrate may be tried by intravenous injection when the sublingual form is ineffective in patients with chest pain due to myocardial infarction or severe ischaemia. Intravenous injections are also useful in the treatment of acute left ventricular failure.

Caution and contraindications

- avoid abrupt withdrawal; tolerance ,hypersensitivity to nitrates; hypotensive conditions and hypovolaemia.

Side effect

- Unwanted effects such as flushing, headache, and postural hypotension may limit therapy, especially when angina is severe or when patients are unusually sensitive to the effects of nitrates.
- Specific side-effects following injection (particularly if given too rapidly) include severe hypotension
- ***Tolerance*** Many patients on long-acting or transdermal nitrates rapidly develop tolerance (with reduced therapeutic effects). Reduction of blood-nitrate concentrations to low levels for 4 to 8 hours each day usually maintains effectiveness in such patients. If tolerance is suspected during the use of transdermal patches they should be left off for several consecutive hours in each 24 hours; in the case of modified-release tablets of isosorbide dinitrate (and conventional formulations of isosorbide mononitrate), the second of the two daily doses should be given after about 8 hours rather than after 12 hours. Conventional formulations of isosorbide mononitrate should not usually be given more than twice daily

unless small doses are used; modified release formulations of isosorbide mononitrate should only be given once daily, and used in this way do not produce tolerance.

Other antianginal drugs

Nicorandil: a potassium-channel activator with a nitrate component, has both arterial and venous vasodilating properties and is licensed for the prevention and longterm treatment of angina . Nicorandil has
similar efficacy to other antianginal drugs in controlling symptoms; it may produce additional symptomatic benefit in combination with other antianginal drugs .

Ivabradine : lowers the heart rate by its action on the sinus node. It is licensed for the treatment of angina in patients in normal sinus rhythm when beta-blockers are contra-indicated or not tolerated.

E. Anticoagulants , Antiplatelet and Fibrinolytic drugs

Drug classifications

- ***Anticoagulants***

Parenteral anticoagulants *Heparin , Fondaparinux ,*
Low molecular weight heparins - (bemiparin, dalteparin, enoxaparin, and tinzaparin
Heparinoids - (Danaparoid)
Hirudins - (Lepirudin) , (Bivalirudin)

Oral anticoagulants Oral *Warfarin, acenocoumarol , phenindione*
Dabigatran etexilate , Rivaroxaban

- ***Antiplatelet drugs*** *Aspirin , Clopidogrel , Dipyridamole*
glycoprotein IIb/IIIa inhibitor - (abciximab, eptifibatide, tirofiban)
- ***Fibrinolytic drugs*** *Streptokinase , Reteplase , Tenecteplase , Alteplase, Streptokinase , urokinase*

Mechanism of action:

➢ ***Anticoagulants***

- Heparin - Irreversibly inactivates factor II_a (thrombin) and factor X_a, as well as activated factors IX, XI, and XII .
- Fondaparinux is a selective indirect factor Xa inhibitor
- Bivalirudin, a hirudin analogue,- is a thrombin inhibitor.
- warfarin, acenocoumarol , phenindione - antagonise the effects of vitamin K.
- Dabigatran etexilate,- a direct thrombin inhibitor
- Rivaroxaban,- a direct inhibitor of activated factor X.

➢ ***Antiplatelet drugs***

- Aspirin , Clopidogrel , Dipyridamole - decrease platelet aggregation and may inhibit thrombus formation in the arterial circulation.
- Glycoprotein IIb/ IIIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets.

➢ ***Fibrinolytic drugs***

- Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

Clinical uses

➢ ***Anticoagulants :***

- Heparin often referred to as ‘standard’ or ‘unfractionated heparin’ have a longer duration of action , used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion.
- Heparins are used for the management of venous thromboembolism in pregnancy because they do not cross the placenta.

- Heparin is also used in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.
- For the initial treatment of deep-vein thrombosis and pulmonary embolism a low molecular weight heparin is used.
- A low molecular weight heparin or, in some circumstances, heparin is also used in regimens for the management of myocardial infarction and unstable angina , and for the prevention of clotting in extracorporeal circuits.
- low molecular weight heparin is effective for the prevention of postoperative deep-vein thrombosis and pulmonary embolism in 'high-risk' patients.
- Danaparoid is a heparinoid used for prophylaxis of deep-vein thrombosis in patients undergoing general or orthopaedic surgery , it also has a role in patients who develop thrombocytopenia in association with heparin
- Lepirudin, a recombinant hirudin, is licensed for anticoagulation in patients with Type II (immune) heparin induced thrombocytopenia who require parenteral antithrombotic treatment.
- Bivalirudin, a hirudin analogue, is a thrombin inhibitor which is licensed as an anticoagulant for patients undergoing percutaneous coronary intervention.
- An oral anticoagulant (usually warfarin,) is started at the same time as the heparin (the heparin needs to be continued for at least 5 days and until the INR has been in the therapeutic range for 2 consecutive days).
- The main indication for these oral anticoagulants is deep-vein thrombosis. Patients with pulmonary embolism should also be treated, as should those with atrial fibrillation who are at risk of embolisation
- Dabigatran , Rivaroxaban are given orally for prophylaxis of venous thromboembolism.

➢ ***Antiplatelet drugs***

- Long-term use of aspirin is of benefit for all patients with established cardiovascular disease.
- Clopidogrel is licensed for the prevention of ischaemic events in patients with a history of symptomatic ischaemic disease. Clopidogrel, in combination with low-dose aspirin, is also licensed for acute coronary syndrome without ST-segment elevation.
- Clopidogrel monotherapy is an alternative when aspirin is contra-indicated, for example in those with aspirin hypersensitivity.
- Dipyridamole is used as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. Modified release preparations are licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks.
- Abciximab is licensed as an adjunct to heparin and aspirin for the prevention of ischaemic complications in high risk patients undergoing percutaneous transluminal coronary intervention.

➢ ***Fibrinolytic drugs***

- Thrombolytic drugs are indicated for any patient with acute myocardial infarction for whom the benefit is likely to outweigh the risk of treatment.

Cautions and contraindications

- ***Anticoagulants***

- ***Monitoring of warfarin*** is essential that the INR be determined daily or on alternate days in early days of treatment, then at longer intervals then up to every 12 weeks.
- These oral anticoagulants should not be used in cerebral artery thrombosis or peripheral artery occlusion.
- Warfarin, acenocoumarol, and phenindione are teratogenic and should not be given in the first trimester of pregnancy.

- ***Antiplatelet drugs***

- Unduly high blood pressure must be controlled before aspirin is given.
- If the patient is at a high risk of gastro-intestinal bleeding, a proton pump inhibitor can be added.

- ***Fibrinolytic drugs***

- Thrombolytic drugs should be used with caution if there is a risk of bleeding including that from venepuncture or invasive procedures , in external chest compression, pregnancy, elderly, hypertension, conditions in which thrombolysis might give rise to embolic complications such as enlarged left atrium with atrial fibrillation
- Thrombolytic drugs are contraindicated in recent haemorrhage, trauma, or surgery.

Side-effect

- ***Anticoagulants***

- If haemorrhage occurs it is usually sufficient to withdraw heparin, but if rapid reversal of the effects of heparin is required, protamine sulphate.
- heparin-induced thrombocytopenia is immune-mediated and does not usually develop until after 5–10 days; it can be complicated by thrombosis.
- Inhibition of aldosterone secretion by heparin (including low molecular weight heparins) can result in hyperkalaemia.
- The main adverse effect of all oral anticoagulants is haemorrhage.

- ***Antiplatelet drugs***

- Aspirin possess high risk of gastro-intestinal bleeding, hypersensitivity and increase bleeding tendency.

- ***Fibrinolytic drugs***

- Side-effects of thrombolytics are mainly nausea and vomiting and bleeding.

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F. Lipid-regulating drugs

Drug classifications

- ***Statins*** (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin).
- ***Bile acid sequestrants*** Colesevelam, colestipol, and colestyramine (cholestyramine)
- ***Ezetimibe***
- ***Fibrates*** (Bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil)
- ***Nicotinic acid group*** (nicotinic acid , Acipimox)
- ***Omega-3 fatty acid compounds*** The omega-3 fatty acid compounds comprise omega-3-acid ethyl esters (Omacorc) and omega-3-marine triglycerides (Maxepac).

Mechanism of action:

- ***Statins*** are competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver.
- ***Bile acid sequestrants*** act by binding bile acids, preventing their reabsorption; this promotes hepatic conversion of cholesterol into bile acids.
- ***Ezetimibe*** inhibits the intestinal absorption of cholesterol.

Clinical uses

- A statin reduces the risk of cardiovascular disease events, irrespective of serum cholesterol concentration, and is the drug of first choice for primary and secondary prevention of cardiovascular disease.
- A statin is also the drug of first choice for treating hypercholesterolaemia and moderate hypertriglyceridaemia.
- Statin therapy should be considered for all patients over 40 years with diabetes mellitus (type 1and 2).
- If statins are contra-indicated or not tolerated, a fibrate or a bile acid sequestrant may be considered for primary or secondary prevention;
- nicotinic acid is an option for secondary prevention.
- Ezetimibe is licensed as an adjunct to dietary manipulation in patients with primary hypercholesterolaemia in combination with a statin or alone.
- Fibrates are first-line therapy only in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin.
- The value of nicotinic acid is limited by its side-effects, especially vasodilatation . Nicotinic acid is licensed for use with a statin if the statin alone cannot adequately control dyslipidaemia.
- Omega-3 fatty acid compounds may be used to reduce triglycerides, as an alternative to a fibrate and in addition to a statin, in patients with combined (mixed) hyperlipidaemia not adequately controlled with a statin alone.

Cautions and contraindications

- Combination of a statin with a fibrate or with nicotinic acid carries an increased risk of side-effects (including rhabdomyolysis) , monitoring of liver function and creatine kinase should also be considered.
- The concomitant administration of gemfibrozil with a statin increases the risk of rhabdomyolysis considerably— this combination should not be used.
- Bile acid sequestrants interfere with the absorption of fat-soluble vitamins; supplements of vitamins A, D, and K may be required when treatment is prolonged.

Side-effect

- The statins can cause various muscular side-effects, including myositis, which can lead to rhabdomyolysis.
- As bile acid sequestrants are not absorbed, gastro-intestinal side-effects predominate.
- Fibrates can cause a myositis-like syndrome, especially if renal function is impaired .

Respirstory System
Drug for asthma and COPD

Drug classification

- *Beta - adrenoceptor agonists*
- *Short-acting beta agonists* — *salbutamol terbutaline*
- *Long-acting beta agonists* — *Formoterol salmeterol*
- *Other adrenoceptor agonists* — *Adrenaline*

- *Bronchodilators*
- *Antimuscarinic bronchodilators* — *Ipratropium*
- *Methylxanthines* — *Theophylline*

- *Corticosteroids*
- *Inhaled* — *Beclomethasone, Budesonide, Flunisolide, Fluticasone, Mometasone, Triamcinolone acetonide*
- *Systemic* — *Methylprednisolone, Prednisolone, Prednisone*

- *Cromoglicate and related therapy* — *sodium cromoglicate, nedocromil*

- *Leukotriene receptor antagonists* — *montelukast, zafirlukast,*

- *Immunomodulatores* — *Omalizumab*

- *5-Lipoxygenase Inhibitor* — *Zileuton*

Mechanism of action

- *Beta-adrenoceptor agonists – Bronchodilation:* Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP, producing functional antagonism of bronchoconstriction.
- *Antimuscarinic bronchodilators*

- *Methylxanthines Bronchodilation.* Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism. May affect eosinophilic infiltration into bronchial mucosa as well as decreases T-lymphocyte numbers in epithelium. Increases diaphragm contractility and mucociliary clearance.

- *Corticosteroids Anti-inflammatory:* Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. Reverse β2-receptor downregulation. Inhibit microvascular leakage.

- *Cromoglicate and related therapy- Anti-inflammatory:* Blocks early and late reaction to allergen. Interferes with chloride channel function. Stabilizes mast cell membranes and inhibits activation and release of mediators from eosinophils and epithelial cells. Inhibits acute response to exercise, cold dry air, and SO_2.

- *Leukotriene receptor antagonists***:** selective competitive inhibitor of CysLT1 receptor
- *Immunomodulatores :* Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE).
- *5-Lipoxygenase Inhibitor :* Inhibits the production of leukotrienes from arachidonic acid, both LTB4 and the cysteinyl leukotrienes.

Clinical uses

- *Short-acting beta agonists* :mild to moderate symptoms of asthma respond rapidly to the inhalation of a selective short-acting beta agonist such as salbutamol or terbutaline. If beta agonist inhalation is needed more often than once daily, prophylactic treatment should be considered. Regular treatment with an inhaled short-acting beta agonist is less effective than 'as required' inhalation and is not appropriate prophylactic treatment. A short-acting beta agonist inhaled immediately before exertion reduces exercise-induced asthma; however, frequent exercise-induced asthma probably reflects poor overall control and calls for reassessment of asthma treatment.
- *Long-acting beta agonists :*Formoterol and salmeterol are longer-acting beta agonists which are administered by inhalation. Added to regular inhaled corticosteroid treatment in the long-term control of chronic asthma and they can be useful in nocturnal asthma. Salmeterol should not be used for the relief of an asthma attack; it has a slower onset of action than salbutamol or terbutaline. Formoterol is licensed for short-term symptom relief and for the prevention of exercise-induced bronchospasm.
- *Other adrenoceptor agonists:* Adrenaline (epinephrine) injection (1 in 1000) is used in the emergency treatment of acute allergic and anaphylactics.

- *Antimuscarinic bronchodilators*: Ipratropium can provide short-term relief in chronic asthma, but short-acting beta agonists act more quicklyand are preferred. Ipratropium by nebulisation can be added to in life-threatening asthma or if acute asthma fails to improve with standard therapy . The aerosol inhalation of ipratropium can be used for short-term relief in mild chronic obstructive pulmonary disease in patients who are not using a long-acting antimuscarinic drug. Tiotropium, a long-acting antimuscarinic bronchodilator, is effective for the management of chronic obstructive pulmonary disease; it is not suitable for the relief of acute bronchospasm.

- *Theophylline*: is a bronchodilator used for asthma and stable chronic obstructive pulmonary disease; it is not generally effective in exacerbations of chronic obstructive pulmonary disease. Aminophylline, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe

attacks of asthma. It must be given by very slow intravenous injection (over at least 20 minutes); it is too irritant for intramuscular use.

- *Corticosteroids:* are used for the management of reversible and irreversible airways disease. An inhaled corticosteroid used for 3–4 weeks may help to distinguish asthma from chronic obstructive pulmonary disease; improvement over 3–4 weeks suggests Asthma.

- *Cromoglicate and related therapy:* They may be of value in asthma with an allergic basis, prophylaxis with sodium cromoglicate is less effective than prophylaxis with corticosteroid inhalation

- *Leukotriene receptor antagonists:* are effective in asthma when used alone or with an inhaled corticosteroid . Montelukast has not been shown to be more effective than a standard dose of inhaled corticosteroid but the two drugs appear to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise-induced asthma and in those with concomitant rhinitis but they are less effective in those with severe asthma who are also receiving high doses of other drugs.
- *Omalizumab:*is licensed for severe persistent allergic asthma cannot be controlled adequately with high-dose inhaled corticosteroid together with a long acting beta agonist.

Cautions and contraindications

- Beta agonists should be used with caution in hyperthyroidism, cardiovascular disease, arrhythmias, susceptibility to QT-interval prolongation, and hypertension. If high doses are needed during pregnancy they should be given by inhalation because a parenteral beta agonist can affect the myometrium and possibly cause cardiac problems. serious hypokalaemia may result from beta agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia.
- Antimuscarinic bronchodilators should be used with caution in patients with prostatic hyperplasia, bladder outflow obstruction, and those susceptible to angle-closure glaucoma .
- With leukotriene receptor antagonist, prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropath.
- Omalizumab should be initiated by physicians experienced in the treatment of severe persistent asthma.

Side-effects

- Side-effects of the beta agonists include fine tremor (particularly in the hands), nervous tension, headache, muscle cramps, and palpitation. Other sideeffects include tachycardia, arrhythmias, peripheral vasodilation, myocardial ischaemia, and disturbances of sleep and behaviour. Paradoxical bronchospasm (occasionally severe), urticaria, angioedema, hypotension, and collapse have also been reported.
- Dry mouth is the most common side effect of antimuscarinic bronchodilators; less commonly nausea and headache occur. Constipation, tachycardia, palpitation, paradoxical bronchospasm, urinary retention, blurred vision, angle-closure glaucoma, and hypersensitivity reactions including rash, urticaria, pruritus, and angioedema occur rarely.
- Measurement of plasma theophylline concentration may be helpful, and is essential if aminophylline is to be given to patients who have been taking theophylline, because serious

side-effects such as conconvulsions and arrhythmias can occasionally precede other symptoms of toxicity.

- Side-effects of inhaled corticosteroids (see Reumatoid arthritis)
- Churg-Strauss syndrome has occurred very rarely in association with the use of leukotriene receptor antagonists followed the reduction or withdrawal of oral corticosteroid therapy.

Drugs for musculoskeletal and joints diseases

1- Non-steroidal anti-inflammatory drugs

Drug classifications

Salicylates (acetylated and nonacetylated)

Aspirin, enteric-coated[c]
Salsalate (Disalcid)[c]
Diflunisal (Dolobid)[c]
Magnesium choline salicylate (Trilisate)

Propionic acid derivatives

Fenoprofen (Nalfon)[c]
Flurbiprofen (Ansaid)[c]
Ibuprofen (Motrin)[c]
Ketoprofen (Orudis, Orudis ER)[c]
Naproxen (Naprosyn)[c]
Naproxen sodium (Anaprox)[c]
Oxaproxin (Daypro)[c]

Acetic acid derivatives

Diclofenac (Voltaren, Voltaren XR)[c]
Etodolac (Lodine, Lodine XL)[c]
Indomethacin (Indocin, Indocin SR)[c]
Ketorolac (Toradol)[c]
Nabumetone (Relafen)
Sulindac (Clinoril)[c]
Tolmetin (Tolectin)[c]

Anthranilic acids

Meclofenamate sodium (Meclomen)[c]

Oxicam derivatives

Piroxicam (Feldene)[c]
Meloxicam (Mobic)[c]

COX-2 inhibitors

DrCelecoxib (Celebrex)

Mechanism of action

- NSAIDs reduce the production of prostaglandins by inhibiting the enzyme cyclo-oxygenase.
- They vary in their selectivity for inhibiting different types of cyclooxygenase; selective inhibition of cyclo-oxygenase-2 reduces gastro-intestinal intolerance.

Clinical uses

- In single doses non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic activity comparable to that of paracetamol
- In regular full dosage NSAIDs have both a lasting analgesic and an anti-inflammatory effect which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation.
- Therefore, although paracetamol often gives adequate pain control in osteoarthritis,
- NSAIDs are more appropriate than paracetamol or the opioid analgesics in the inflammatory arthritides (e.g. rheumatoid arthritis) and in some cases of advanced osteoarthritis.

- NSAIDs can also be of benefit in the less well defined conditions of back pain and soft-tissue disorders.

Cautions and contra-indications

- NSAIDs should be used with caution in the elderly (risk of serious side effects and fatalities),
- In allergic disorders (they are contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID).
- During pregnancy and breast-feeding .
- In coagulation defects.
- Long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.
- In patients with renal, cardiac, or hepatic impairment caution is required since NSAIDs may impair renal function ,the dose should be kept as low as possible and renal function should be monitored.
- All NSAIDs are contra-indicated in severe heart failure.
- The selective inhibitors of cyclo-oxygenase-2 (celecoxib, etoricoxib, and parecoxib) are contra-indicated in ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, and moderate or severe heart failure.
- The selective inhibitors of cyclo-oxygenase-2 should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, hypertension, in patients with oedema for any other reason, and in patients with risk factors for heart disease.

Side-effects

- Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration occur. Systemic as well as local effects of NSAIDs contribute to gastro-intestinal damage; taking oral formulations with milk or food, or using enteric-coated formulations, or changing the route of administration may only partially reduce symptoms such as dyspepsia. Those at risk of duodenal or gastric ulceration (including the elderly) who need to continue NSAID treatment should receive either a selective inhibitor of cyclo-oxygenase-2 alone, or a non-selective NSAID with gastroprotective treatment.
- hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm, headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivity, and haematuria.
- Blood disorders have also occurred.
- Fluid retention may occur (rarely precipitating congestive heart failure); blood pressure may be raised.
- Renal failure may be provoked by NSAIDs, especially in patients with renal impairment. Rarely, papillary necrosis or interstitial fibrosis associated with NSAIDs can lead to renal failure.
- Hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, eye changes, Stevens-Johnson syndrome and toxic epidermal necrolysis are other rare sideeffects.
- Induction of or exacerbation of colitis has been reported.
- Aseptic meningitis has been reported rarely with NSAIDs;
- patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible.

2- CORTICOSTEROIDS

The adrenal cortex normally secretes hydrocortisone (cortisol) which has **glucocorticoid** activity and weak **mineralocorticoid** activity.

Drug classifications

Prednisolone *Betamethasone* *Cortisone acetate*
Deflazacort *Dexamethasone* *Hydrocortisone*
Methylprednisolone *Triamcinolone*

Clinical Use of corticosteroids

- Dosages of corticosteroids vary widely in different diseases and in different patients. If the use of a corticosteroid can save or prolong life, as in exfoliative dermatitis , pemphigus, acute leukaemia or acute transplant rejection, high doses may need to be given, because the complications of therapy are likely to be less serious than the effects of the disease itself.
- -When long-term corticosteroid therapy is used in some chronic diseases, the adverse effects of treatment may become greater than the disabilities caused by the disease. To minimise side-effects the maintenance dose should be kept as low as possible.
- - Corticosteroids are used topically for the treatment of inflammatory conditions of the skin , ulcerative colitis and Crohn's disease, haemorrhoids , avoided in psoriasis .
- -fludrocortisone to treat postural hypotension in autonomic neuropathy .
- -there is evidence that administration of lower doses for septic shock.
- -Betamethasone and dexamethasone are also appropriate for conditions where water retention would be a disadvantage.
- corticosteroid may be used in the management of raised intracranial pressure or cerebral oedema that occurs as a result of malignancy ; high doses of betamethasone or dexamethasone are generally used. However, a corticosteroid should not be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.
- -In acute hypersensitivity reactions such as angioedema of the upper respiratory tract and anaphylactic shock, corticosteroids are indicated as an adjunct to emergency treatment with adrenaline (epinephrine) .
- -Corticosteroids are preferably used by inhalation in the management of asthma but systemic therapy in association with bronchodilators is required for the emergency treatment of severe acute asthma .
- -Corticosteroids may also be useful in conditions such as autoimmune hepatitis, rheumatoid arthritis and sarcoidosis; they may also lead to remissions of acquired haemolytic anaemia , and some cases of the nephrotic syndrome (particularly in children) and thrombocytopenic purpura .
- -Corticosteroids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis, and polyarteritis nodosa.

cautions and contra-indications

- Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension or death. Withdrawal can also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.
- Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections. Fungal or viral ocular infections may also be exacerbated .
- There is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities during pregnancy.
- Other cautions include: children and adolescents (growth restriction possibly irreversible), elderly (close supervision required particularly on long-term treatment); frequent monitoring required if history of tuberculosis (or X-ray changes), hypertension, recent myocardial infarction , congestive heart failure, hepatic impairment , renal impairment, diabetes mellitus including family history, osteoporosis , glaucoma (including family history), ocular herpes simplex—risk of corneal perforation, severe affective disorders (particularly if history of steroid-induced psychosis), epilepsy, peptic ulcer, hypothyroidism, history of steroid myopathy, ulcerative colitis, diverticulitis, recent intestinal anastomoses, thromboembolic disorders; myasthenia gravis; avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished).

Side-effects of corticosteroids

- Overdosage or prolonged use can exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid side-effects.
- Mineralocorticoid side-effects include hypertension, sodium and water retention, and potassium and calcium loss. They are most marked with fludrocortisone, but are significant with cortisone, hydrocortisone, corticotropin, and tetracosactide (tetracosactrin). Mineralocorticoid actions are negligible with the high potency glucocorticoids, betamethasone and dexamethasone, and occur only slightly with methylprednisolone, prednisolone, and triamcinolone.
- Glucocorticoid side-effects include diabetes and osteoporosis , which is a danger, particularly in the elderly, as it can result in osteoporotic fractures for example of the hip or vertebrae; in addition high doses are associated with avascular necrosis of the femoral head. Muscle wasting (proximal myopathy) can also occur. Corticosteroid therapy is also weakly linked with peptic ulceration and perforation (the potential advantage of soluble or enteric-coated preparations to reduce the risk is speculative only).
- High doses of corticosteroids can cause Cushing's syndrome, with moon face, striae, and acne; it is usually reversible on withdrawal of treatment, but this must always be gradually tapered to avoid symptoms of acute adrenal insufficiency .
- In children, administration of corticosteroids may result in suppression of growth.
- Side-effects can be minimised by using lowest effective dose for minimum period possible.
- Other side-effects include:
- gastro-intestinal effects: dyspepsia, abdominal distension, acute pancreatitis, oesophageal ulceration and candidiasis;
- musculoskeletal effects: muscle weakness, vertebral and long bone fractures, tendon rupture;

1. endocrine effects: menstrual irregularities and amenorrhoea, hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite;
2. increased susceptibility to and severity of infection, reactivation of dormant tuberculosis;
3. neuropsychiatric effects: psychological dependence, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), aggravation of schizophrenia, aggravation of epilepsy;
4. ophthalmic effects: glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease, increased intra-ocular pressure, exophthalmos;
5. also impaired healing, petechiae, ecchymoses, facial erythema, suppression of skin test reactions, urticaria, hyperhidrosis, skin atrophy, bruising, telangiectasia, myocardial rupture following recent myocardial infarction, congestive heart failure, leucocytosis, hyperglycaemia, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise, hiccups, headache, vertigo.

Withdrawal of corticosteroids

1. gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:
2. . recently received repeated courses (particularly if taken for longer than 3 weeks);
3. . taken a short course within 1 year of stopping long-term therapy;
4. . other possible causes of adrenal suppression;
5. . received more than 40 mg daily prednisolone (or equivalent);
6. . been given repeat doses in the evening;
7. . received more than 3 weeks' treatment.
8. Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.
9. Patients on long-term corticosteroid treatment should carry a Steroid Treatment Card which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.

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Endocrine system
INSULIN & ORAL ANTIDIABETIC AGENTS

A. INSULIN

Drug classifications

* those of short duration which have a relatively rapid onset of action e.g soluble insulin, insulin lispro and insulin aspart;
* those with an intermediate action, e.g. isophane insulin and insulin zinc suspension,
* those whose action is slower in onset and lasts for long periods, e.g. insulin zinc suspension.

Mechanism of action

Insulin plays a key role in the regulation of carbohydrate, fat, and protein metabolism.

Clinical uses

Insulin is required by almost all children with diabetes. It is also needed for type 2 diabetes when other methods have failed to achieve good control, and temporarily in the presence of intercurrent illness or peri-operatively. Pregnant women with type 2 diabetes may be treated with insulin when diet alone fails.

Short-acting insulins

- Soluble insulin is a short-acting form of insulin. For maintenance regimens it is usual to inject it 15 to 30 minutes before meals.
- Soluble insulin is the most appropriate form of insulin for use in diabetic emergencies e.g. diabetic ketoacidosis and at the time of surgery.
- It can be given intravenously and intramuscularly, as well as subcutaneously. When injected subcutaneously, soluble insulin has a rapid onset of action (30 to 60 minutes), a peak action between 2 and 4 hours, and a duration of action of up to 8 hours.
- When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.
- The human insulin analogues, insulin aspart, insulin glulisine, and insulin lispro have a faster onset and Shorter duration of action than soluble insulin; as a result, fasting and preprandial blood-glucose concentration is a little higher, postprandial blood-glucose concentration is a little lower, and hypoglycaemia occurs slightly less frequently.
- Subcutaneous injection of insulin analogues may be convenient for those who wish to inject shortly before or, when necessary, shortly after a meal. They can also help those susceptible to hypoglycaemia before lunch and those who eat late in the evening and are prone to nocturnal hypoglycaemia. They can also be administered by subcutaneous infusion .
- Insulin aspart and insulin lispro can be administered intravenously and can be used as alternatives to soluble insulin for diabetic emergencies and at the time of surgery.

Intermediate- and long-acting insulins

- When given by subcutaneous injection, intermediate and long-acting insulins have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours, and a duration of 16–35 hours.
- Some are given twice daily in conjunction with short-acting (soluble) insulin, and others are given once daily, particularly in elderly patients.

- Soluble insulin can be mixed with intermediate and long-acting insulins (except insulin detemir and insulin glargine) in the syringe, although there may be some blunting of the initial effect of the soluble insulin component (especially on mixing with protamine zinc insulin .
- Isophane insulin is a suspension of insulin with protamine which is of particular value for initiation of twice daily insulin regimens. Patients usually mix isophane with soluble insulin but ready-mixed preparations may be appropriate (biphasic isophane insulin, biphasic insulin aspart, or biphasic insulin lispro).
- Insulin zinc suspension (30% amorphous, 70% crystalline) has a more prolonged duration of action.
- Protamine zinc insulin is usually given once daily with short-acting (soluble) insulin. It has the drawback of binding with the soluble insulin when mixed in the same syringe and is now rarely used.
- Insulin glargine and insulin detemir are both human insulin analogues with a prolonged duration of action; insulin glargine is given once daily and insulin detemir is given once or twice daily.

Cautions and contraindication

- The dose of insulin is increased gradually, taking care to avoid troublesome hypoglycaemic reactions.
- Patient education about Insulin:
- Injection technique -s.c , I.v , insulin pump
- sites of injection - Insulin is usually injected into the upper arms, thighs, buttocks, or abdomen; absorption from a limb site may be increased if the limb is used in strenuous exercise after the injection.
- Types of insulin
- Onset and peak of actions
- Storage - 4° C in freg
- Stability (look for crystallization and precipitation with NPH insulin)
- Many patients now monitor their own blood-glucose concentrations since blood-glucose concentrations vary substantially throughout the day.

Side-effect

- ***Hypoglycaemia*** Hypoglycaemia is a potential problem with insulin therapy. All patients must be carefully instructed on how to avoid it. Loss of warning of hypoglycaemia is common among insulin-treated patients and can be a serious hazard.
- Generally subcutaneous insulin injections cause few problems; fat hypertrophy does, however, occur but can be minimised by using different injection sites in rotation. Local allergic reactions are rare.

Examples of recommended insulin regimens

- Short-acting insulin mixed with intermediate-acting insulin : twice daily (before meals)
- Short-acting insulin mixed with intermediate-acting insulin: before breakfast
- Short-acting insulin: before evening meal

- Intermediate-acting insulin: at bedtime
- Short-acting insulin: three times daily (before breakfast ,midday, and evening meal) Intermediate-acting insulin: at bedtime
- Intermediate-acting insulin with or without short acting insulin: once daily either before breakfast or at bedtime suffices for some patients with type 2 diabetes who need insulin.

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B. ORAL ANTIDIABETIC DRUGS

Drug classifications

- ***Sulphonylureas*** *chlorpropamide , glibenclamide, gliclazide , tolbutamide , glipizide , glimepiride*
- ***Biguanides*** *Metformin*
- ***Thiazolidinediones*** *pioglitazone , rosiglitazone*
- ***Glinides*** *Nateglinide , repaglinide*
- ***Acarbose*** *(α-Glucosidase inhibitors)*
- ***Exenatide*** *(GLP-1 receptor agonists/incretin mimetics)*
- ***Sitagliptin*** *(dipeptidyl peptidase-4 Inhibitors)*
- ***Pramlintide*** *(Amylin Mimetics).*

Mechanism of Action

➢ *Sulphonylureas*

- *Pancreatic effects ;* The sulphonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present.
- *Extrapancreatic action. ;* during long-term administration.

➢ *Biguanides*

- It exerts its effect mainly by decreasing gluconeogenesis
- increasing peripheral utilisation of glucose;
- since it acts only in the presence of endogenous insulin it is effective only if there are some residual functioning pancreatic islet cells.

➢ *Thiazolidinediones*

- Reduce peripheral insulin resistance, leading to areduction of blood-glucose concentration.

➢ *Glinides*

- They stimulate insulin release.
- Both drugs have a rapid onset of action and short duration of activity, and should be administered shortly before each main meal.

➢ *Acarose--α-Glucosidase inhibitors*

- An inhibitor of intestinal alpha glucosidases, delays the digestion and absorption of starch and sucrose.

➢ *Sitagliptin and vildagliptin*

- They inhibit dipeptidylpeptidase- 4 to increase insulin secretion and lower glucagon secretion.

➢ *Exenatide*

- A synthetic form of exendin-4, is an incretinmimetic which increases insulin secretion,
- suppresses glucagon secretion,
- and slows gastric emptying.

Clinical Use

➢ *Sulphonylureas*

- Sulphonylureas are considered for patients who are not overweight,
- in whom metformin is contra-indicated or not tolerated.
- The long-acting sulphonylureas chlorpropamide and glibenclamide are associated with a greaterrisk of hypoglycaemia; for this reason they should be avoided in the elderly and shorter-acting alternatives, such as gliclazide or tolbutamide, should be used instead.
- Chlorpropamide also has more side-effects than the other sulphonylureas and therefore it is no longer recommended.
- When the combination of strict diet and sulphonylurea treatment fails other options include:

❖ combining with metformin
❖ combining with acarbose , but flatulence can be a problem
❖ combining with pioglitazone or rosiglitazone.
❖ combining with bedtime isophane insulin) but weight gain and hypoglycaemia can occur.

➢ *Biguanides*

- Hypoglycaemia does not usually occur with metformin; other advantages are the lower incidence of weight gain and lower plasma-insulin concentration.
- Metformin is the drug of first choice in overweight patients in whom strict dieting has failed to control diabetes, it may also be an option in patients who are not overweight.
- It is also used when diabetes is inadequately controlled with sulphonylurea treatment.
- When the combination of strict diet and metformin treatment fails, other options include:

❖ combining with acarbose , but flatulence can be a problem;
❖ combining with insulin but weight gain and hypoglycaemia can be problems (weight gain minimised if insulin given at night).
❖ combining with a sulphonylurea.
❖ combining with pioglitazone or rosiglitazone .
❖ combining with repaglinide or nateglinide

- [unlicensed indication] Metformin is used for the symptomatic management of polycystic ovary syndrome; it improves insulin sensitivity, may aid weight reduction, helps to normalise menstrual cycle (increasing the rate of spontaneous ovulation), and may improve hirsutism.

➢ *Thiazolidinediones*

- Either drug can be used alone or in combination with metformin or with a sulphonylurea (if metformin inappropriate);

- the combination of a thiazolidinedione plus metformin is preferred to a thiazolidinedione plus sulphonylurea, particularly for obese patients. Inadequate response to a combination of metformin and sulphonylurea may indicate failing insulin release the initiation of insulin is often more appropriate.

➢ *Glinides*

- Repaglinide may be given as monotherapy for patients who are not overweight.
- used for those in whom metformin is contra-indicated or not tolerated.
- it may be given in combination with metformin. Nateglinide is licensed only for use with metformin.

➢ *Acarbose*

- Use of acarbose is usually reserved for when other oral hypoglycaemics are not tolerated or are contra-indicated.
- Postprandial hyperglycaemia in type 1 diabetes can be reduced by acarbose, but it has been little used for this purpose.

➢ *Sitagliptin and vildagliptin*

- Both drugs are licensed for use in type 2 diabetes in combination with metformin or a sulphonylurea (if metformin inappropriate) or a thiazolidinedione, when treatment with either metformin or a sulphonylurea or a thiazolidinedione fails to achieve adequate glycaemic control.
- Sitagliptin is also licensed for use in combination with both metformin and a sulphonylurea when dual therapy with these drugs fails to achieve adequate glycaemic control.

➢ *Exenatide*

- It is given by subcutaneous injection for the treatment of type 2 diabetes in combination with metformin or a sulphonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination.
- Exenatide use is associated with the prevention of weight gain and possible promotion of weight loss which can be beneficial in overweight patients.

Cautions and contraindication

➢ *Sulphonylureas*

- Caution is needed in the elderly
- mild to moderate hepatic impairment because of the hazard of hypoglycaemia.
- Renal impairment: mild to moderate renal impairment, because of the hazard of hypoglycaemia;. If necessary, the short-acting tolbutamide can be used in renal impairment, as can gliclazide which is principally metabolised in the liver, but careful monitoring of blood-glucose concentration is essential.
- Sulphonylureas should be avoided in severe hepatic impairment
- in acute porphyria .
- They should not be used during pregnancy and while breast-feeding .
- Sulphonylureas are contra-indicated in the presence of ketoacidosis.
- they should be avoided where possible if creatinine clearance is less than 10 mL/minute.

- *Biguanides*

Cautions: in patients with renal impairment.

- *Thiazolidinediones*

Rosiglitazone and pioglitazone should not be used in patients with heart failure or history of heart failure; incidence of heart failure is increased when rosiglitazone or pioglitazone is combined with insulin.
monitor liver function.

Glinides-See drugs
Acarbose-See drugs
Sitagliptin and vildagliptin-See drugs
Exenatide-See drugs

Side-effects

- *Sulphonylureas*

- Side-effects of sulphonylureas are generally mild and infrequent. All may cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulphonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital.
- Sulphonylureas can encourage weight gain; metformin is considered the drug of choice in obese patients.
- gastro-intestinal disturbances such as nausea, vomiting, diarrhoea and constipation.
- Chlorpropamide has appreciably more side-effects, mainly because of its very prolonged duration of action and the consequent hazard of hypoglycaemia and it may also cause facial flushing after drinking alcohol
- Chlorpropamide may also enhance antidiuretic hormone secretion and very rarely cause hyponatraemia (hyponatraemia is also reported with glimepiride and glipizide).
- Sulphonylureas can occasionally lead to cholestatic jaundice, hepatitis and hepatic failure.
- Hypersensitivity reactions can occur, usually in the first 6–8 weeks of therapy, they consist mainly of allergic skin reactions, fever and jaundice; photosensitivity has rarely been reported with chlorpropamide and glipizide.
- Blood disorders are also rare but may include leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia.

- *Biguanides*

- Very rarely, metformin can provoke lactic acidosis which is most likely to occur in patients with renal impairment.
- . Gastro-intestinal side-effects are initially common with metformin, and may persist in some patients, particularly when very high doses such as 3 g daily are given.
- It does not exert a hypoglycaemic action in non-diabetic subjects unless given in overdose.

- *Thiazolidinediones - See drugs*

Glinides - See drugs

- *Acarbose*
- Flatulence deters some from using acarbose although this side-effect tends to decrease with time.

- *Sitagliptin and vildagliptin - See drugs*
- *Exenatide - See drugs*

Pregnancy and breast-feeding

During pregnancy, women with either pre-existing or gestational diabetes may be treated with metformin [unlicensed use], either alone or in combination with insulin .
Women with gestational diabetes should discontinue hypoglycaemic treatment after giving birth.
Metformin can be continued during breast-feeding for those with pre-existing diabetes.
Other oral hypoglycaemic drugs, including sulphonylureas, are contra-indicated in pregnancy and in breast-feeding.

NOTE

For patients not adequately controlled by diet and oral hypoglycaemic drugs, insulin may be added to the treatment regimen or substituted for oral therapy.
When insulin is added to oral therapy, it is generally given at bedtime as isophane insulin, and when insulin replaces an oral regimen it is generally given as twice daily injections of a biphasic insulin (or isophane insulin mixed with soluble insulin). Weight gain and hypoglycaemia may be complications of insulin therapy but weight gain may be reduced if the insulin is given in combination with metformin

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C. Thyroid and antithyroid drugs

Drug classifications

- *THYROID HORMONES - Levothyroxine sodium, Liothyronine sodium*
- *ANTITHYROID DRUGS - carbimazole , Propylthiouracil , Iodine*

Clinical uses

- *THYROID HORMONES*

- Thyroid hormones are used in hypothyroidism (myxoedema),and also in diffuse non-toxic goitre, Hashimoto's thyroiditis (lymphadenoid goitre), and thyroid carcinoma.
- Neonatal hypothyroidism requires prompt treatment for normal development.
- *Levothyroxine sodium (thyroxine sodium) is the treatment of choice for maintenance therapy.
- In infants and children with congenital hypothyroidism and juvenile myxoedema, the dose of levothyroxine should be titrated according to clinical response, growth assessment, and measurements of plasma thyroxine and thyroid-stimulating hormone.
- *Liothyronine sodium has a similar action to levothyroxine but is more rapidly metabolised and has a more rapid effect; 20 micrograms is equivalent to 100 micrograms of levothyroxine. Its effects develop after a few hours and disappear within 24 to 48 hours of discontinuing treatment. It may be used in severe hypothyroid states when a rapid response is desired.
- Liothyronine by intravenous injection is the treatment of choice in hypothyroid coma.
- *Adjunctive therapy includes intravenous fluids, hydrocortisone, and treatment of infection; assisted ventilation is often required.

- *ANTITHYROID DRUGS*

- Antithyroid drugs are used for hyperthyroidism either to prepare patients for thyroidectomy or for long-term management.
- Propylthiouracil is given until the patient becomes euthyroid; the dose may then be gradually reduced to a maintenance dose.
- Antithyroid drugs only need to be given once daily because of their prolonged effect on the thyroid.
- A combination of carbimazole, with levothyroxine, may be used in a blocking-replacement regimen; therapy is usually given for 18 months. The blocking-replacement regimen is not suitable during pregnancy.
- Iodine has been used as an adjunct to antithyroid drugs for 10 to 14 days before partial thyroidectomy; however, there is little evidence of a beneficial effect. Iodine should not be used for long-term treatment because its antithyroid action tends to diminish.
- Radioactive sodium iodide solution is used increasingly for the treatment of thyrotoxicosis at all ages, particularly where medical therapy or compliance is a problem, in patients with cardiac disease, and in patients who relapse after thyroidectomy.
- Propranolol is useful for rapid relief of thyrotoxic symptoms and may be used in conjunction with antithyroid drugs or as an adjunct to radioactive iodine.
- Beta-blockers are also useful in neonatal thyrotoxicosis and in supraventricular arrhythmias due to hyperthyroidism.

Cautions and contraindication

- . Patient should be asked to report symptoms and signs suggestive of infection, especially sore throat. recognizing bone marrow suppression induced by carbimazole.
- A white blood cell count should be performed if there is any clinical evidence of infection.
- Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.
- Carbimazole and propylthiouracil appear in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used. Both cross the placenta and in high doses may cause fetal goitre and hypothyroidism.
- Radioactive iodinetherapy is contra-indicated during pregnancy.

Side-effect

- Overtreatment with antithyroid drugs can result in the rapid development of hypothyroidism and should be avoided particularly during pregnancy because it can cause fetal goitre.
- Rashes and pruritus are common with carbimazole but they can be treated with antihistamines without discontinuing therapy; alternatively propylthiouracil can be substituted.

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Antimicrobial drugs - part I

Drug classifications

β-Lactam Antibiotics

Cephalosporins

First-generation

Cefadroxil (Duricef)
Cefazolin (Ancef)
Cephalexin (Keflex)

Second-generation

Cefaclor (Ceclor)
Cefamandole (Mandol)
Cefonicid (Monocid)
Ceforanide (Precef)
Cefotetan (Cefotan)
Cefoxitin (Mefoxin)
Cefprozil (Cefzil)
Cefuroxime (Zinacef)
Cefuroxime axetil (Ceftin)

Third-generation

Cefdinir (Omnicef)
Cefditoren (Spectracef)
Cefixime (Suprax)
Cefotaxime (Claforan)
Cefpodoxime proxetil (Vantin)
Ceftazidime (Fortaz)
Ceftibuten (Cedax)
Ceftizoxime (Cefizox)
Ceftriaxone (Rocephin)

Fourth-generation

Cefepime (Maxipime)

Carbacephems

Loracarbef (Lorabid)

Monobactams

Aztreonam (Azactam)

Penems

Doripenem (Doribax)
Ertapenem (Invanz)
Imipenem (Primaxin)
Meropenem (Merem)

Penicillins

Natural Penicillins

Penicillin G

Penicillin V
Aminopenicillins
Ampicillin (Omnipen)
Amoxicillin (Amoxil)
Bacampicillin (Spectrobid)
Penicillinase-Resistant Penicillins
Isoxazolyl penicillins (dicloxacillin, oxacillin, cloxacillin)
Nafcillin (Unipen)
Combination with β-lactamase Inhibitors
Augmentin (amoxicillin plus clavulanic acid)
Unasyn (ampicillin plus sulbactam)
Zosyn (piperacillin plus tazobactam)

A. β-Lactam Antibiotics

Mechanism of action

- The penicillins are bactericidal and act by interfering with bacterial cell wall synthesis.
- The pharmacology of the cephalosporins is similar to that of the penicillins.

Clinical uses

- **Benzathine benzylpenicillin** is used for the treatment of early syphilis and late latent syphilis.
- **Phenoxymethylpenicillin (Penicillin V)** should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable. It is indicated principally for respiratory-tract infections in children, for streptococcal tonsillitis, and for continuing treatment after one or more injections of benzylpenicillin when clinical response has begun. It should not be used for meningococcal or gonococcal infections. Phenoxymethylpenicillin is used for prophylaxis against streptococcal infections following rheumatic fever and against pneumococcal infections following splenectomy or in sickle-cell disease.
- **Penicillinase-resistant penicillins - Flucloxacillin,Temocillin** is active against Gram-negative bacteria and is stable against a wide range of beta-lactamases. It should be reserved for the treatment of infections caused by beta-lactamase-producing strains of Gram negative bacteria, including those resistant to third-generation cephalosporins. Temocillin is not active against Pseudomonas aeruginosa or Acinetobacter spp.
    - **Broad-spectrum penicillins – Ampicillin** is active against certain Gram-positive and Gram-negative organisms but is inactivated by penicillinases. principally indicated for the treatment of exacerbations of chronic bronchitis and middle ear infections, both of which may be due to Streptococcus pneumoniae and H. influenzae, and for urinary-tract infections

      Amoxicillin (amoxycillin) is a derivative of ampicillin and has a similar antibacterial spectrum. It is better absorbed than ampicillin when given by mouth, producing higher plasma and tissue concentrations; unlike ampicillin, absorption is not affected by the presence of food in the stomach. Amoxicillin may also be used for the treatment of Lyme disease.

      Co-amoxiclav consists of amoxicillin with the beta lactamase inhibitor clavulanic acid. Clavulanic acid itself has no significant antibacterial activity but, by inactivating beta-

lactamases, it makes the combination active against beta-lactamase-producing bacteria that are resistant to amoxicillin.

- A combination of **ampicillin with flucloxacillin (as cofluampicil)** is available to treat infections involving either streptococci or staphylococci e.g. cellulitis.
- **Antipseudomonal penicillins - carboxypenicillin, ticarcillin**, is principally indicated for serious infections caused by Pseudomonas aeruginosa.
- **The cephalosporins** are broad-spectrum antibiotics which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections.

  The orally active **'first generation'** cephalosporins, and the 'second generation' cephalosporin , have a similar antimicrobial spectrum. They are useful for urinary-tract infections which do not respond to other drugs or which occur in pregnancy, respiratory-tract infections, otitis media, sinusitis, and skin and soft-tissue infections.

  Cefaclor has good activity against H. influenzae, but it is associated with protracted skin reactions especially in children. Cefadroxil has a long duration of action and can be given twice daily; it has poor activity against H. influenzae. Cefuroxime is a **'second generation'** cephalosporin active against certain bacteria which are resistant to the other drugs and has greater activity against Haemophilus influenza and Neisseria gonorrhoeae. **'third generation'** cephalosporins with greater activity than the 'second generation' cephalosporins against certain Gram-negative bacteria. Their broad antibacterial spectrum may encourage superinfection with resistant bacteria or fungi.

  Cefixime has a longer duration of action than the other cephalosporins that are active by mouth. It is only licensed for acute infections.

  Cefpodoxime proxetil is more active than the other oral cephalosporins against respiratory bacterial pathogens and it is licensed for upper and lower respiratorytract infections. cefotaxime is a suitable cephalosporin for infections of the CNS (e.g meningitis).

  Ceftazidime has good activity against pseudomonas. It is also active against other Gram-negative bacteria.

  Ceftriaxone has a longer half-life and therefore needs to be given only once daily. Indications include serious infections such as septicaemia, pneumonia, and meningitis.

  - **The carbapenems** are beta-lactam antibacterials with a broad-spectrum of activity which includes many Gram positive and Gram-negative bacteria, and anaerobes; The carbapenems are not active against meticillin-resistant Staphylococcus aureus and Enterococcus faecium.

    Imipenem and meropenem are used for the treatment of severe hospital-acquired infections and polymicrobial infections including septicaemia, hospital-acquired pneumonia, intra-abdominal infections, skin and softtissue infections, and complicated urinary-tract infections.

    Doripenem is an alternative for hospital-acquired pneumonia, complicated intra-abdominal infections, and complicated
    urinary-tract infections.

    Ertapenem is licensed for treating abdominal and gynaecological infections and for community-acquired pneumonia, but it is not active against atypical respiratory pathogens and it has limited activity against penicillin-resistant pneumococci. It is also licensed for treating foot infections of the skin and soft tissue in patients with diabetes.

- **Other beta-lactam antibiotics- Aztreonam** is a monocyclic beta-lactam ('monobactam') antibiotic with an antibacterial spectrum limited to Gram-negative aerobic bacteria including Pseudomonas aeruginosa, Neisseria meningitidis, and Haemophilus influenza.

Cautions and contraindications

- If a penicillin (or another beta-lactam antibiotic) is essential in an individual with immediate hypersensitivity to penicillin then specialist advice should be sought on hypersensitivity testing or using a beta-lactam antibiotic with a different structure to the penicillin that caused the hypersensitivity.
- Patients with a history of immediate hypersensitivity to penicillin should not receive a cephalosporin . If a cephalosporin is essential in these patients because a suitable alternative antibacterial is not available, then cefixime, cefotaxime, ceftazidime, ceftriaxone, or cefuroxime can be used with caution; cefaclor, cefadroxil, cefalexin, and cefradine should be avoided.

side-effect

- side effect of the **penicillins** is hypersensitivity which causes rashes and anaphylaxis and can be fatal. anaphylactic reactions occur in fewer than 0.05% of treated patients. Patients with a history of atopic allergy (e.g. asthma, eczema, hay fever) are at a higher risk of anaphylactic reactions to penicillins, these individuals should not receive a penicillin.
- Patients who are allergic to one penicillin will be allergic to all because the hypersensitivity is related to the basic penicillin structure.
- As patients with a history of immediate hypersensitivity to penicillins may also react to the cephalosporins and other beta-lactam antibiotics, they should not receive these antibiotics.
- Maculopapular rashes commonly occur with ampicillin (and amoxicillin) but are not usually related to true penicillin allergy. They almost always occur in patients with glandular fever.
- Owing to the sodium content of many of these antibiotics, high doses may lead to hypernatraemia .
- The principal side-effect of the **cephalosporins** is hypersensitivity and about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins.

Antibiotic-associated colitis may occur with the use of broad-spectrum cephalosporins.

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Antimicrobial drugs - part II

Drug classifications

Aminoglycosides

Amikacin (Amikin)
Gentamicin (Garamycin)
Neomycin (Mycifradin)
Netilmicin (Netromycin)
Streptomycin
Tobramycin (Nebcin)

Protein Synthesis Inhibitors

Azithromycin (Zithromax)
Clarithromycin (Biaxin)
Clindamycin (Cleocin)

Chloramphenicol (Chloromycetin)
Dalfopristin/Quinupristin (Synercid)
Dirithromycin (Dynabac)
Erythromycin (Erythrocin)
Linezolid (Zyvox)
Telithromycin (Ketek)
Tetracyclines (doxycycline, minocycline, tetracycline)

Folate Inhibitors

Sulfadiazine
Sulfadoxine (Fansidar)
Trimethoprim (Trimpex)
Trimethoprim-sulfamethoxazole (Bactrim, Septra)

Quinolones

Ciprofloxacin (Cipro)
Gemifloxacin (Factive)
Levofloxacin (Levoquin)
Moxifloxacin (Avelox)
Norfloxacin (Noroxin)
Ofloxacin (Floxin)

Daptomycin *(Cubicin)*
Vancomycin *(Vancocin)*
Metronidazole *(Flagyl)*

B. Aminoglycosides

Mechanism of action

- All are bactericidal and active against some Gram-positive and many Gram-negative organisms.
  Amikacin, gentamicin, and tobramycin are also active against *Pseudomonas aeruginosa*, streptomycin is active against *Mycobacterium tuberculosis* and is now almost entirely reserved for tuberculosis.

Clinical uses

- The aminoglycosides are not absorbed from the gut , Excretion is principally via the kidney and accumulation occurs in renal impairment.
- Gentamicin is the aminoglycoside of choice used widely for the treatment of serious infections. septicaemia and neonatal sepsis; meningitis and other CNS infections; biliary-tract infection, acute pyelonephritis or prostatitis, endocarditis pneumonia in hospital
- patients, adjunct in listerial meningitis
- When used for the 'blind' therapy of undiagnosed serious infections it is usually given in conjunction with a penicillin or metronidazole . Gentamicin is used in combination with other antibiotics for the treatment of bacterial endocarditis .
- Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram negative bacilli.
- Tobramycin has similar activity to gentamicin. It is slightly more active against Ps. Aeruginosa , Tobramycin may be administered by nebuliser on a cyclical basis .
- Neomycin is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure.

Cautions and contraindications

- Cautions in pregnancy, renal impairment, neonates, infants and elderly (adjust dose and monitor renal, auditory and vestibular function together with serum gentamicin concentrations).
- Aminoglycosides should not be given to patients with myasthenia gravis.
- A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with endocarditis, extensive burns of more than 20% of the total body surface area, or creatinine clearance less than 20 mL/minute.

Side-effect

- Most side-effects of this group of antibiotics are dose related therefore care must be taken with dosage and whenever possible treatment should not exceed 7 days.
- The important side-effects are ototoxicity, and nephrotoxicity; they occur most commonly in the elderly and in patients with renal failure.
- If there is impairment of renal function (or high pre-dose serum concentrations) the interval between doses must be increased; if the renal impairment is severe the dose itself should be reduced as well.

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C. *Macrolides*

Mechanism of action

- Protein Synthesis Inhibitors
- Erythromycin has an antibacterial spectrum that is similar but not identical to that of penicillin; it is thus an alternative in penicillin-allergic patients.

Clinical uses

- Indications for erythromycin include respiratory infections, whooping cough, legionnaires' disease, and campylobacter enteritis.
- Azithromycin has enhanced activity against some Gram-negative organisms including H. influenza, has a long tissue half-life and once daily dosage is recommended.
- Clarithromycin is an erythromycin derivative with slightly greater activity than the parent compound.
- Telithromycin should only be used to treat beta-haemolytic streptococcal pharyngitis and tonsillitis, sinusitis, community-acquired pneumonia, and exacerbations of chronic bronchitis if caused by organisms resistant to beta-lactam antibacterials and other macrolides, or if conventional treatment is contra- indicated.
- Spiramycin is also a macrolide.

Cautions and contraindications

- neonate under 2 weeks (risk of hypertrophic pyloric stenosis);
- predisposition to QT interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); avoid in acute porphyria hepatic impairment ,renal impairment ,pregnancy (not known to be harmful) and breastfeeding (only small amounts in milk);

Side-effect

- Erythromycin causes nausea, vomiting, and diarrhoea in some patients; in mild to moderate infections this can be avoided by giving a lower dose but if a more serious infection, such as Legionella pneumonia, is suspected higher doses are needed
- Less frequently urticaria, rashes and other allergic reactions;
- reversible hearing loss reported after large doses;
- cholestatic jaundice, pancreatitis,

- cardiac effects (including chest pain and arrhythmias),
- myasthenia- like syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis also reported

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D. Tetracyclines

Mechanism of action

- Protein Synthesis Inhibitors
- The tetracyclines are broad-spectrum antibiotics whose value has decreased owing to increasing bacterial resistance..

Clinical uses

- Tetracyclines, the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and lymphogranuloma venereum), rickettsia (including Q-fever), brucella (doxycycline with either streptomycin or rifampicin), and the spirochaete, Borrelia burgdorferi .They are also used in respiratory and genital mycoplasma infections, in acne, in destructive (refractory) periodontal disease, in exacerbations of chronic bronchitis (because of their activity against Haemophilus influenzae), and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin).
- Doxycycline has a longer duration of action than tetracycline or oxytetracycline and need only be given once daily; it is reported to be more active against anaerobes than some other tetracyclines.
- **Tigecycline** is a glycylcycline antibacterial structurally related to the tetracyclines .Tigecycline should be reserved for the treatment of complicated skin and soft-tissue infections and complicated abdominal infections caused by multiple-antibacterial resistant organisms.

Cautions and contraindications

- Tetracyclines should be used with caution in patients with hepatic impairment or those receiving potentially hepatotoxic drugs. Tetracyclines may increase muscle weakness in patients with myasthenia gravis, and exacerbate systemic lupus erythematosus. Antacids, and aluminium, calcium, iron, magnesium and zinc salts decrease the absorption of tetracyclines; milk also reduces it.
- Contra-indications - Deposition of tetracyclines in growing bone and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia, and they should not be given to children under 12 years, or to pregnant or breast-feeding women. tetracyclines may exacerbate renal failure and should not be given to patients with kidney disease Tetracyclines should not be given to patients with acute porphyria .

Side-effect

- Side-effects of the tetracyclines include nausea, vomiting, diarrhoea (antibiotic-associated colitis reported occasionally), dysphagia, and oesophageal irritation.
- Other rare side-effects include hepatotoxicity, pancreatitis, blood disorders, photosensitivity (particularly with demeclocycline), and hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens- Johnson syndrome, urticaria, angioedema, anaphylaxis, pericarditis).
- Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment); bulging fontanelles have been reported in infants.

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E. Clindamycin

Mechanism of action

- Protein Synthesis Inhibitors
- Clindamycin is active against Gram-positive cocci,

Clinical uses

- It is well concentrated in bone and excreted in bile and urine.
- Clindamycin is recommended for staphylococcal joint and bone infections such as osteomyelitis, and intraabdominal sepsis; it is an alternative to macrolides for erysipelas or cellulitis in penicillin-allergic patients. Clindamycin can also be used for infections associated with meticillin-resistant Staphylococcus aureus (MRSA) in bronchiectasis, bone and joint infections, and skin and soft-tissue infections. Clindamycin can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or to metronidazole.

***Cautions and contraindications*:**

- monitor liver and renal function on prolonged therapy and in neonates and infants; pregnancy ; breast-feeding ; avoid rapid intravenous administration; avoid in acute porphyria.

Side-effect

- Clindamycin has been associated with antibiotic-associated colitis , which may be fatal , Patients should therefore discontinue treatment immediately if diarrhoea develops.
- Abdominal discomfort , oesophageal ulcers, taste disturbances, nausea, vomiting , jaundice; leucopenia, eosinophilia, and thrombocytopenia reported; rash, , anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative and vesiculobullous dermatitis reported; and abscess after intramuscular injection; thrombophlebitis after intravenous injection.

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F. Chloramphenicol

Mechanism of action

- Protein Synthesis Inhibitors
- Chloramphenicol is a potent broad-spectrum antibiotic.

Clinical uses

- It is reserved for the treatment of life-threatening infections, particularly those caused by Haemophilus influenzae, and also for typhoid fever.

Cautions and contraindications

- Avoid repeated courses and prolonged treatment; reduce doses in hepatic impairment ; renal impairment ; blood counts required before and periodically during treatment;.
- Contra-indications pregnancy , breastfeeding , acute porphyria.

Side-effect

- It is associated with serious haematological side-effects when given systemically. blood disorders including reversible and irreversible aplastic anaemia (with reports of resulting leukaemia).
- peripheral neuritis, , headache, depression, urticaria, erythema multiforme, nausea, vomiting, diarrhoea, , dry mouth; ; grey syndrome (abdominal distension, pallid cyanosis, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism .

G. ***Sulphonamides and trimethoprim***

Mechanism of action

- Folate Inhibitors.
- Co-trimoxazole should be limited to the role of drug of choice in Pneumocystis jiroveci (Pneumocystis carinii) pneumonia;

Clinical uses

- The importance of the sulphonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic.
- Sulfamethoxazole (sulphamethoxazole) and trimethoprim are used in combination (as co-trimoxazole) because of their synergistic activity.
- It is indicated for toxoplasmosis and nocardiasis. It should now only be considered for use in acute exacerbations of chronic bronchitis and infections of the urinary tract , it should only be used in acute otitis media in children when there is good reason to prefer it.
- Trimethoprim can be used alone for urinary- and respiratory- tract infections and for prostatitis, shigellosis, and invasive salmonella infections
- For topical preparations of sulphonamides used in the treatment of burns.

Cautions and contraindications

- Cautions is to maintain adequate fluid intake; avoid in blood disorders ; discontinue immediately if blood disorders or rash develop; predisposition to folate deficiency or hyperkalaemia; elderly ; asthma; G6PD deficiency ; avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia); hepatic impairment (avoid if severe); renal impairment (avoid if creatinine clearance less than 15 mL/minute; pregnancy ; breast-feeding . Contra-indications in acute porphyria .

Side-effect

- Co-trimoxazole is associated with rare but serious side-effects (e.g. Stevens-Johnson syndrome and blood dyscrasias, notably bone marrow depression and agranulocytosis) especially in the elderly .
- GIT -nausea, diarrhoea; anorexia, liver damage (including jaundice and hepatic necrosis), pancreatitis.
- Hypersensitivity, cough and shortness of breath, pulmonary infiltrates.
- Renal disorders including interstitial nephritis.

H. ***Quinolones***

Mechanism of action

- Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, campylobacter, neisseria, and pseudomonas.

Clinical uses

- Nalidixic acid and norfloxacin are effective in uncomplicated urinary-tract infections.
- Ciprofloxacin can be used for respiratory tract infections (but not for pneumococcal pneumonia), urinary-tract infections, infections of the gastro-intestinal system (including typhoid fever), bone and joint infections, gonorrhoea and septicaemia caused by sensitive organisms.

- Ofloxacin is used for urinary-tract infections, lower respiratory-tract infections, gonorrhoea, and non-gonococcal urethritis and cervicitis.
- Levofloxacin is licensed for community-acquired pneumonia but it is considered to be second-line treatment for this indication.
- Moxifloxacin should be reserved for the treatment of sinusitis, community-acquired pneumonia, or exacerbations of chronic bronchitis.

Cautions and contraindications

- Quinolones should be used with caution in patients with a history of epilepsy or conditions that predispose to seizures, in G6PD deficiency , myasthenia gravis (risk of exacerbation), in renal impairment ; pregnancy , during breast-feeding , and in children or adolescents.
- Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs).
- Healthcare professionals are reminded that:

❖ quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use;
❖ patients over 60 years of age are more prone to tendon damage;
❖ kidney, heart, or lung transplant recipients are more prone to tendon damage;
❖ the risk of tendon damage is increased by the concomitant use of corticosteroids;
❖ if tendinitis is suspected, the quinolone should be discontinued immediately.

Side-effect

- GIT - nausea, vomiting, dyspepsia, abdominal pain, diarrhea .
- Less frequent side-effects include anorexia, sleep disturbances, asthenia, confusion, anxiety, depression, hallucinations, tremor.
- Blood disorders (including eosinophilia, leucopenia, thrombo- cytopenia).
- Other side-effects reported very rarely include hepatic dysfunction , hypotension, , renal failure, interstitial nephritis, tendon inflammation and damage .

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I. Other antibacterials

1.Fusidic acid

Mechanism of action

- Fusidic acid and its salts are narrow-spectrum antibiotics.

Clinical uses

- The only indication for their use is in infections caused by penicillin-resistant staphylococci, especially osteomyelitis,
- as they are well concentrated in bone; they are also used for staphylococcal endocarditis.
- A second anti staphylococcal antibiotic is usually required to prevent emergence of resistance.

Cautions and contraindications

- monitor liver function with high doses, on prolonged therapy or in hepatic impairment ; elimination may be reduced in hepatic impairment or biliary disease or biliary obstruction

Side-effect

- nausea, vomiting, reversible jaundice, especially after high dosage or rapid infusion , rarely hypersensitivity reactions, acute renal failure (usually with jaundice), blood disorders.

2. Vancomycin and teicoplanin

Mechanism of action

- The glycopeptide antibiotics vancomycin and teicoplanin have bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci.

Clinical uses

- Vancomycin should not be given by mouth for systemic infections since it is not significantly absorbed.
- Teicoplanin is similar to vancomycin but has a significantly longer duration of action. Unlike vancomycin, teicoplanin can be given by intramuscular as well as by intravenous injection .
- Both are used in endocarditis, dialysis-associated peritonitis, and serious infections ; prophylaxis in orthopaedic surgery at risk of infection with Gram-positive organisms

Cautions and contraindications

- Avoid rapid infusion of vancomycin (risk of anaphylactoid Reactions), renal Impairment ; elderly; avoid if history of deafness; all patients require plasma-vancomycin measurement (after 3 or 4 doses if renal function normal, earlier if renal impairment), monitor auditory function in elderly or if renal impairment
- Caution of teicoplanin in vancomycin sensitivity; blood counts and liver and kidney function tests required.

Side-effect

- Vancomycin- Nephrotoxicity including renal failure and interstitial nephritis; ototoxicity (discontinue if tinnitus occurs); blood disorders including neutropenia (usually after 1 week or cumulative dose of 25 g); phlebitis (irritant to tissue); on rapid infusion, severe hypotension (including shock and cardiac arrest), flushing of the upper body (‘red man’ syndrome).
- Side-effects of teicoplanin- nausea, vomiting, diarrhoea; anaphylaxis; headache; blood disorders ; disturbances in liver enzymes, transient increase of serum creatinine.
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3.Polymyxins and Colistin

Mechanism of action

- The polymyxin antibiotic, colistin, is active against Gram-negative organisms including Pseudomonas aeruginosa, Acinetobacter baumanii, and Klebsiella pneumoniae.

Clinical uses

- Polymyxin is not absorbed by mouth and thus needs to be given by injection for a systemic effect.
- Intravenous administration of colistin should be reserved for Gram negative infections resistant to other antibacterials;
- Both colistin and polymyxin B are included in some preparations for topical application
- Colistin is used by mouth in bowel sterilisation regimens in neutropenic patients (usually with nystatin); it is not recommended for gastro-intestinal infections. It is also given by inhalation of a nebulised solution as an adjunct to standard antibacterial therapy in patients with cystic fibrosis.

Cautions and contraindications:

- Cautions - renal impairment ; acute porphyria; risk of bronchospasm on inhalation— may be prevented or treated with a selective beta agonist;
- Contra-indications- myasthenia gravis.

Side-effect

- Colistin major adverse effects are dose-related neurotoxicity and nephrotoxicity.
- neurotoxicity reported especially with excessive doses (including apnoea, perioral and peripheral paraesthesia, vertigo; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances);
- hypersensitivity reactions including rash; injection-site reactions;
- inhalation may cause sore throat, sore mouth, cough, bronchospasm.

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4. *Metronidazole and Tinidazole*

***Mechanism of action*:**

- Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa.

***Clinical uses*:**

- Indications include trichomonal vaginitis,
- Entamoeba histolytica
- Giardia lamblia infections
- It is also used for surgical and gynaecological sepsis
- Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible.
- Intravenous metronidazole is used for the treatment of established cases of tetanus.
- Metronidazole by mouth is effective for the treatment of Clostridium difficile infection ,
- Topical metronidazole reduces the odour produced by anaerobic bacteria in fungating tumours
- Tinidazole is similar to metronidazole but has a longer duration of action.);
- Both used in Helicobacter pylori eradication
- Metronidazole is an alternative to a penicillin for the treatment of many oral infections where the patient is allergic to penicillin or the infection is due to beta-lactamase-producing anaerobes.

Cautions and contraindications

- METRONIDAZOLE Cautions - disulfiram-like reaction with alcohol, hepatic impairment and hepatic encephalopathy , avoid in acute porphyria .
- TINIDAZOLE avoid in acute porphyria .

Side-effect

- GIT-gastro-intestinal disturbances (including nausea and vomiting), taste disturbances, furred tongue , anorexia;
- very rarely hepatitis, jaundice, pancreatitis, drowsiness, dizziness, headache, darkening of urine, thrombocytopenia,
- on prolonged or intensive therapy peripheral neuropathy, transient epileptiform seizures, and leucopenia.

Antimicrobial drugs - part III

A. Antifungal drugs

Drug classifications

Polyene antifungals	*Amphotericin ,nystatin*
Imidazole antifungals	*clotrimazole, econazole, ketoconazole, sulconazole, and tioconazole*
Triazole antifungals	*Fluconazole, Itraconazole*
Echinocandin antifungals	*Caspofungin*
Other antifungals	*Flucytosine , amphotericin Griseofulvin Terbinafine*

Clinical uses

- **Amphotericin and nystatin** - neither drug is absorbed when given by mouth .They are used for oral, oropharyngeal, and perioral infections by local application in the mouth Amphotericin by intravenous infusion is used for the treatment of systemic fungal infections and is active against most fungi and yeasts . Nystatin is used for Candida albicans infections of the skin and mucous membranes, including oesophageal and intestinal candidiasis
- **The imidazole antifungals** are used for the local treatment of vaginal candidiasis and for dermatophyte infections . Miconazole can be used locally for oral infections; it is also effective in intestinal infections.
- **Triazole antifungals** Fluconazole is used for treating Candida albicans infection. It also achieves good penetration into the cerebrospinal fluid to treat fungal meningitis. Itraconazole is active against a wide range of dermatophytes . Posaconazole is licensed for the treatment of invasive fungal infections unresponsive to conventional treatment . Voriconazole is a broad-spectrum antifungal drug use in life-threatening infections.
- **Echinocandin antifungals** Caspofungin is active against Aspergillus spp. and Candida spp. Anidulafungin and micafungin are licensed for the treatment of invasive candidiasis.
- **Other antifungals** Flucytosine is used with amphotericin in a synergistic combination. Amphotericin by intravenous infusion is used for the empirical treatment of serious fungal infections. Griseofulvin is effective for widespread dermatophyte infections but has been superseded by newer antifungals, particularly for nail infections. It is the drug of choice for trichophyton infections in children.. Terbinafine is the drug of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate.

Cautions and contraindications

- It should weigh the potential benefits of treatment against the risk of liver damage and should carefully monitor patients both clinically and biochemically.
- Contra-indications acute porphyria

Side-effect

- Potentially life-threatening hepatotoxicity reported very rarely; risk of hepatotoxicity greater if given for longer than 10 days. Monitor liver function before treatment, then on weeks 2 and 4 of treatment, then every month. Avoid or use with caution if abnormal liver function tests

(avoid in active liver disease)

- GIT- nausea, abdominal discomfort, diarrhoea, flatulence,
- Stevens-Johnson syndrome (severe cutaneous reactions more likely in AIDS patients).

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B. Antiprotozoal drugs

Drug classifications

Antimalarials *Chloroquine Mefloquine Primaquine Quinine*

Pyrimethamine Riametc (artemether with lumefantrine).
Malaronec (Proguanil with Atovaquone)

Amoebicides *Metronidazole tinidazole Diloxanide furoate*

Trichomonacides *Metronidazole tinidazole*

Antigiardial drugs *Metronidazole tinidazole Mepacrine Hydrochloride*

Leishmaniacides *Sodium stibogluconate Amphotericin*

Pentamidine -isetionate

Toxoplasmosis *Spiramycin pyrimethamine +sulfadiazine*

Pneumocystis pneumonia *Co - trimoxazole Atovaquone*

pentamidine- isetionate

Clinical uses

- *Antimalarials*

- Quinine, Malaronec (proguanil with atovaquone), or Riametc (artemether with lumefantrine) are used as initial treatment for falciparum malaria.
- Malaronec and Riametc are licensed for the treatment of acute uncomplicated falciparum malaria.
- Chloroquine is used for the prophylaxis of malaria in areas of the world where the risk of chloroquine-resistant falciparum malaria is still low
- proguanil is used when chloroquine-resistant falciparum malaria is present but this regimen may not give optimal protection
- Mefloquine is used for the prophylaxis of malaria in areas of the world where there is a high risk of chloroquine resistant.
- Primaquine is used to eliminate the liver stages of P. vivax or P. ovale following chloroquine treatment. It is rarely used for the treatment of benign malarias.
- Pyrimethamine with sulfadoxine is not recommended for the prophylaxis of malaria, but it can be used in the treatment of falciparum malaria with (or following) quinine.
- Doxycycline is used for the prophylaxis of malaria in areas of widespread mefloquine or chloroquine resistance.

- *Amoebicides*

- Metronidazole is the drug of choice for acute invasive amoebic dysentery since it is very effective against vegetative forms of Entamoeba histolytica in ulcers
- Metronidazole and tinidazole are also active against amoebae which may have migrated to the liver.
- Diloxanide furoate is the drug of choice for asymptomatic patients with E. histolytica cysts in the faeces;
- Diloxanide furoate is not effective against hepatic amoebiasis, but a 10-day course should be given at the completion of metronidazole or tinidazole treatment to destroy any amoebae in the gut

➢ *Trichomonacides*

- Metronidazole is the treatment of choice for Trichomonas vaginalis infection. Contact tracing is recommended and sexual contacts should be treated simultaneously. If metronidazole is ineffective, tinidazole may be tried.

➢ *Antigiardial drugs*

- Metronidazole is the treatment of choice for Giardia lamblia infections. Alternative treatments are tinidazole or mepacrine hydrochloride

➢ *Leishmaniacides*

- Sodium stibogluconate, an organic pentavalent antimony compound, is used for visceral leishmaniasis.
- Amphotericin is used with or after an antimony compound for visceral leishmaniasis unresponsive to the antimonial alone;
- Pentamidine isetionate (pentamidine isethionate) has been used in antimony-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high; it is associated with serious side-effects.

➢ *toxoplasmosis*

- The treatment of choice is a combination of pyrimethamine and sulfadiazine (sulphadiazine), given for several weeks
- Spiramycin may reduce the risk of transmission of maternal infection to the fetus in pregnancy .

➢ *pneumocystis pneumonia*

- Atovaquone is licensed for the treatment of mild to moderate pneumocystis infection in patients who cannot tolerate co-trimoxazole.
- Inhaled pentamidine isetionate is sometimes used for mild disease. It is better tolerated than parenteral pentamidine but systemic absorption may still occur.

C. Antituberculosis drugs

Drug classifications *Isoniazid , rifampicin , pyrazinamide,*

Streptomycin , ethambutol

Clinical uses

- Isoniazid is cheap and highly effective. Like rifampicin it should always be included in any antituberculous regimen unless there is a specific contra-indication. should be given prophylactically from the start of treatment.
- Rifampicin, a rifamycin, is a key component of any antituberculous regimen. Like isoniazid it should always be included unless there is a specific contra-indication..
- Pyrazinamide is a bactericidal drug , is useful in tuberculous meningitis because of good meningeal penetration.

- Ethambutol is included in a treatment regimen if isoniazid resistance is suspected; it can be omitted if the risk of resistance is low.
- Streptomycin is now rarely used except for resistant organisms.

Cautions and contraindications

- Since isoniazid, rifampicin and pyrazinamide are associated with liver toxicity , hepatic function should be checked before treatment with these drugs.
- Streptomycin or ethambutol should preferably be avoided in patients with renal impairment, but if used, the dose should be reduced and the plasmadrug concentration monitored.
- Visual acuity should be tested before ethambutol is used
- Chemoprophylaxis may be required in those who have evidence of latent tuberculosis and are receiving treatment with immunosuppressants (including cytotoxics and possibly long-term treatment with systemic corticosteroids) , HIV-positive individual.
- Plasma-drug concentration should be measured in patients with impaired renal function in whom streptomycin must be used with great care.

Side-effect

- Isoniazid common side-effect is peripheral neuropathy which is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, malnutrition and HIV infection
- During the first two months ('initial phase') of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common but generally does not require interruption of treatment..
- Serious liver toxicity may occasionally occur with Pyrazinamide.
- Side-effects of ethambutol are largely confined to visual.

Recommended dosage for intermittent supervised 6-month Treatment

- Isoniazid (for 2-month initial and 4-month continuation phases)
- ADULT AND CHILD 15 mg/kg (max. 900 mg) 3 times a week
- Rifampicin (for 2-month initial and 4-month continuation phases)
- ADULT 600–900 mg 3 times a week; CHILD 15 mg/kg (max.
- *900 mg) 3 times a week Pyrazinamide (for 2-month initial phase only)
- ADULT under 50 kg 2 g 3 times a week, 50 kg and over 2.5 g 3 times a week; CHILD 50 mg/kg 3 times a week
- Ethambutol (for 2-month initial phase only)
- ADULT AND CHILD 30 mg/kg 3 times a week.

D. Antiviral drugs

Drug classifications

HIV infection

- ***Nucleoside reverse transcriptase inhibitor*** *(or 'nucleoside analogue') - Zidovudine , abacavir, didanosine, emtricitabine, lamivudine, stavudine, and tenofovir.*
- ***The protease inhibitors*** *- atazanavir, darunavir, fosamprenavir (a pro-drug of amprenavir), indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.,*
- ***The non-nucleoside reverse transcriptase inhibitors*** *-- efavirenz, etravirine, and nevirapine .*
- *Enfuvirtide, which* ***inhibits HIV from fusing to the host cell****.*
- *Maraviroc is* ***an antagonist of the CCR5 chemokine receptor****.*
- *Raltegravir is* ***an inhibitor of HIV integrase*****.**

- ***Herpesvirus :*** ***Herpes simplex and varicella–zoster infection***
- *Aciclovir Famciclovir Valaciclovir*
- ***Cytomegalovirus infection*** *Ganciclovir Valaciclovir Valganciclovir Foscarnet Cidofovir*

Viral hepatitis *Peginterferon alfa-2a Adefovir dipivoxil, entecavir, lamivudine telbivudine, tenofovir disoproxil*

.

Influenza *Oseltamivir zanamivir Amantadine*

Respiratory syncytial virus *Ribavirin (tribavirin) Palivizumab*

Clinical uses

➢ *Drugs for HIV infection*

- The non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine, and nevirapine are active against the subtype HIV-1 but not HIV-2
- Enfuvirtide is licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs; enfuvirtide should be combined with other potentially active antiretroviral drugs.
- Maraviroc is licensed for patients exclusively infected with CCR5-tropic HIV.
- Raltegravir is licensed for the treatment of HIV infection resistant to multiple antiretrovirals.

➢ *Herpes simplex and varicella–zoster infection Chickenpox*

- Aciclovir is active against herpesviruses but does not eradicate them. Uses of aciclovir include systemic treatment of varicella–zoster and the systemic and topical treatment of herpes simplex infections of the skin and mucous membranes . It is used by mouth for severe herpetic stomatitis .
- Famciclovir, a prodrug of penciclovir, is similar to aciclovir and is licensed for use in herpes zoster and genital herpes.
- Valaciclovir is an ester of aciclovir, licensed for herpes zoster and herpes simplex infections of the skin and mucous membranes (including genital herpes); also for preventing cytomegalovirus disease following renal transplantation.
- Idoxuridine has been used topically for treating herpes simplex infections of the skin and external genitalia with variable results. Its value in the treatment of shingles is unclear.
- Inosine pranobex has been used by mouth for herpes simplex infections; its effectiveness

remains unproven.

- *Cytomegalovirus infection CMV*

- Ganciclovir is related to aciclovir but it is more active against cytomegalovirus;
- Valaciclovir is licensed for prevention of cytomegalovirus disease following renal transplantation.
- Valganciclovir is an ester of ganciclovir which is licensed for the initial treatment and maintenance treatment of CMV retinitis in AIDS patients.
- Foscarnet is also active against cytomegalovirus; it is toxic and can cause renal impairment.
- Cidofovir is given in combination with probenecid for CMV retinitis in AIDS patients when ganciclovir and foscarnet are contra-indicated.

- *Viral hepatitis*

- Peginterferon alfa-2a is an option for the initial treatment of chronic hepatitis B and may be preferable to interferon alfa.
- Adefovir dipivoxil, entecavir, lamivudine ,telbivudine, or tenofovir disoproxil are licensed for the treatment of chronic hepatitis .

- *Influenza*

- Oseltamivir and zanamivir reduce replication of influenza . And can reduce the risk of complications from influenza in the elderly and in patients with chronic disease.
- Amantadine is licensed for prophylaxis and treatment of influenza A but it is no longer recommended

- *Respiratory syncytial virus*

- Ribavirin (tribavirin) inhibits a wide range of DNA and RNA viruses. It is licensed for administration by inhalation for the treatment of severe bronchiolitis caused by the respiratory syncytial virus (RSV) in infants, especially when they have other serious diseases.
- Palivizumab is a monoclonal antibody licensed for preventing serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease.

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E.Anthelmintics

Drug classifications

Drugs for threadworms	*Mebendazole Piperazine*
Ascaricides	*Mebendazole Levamisole Piperazine*
Drugs for tapeworm infections	*Niclosamide Praziquantel albendazole*
Drugs for hookworms	*Mebendazole albendazole*
Schistosomicides	*Praziquantel*
Filaricides	*Diethylcarbamazine*
Drugs for cutaneous larva migrans	*albendazole tiabendazole*
Drugs for strongyloidiasis	*Ivermectin Albendazole*

Clinical uses

- *Drugs for threadworms*

- Mebendazole is the drug of choice for treating threadworm infection in patients of all ages over 2 years. It is given as a single dose; as reinfection is very common, a second dose may

be given after 2 weeks.

- Piperazine is available in combination with sennosides as a single-dose preparation.

➢ *Ascaricides (common roundworm infections)*

- Mebendazole is effective against Ascaris lumbricoides and is generally considered to be the drug of choice.
- Levamisole is an alternative. It is very well tolerated.
- Piperazine may be given in a single adult dose.

➢ *Drugs for tapeworm infections -Taenicides*

- Niclosamide is the most widely used drug for tapeworm infections. it is not effective against larval worms.
- Praziquantel is as effective as niclosamide.

➢ *Hydatid disease*

- Surgical removal with albendazole cover is the treatment of choice, but where effective surgery is impossible, repeated cycles of albendazole (for a year or more) may help. Careful monitoring of liver function is particularly important during drug treatment

➢ *Drugs for hookworms*

- Mebendazole has a useful broad-spectrumbactivity, and is effective against hookworms.
- Albendazole, is an alternative

➢ *Schistosomicides (bilharziasis)*

- Praziquantel is effective against all human schistosomes. Of all the available schistosomicides, it has the most attractive combination of effectiveness, broad-spectrum activity, and low toxicity.
- Hycanthone, lucanthone, niridazole, oxamniquine, and sodium stibocaptate have now been superseded

➢ *Drugs for strongyloidiasis*

- Ivermectin is the treatment of choice for chronic Strongyloides infection.
- Albendazole is an alternative.

Central nervous system

A. Analgesics

Drug classifications

- ***Non-opioid analgesics*** *Aspirin , paracetamol , NSAIDs, Nefopam*

- ***Compound analgesic preparations*** ***(*** *paracetamol or aspirin +codeine)*
  Co-proxamol (dextropropoxyphene +paracetamol)

- ***Opioid analgesics*** *Morphine , Buprenorphine , Codeine,Diphenoxylate,*
  Diamorphine (heroin) , Alfentanil, fentanyl , Methadone
  Dihydrocodeine , Pentazocine Pethidine Tramadol Meptazinol

Clinical uses

➢ *Non-opioid analgesics*

- Aspirin is indicated for headache, transient musculoskeletal pain, dysmenorrhoea and pyrexia. In inflammatory conditions, most physicians prefer anti-inflammatory treatment with another NSAIDs.
- Paracetamol is similar in efficacy to aspirin, but has no demonstrable anti-inflammatory activity; it is less irritant to the stomach and for that reason is now generally preferred to aspirin, particularly in the elderly.
- Nefopam may have a place in the relief of persistent pain unresponsive to other non-opioid analgesics.
- Non-steroidal anti-inflammatory analgesics are particularly useful for the treatment of patients with chronic disease accompanied by pain and inflammation, in the short-term treatment of mild to moderate pain including transient musculoskeletal pain but paracetamol is now often preferred, particularly in the elderly. They are also suitable for the relief of pain in dysmenorrhoea and to treat pain caused by secondary bone tumours.
- Most dental pain is relieved effectively by NSAIDs . Aspirin is effective against mild to moderate dental pain.

➢ *Opioid analgesics*

- Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause dependence and tolerance.
- Morphine remains the most valuable opioid analgesic for severe pain although it frequently cause nausea and vomiting.
- Morphine is the opioid of choice for the oral treatment of severe pain in palliative care.
- Codeine is effective for the relief of mild to moderate pain but is too constipating for long-term use.
- Diphenoxylate (in combination with atropine) is used in acute diarrhea.
- Methadone is less sedating than morphine and acts for longer periods.
- Pethidine produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic.
- Tramadol produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects.
- Alfentanil, fentanyl and remifentanil are used by injection for intra-operative analgesia.

Cautions and contraindications

- Contra-indications of aspirin in children under 16 years and in breast-feeding , avoid during fever or viral infection in children (Reye's syndrome).
- Aspirin and other NSAIDs are contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria.
- Opioids should be used with caution in patients with impaired respiratory function.
- Repeated use of opioid analgesics is associated with the development of psychological and physical dependence;.
- Avoid abrupt withdrawal of opioid after long-term treatment.

Side-effect

- Aspirin tablets - Gastric irritation may be a problem; it is minimised by taking the dose after food. Enteric-coated preparations are available.
- Overdosage with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not apparent for 4 to 6 days .
- Nefopam causes little or no respiratory depression, but sympathomimetic and antimuscarinic side-effects may be troublesome.
- The low dose of the opioid may be enough to cause opioid side-effects (constipation).A full dose of the opioid component (e.g. 60 mg codeine phosphate) in compound analgesic preparations is associated with the full range of opioid side-effects (including nausea, vomiting, severe constipation, drowsiness, respiratory depression, and risk of dependence on long-term administration).

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B. Hypnotics and anxiolytics

***Drug classifications*:**

Anxiolytics Benzodiazepines – diazepam , chlordiazepoxide , loprazolam , lorazepam , lormetazepam , oxazepam , temazepam

Hypnotics Benzodiazepines - nitrazepam , flurazepam

Zaleplon, zolpidem, and zopiclone
Chloral and derivatives
Barbiturates

Mechanism of action

- Benzodiazepines they act at benzodiazepine receptors which are associated with gamma-aminobutyric acid (GABA) receptors.
- Zaleplon, zolpidem and zopiclone are non-benzodiazepine hypnotics, but they act at the benzodiazepine receptor

Clinical uses

- Benzodiazepines are the most commonly used anxiolytics and hypnotics;
- Transient insomnia - If a hypnotic is indicated one that is rapidly eliminated should be chosen, and only one or two doses should be given.

- Short-term insomnia - Intermittent use is desirable with omission of some doses. A rapidly eliminated drug is generally appropriate.
- Chronic insomnia is rarely benefited by hypnotics and is sometimes due to mild dependence.
- Loprazolam, lormetazepam, and temazepam act for a shorter time and they have little or no hangover effect. Withdrawal phenomena are more common with the short-acting benzodiazepines.
- Nitrazepam or temazepam are used at night for dental patients.
- Chloral hydrate and derivatives were formerly popular hypnotics for children.
- The intermediate-acting barbiturates have a place only in the treatment of severe intractable insomnia .
- Zolpidem and zopiclone have a short duration of action; are not licensed for long-termuse; dependence has been reported in a small number of patients.

Cautions and contraindication

- A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines.
- Hypnotics and anxiolytics may impair judgement and increase reaction time, and so affect ability to drive or operate machinery
- Withdrawal of a benzodiazepine should be gradual because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens.
- Abrupt withdrawal of a barbiturate is even more likely to have serious effect. barbiturates should be avoided in the elderly.
- Hypnotics should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused and so liable to fall and injure themselves.

Side-effect

- Prescribing of benzodiaepins is widespread but dependence (both physical and psychological) and tolerance occurs.
- Tolerance to hypnotics develops within 3 to 14 days of continuous use and long-term efficacy cannot be assured.
- A major drawback of long-term use is that withdrawal can cause rebound insomnia and a withdrawal syndrome.
- Common s.e of benzodiazepins are drowsiness and lightheadedness the next day; confusion and ataxia.

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C. Antiepileptic drugs

Drug classifications

Carbamazepine , clobazam, clonazepam, , phenytoin , phenobarbital , tiagabine, topiramate, valproate, zonisamide , Ethosuximide, primidone Gabapentin , Lamotrigine , Levetiracetam , Oxcarbazepine , Pregabalin , Rufinamide , Topiramate , Vigabatrin.

Clinical uses

- *Partial seizures with or without secondary generalization* Carbamazepine, lamotrigine, oxcarbazepine, and sodium valproateare the drugs of choice for partial (focal) seizures; second-line drugs include clobazam, gabapentin, levetiracetam, pregabalin, tiagabine, topiramate, and zonisamide.
- *Generalised seizures Tonic-clonic seizures (grand mal)* The drugs of choice for tonic-clonic

- seizures are carbamazepine, lamotrigine, and sodium valproate. Clobazam, levetiracetam, oxcarbazepine, and topiramate are second-line drugs.
- *Absence seizures (petit mal)* Ethosuximide and sodium valproate are the drugs of choice in typical absence seizures; alternatives include clonazepam and lamotrigine. Sodium valproate is also highly effective in treating the generalised tonic-clonic seizures which can co-exist with absence seizures in idiopathic primary generalised epilepsy.
- *Myoclonic seizures (myoclonic jerks)* . Sodium valproate is the drug of choice; clonazepam and levetiracetam can also be used. Alternatives include lamotrigine and topiramate, but lamotrigine may occasionally exacerbate myoclonic seizures. For reference to the adjunctive use of piracetam, Sodium valproate and levetiracetam are effective in treating the generalised tonic-clonic seizures that coexist with myoclonic seizures in idiopathic generalized epilepsy.
- *Atypical absence, atonic, and tonic seizures* are usually seen in childhood . Sodium valproate, lamotrigine, and clonazepam can be tried. Second-line drugs that are occasionally helpful include clobazam, ethosuximide, levetiracetam, and topiramate.

Cautions and contraindications

- Antiepileptic drugs have been associated with a small increased risk of suicidal thoughts and behaviour; this can occur as early as 1 week after starting treatment. Patients should be advised to seek medical advice if they develop mood changes or suicidal thoughts.
- Interactions between antiepileptic drugs are complex and may enhance toxicity without a corresponding increase in antiepileptic effect. Interactions are usually caused by hepatic enzyme induction or hepatic enzyme inhibition;
- Patients affected by drowsiness should not drive or operate machinery.
- There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (reduced if treatment is limited to a single drug).
- Breast-feeding is acceptable with all antiepileptic drugs, taken in normal doses, with the possible exception of the barbiturates.

Side-effect

- Abrupt withdrawal, particularly of the barbiturates and benzodiazepines, should be avoided because this may precipitate severe rebound seizures.
- Patients affected by drowsiness.

D. Drugs used in parkinsonism

Drug classifications

- ***Dopamine receptor agonists*** *Bromocriptine, cabergoline, Amantadine Apomorphine , pergolide, pramipexole, ropinirole, Rotigotine.*
- ***Levodopa*** *L-dopa*
- ***Monoamine-oxidase-B inhibitors*** *Rasagiline, Selegiline*
- ***Catechol-O-methyltransferase inhibitors*** *Entacapone , tolcapone*
- ***Antimuscarinic drugs*** *orphenadrine, procyclidine, trihexyphenidyl (benzhexol)*

Mechanism of action

- The dopamine receptor agonists, bromocriptine, cabergoline, pergolide, pramipexole, ropinirole, and rotigotine have a direct action on dopamine receptors.
- Levodopa, the amino-acid precursor of dopamine, acts by replenishing depleted striatal dopamine; it is given with an extracerebral dopa-decarboxylase inhibitor that reduces the peripheral conversion of levodopa todopamine, thereby limiting side-effects such as nausea, vomiting and cardiovascular effects.
- Entacapone and tolcapone prevent the peripheral breakdown of levodopa, by inhibiting catechol-Omethyltransferase, allowing more levodopa to reach the brain.

Clinical uses

- The treatment of new patients is often started with dopamine receptor agonists. They are also used with levodopa in more advanced disease.
- Rotigotine is licensed for use as monotherapy in early-stage Parkinson's disease.
- Apomorphine is a potent dopamine agonist that is sometimes helpful in advanced disease for patients experiencing unpredictable 'off ' periods with levodopa treatment.
- Amantadine is a weak dopamine agonist with modest antiparkinsonian effects. It improves mild bradykinetic disabilities as well as tremor and rigidity. It may also be useful for dyskinesias in more advanced disease.
- Rasagiline, a monoamine-oxidase-B inhibitor, is licensed for the management of Parkinson's disease used alone or as an adjunct to levodopa for 'end-ofdose' fluctuations.
- Selegiline is a monoamine-oxidase-B inhibitor used in conjunction with levodopa to reduce 'end-of-dose' deterioration in advanced Parkinson's disease.
- Entacapone and tolcapone are licensed for use as an adjunct toco-beneldopa or co-careldopa for patients with Parkinson's disease who experience 'end-of-dose' deterioration and cannot be stabilised on these combinations.
- In idiopathic Parkinson's disease, antimuscarinic drugs reduce tremor and rigidity but they have little effect on bradykinesia. They may be useful in reducing sialorrhoea.

Cautions and contraindications

- Hypotensive reactions can occur in some patients taking dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.
- Doses of dopamine receptor agonists should be increased slowly according to response and tolerability.
- Treatment with dopamine receptor agonists should not be withdrawn abruptly.

- Antiparkinsonian drugs can cause confusion in the elderly.
- Levodopa should be used with caution in severe cardiovascular or pulmonary disease, psychiatric illness ,open-angle glaucoma and patients susceptible to angle-closure glaucoma, and in hepatic or renal impairment
- Levodopa should be avoided in breast-feeding.
- Antimuscarinics should be avoided in gastro-intestinal obstruction and myasthenia gravis.

Side-effect

- Hypotensive reactions can occur in some patients on dopamine receptore agonist.
- Side-effects of levodopa include nausea, vomiting, taste disturbances, dry mouth, anorexia, arrhythmias, postural hypotension.
- Side-effects of antimuscarinics include anticholinergic advers effects.

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Drugs used in Anaemias

Drug classifications

- ***Oral iron*** ***Ferrous fumarate 200 mg - 65 mg iron***
  Ferrous gluconate 300 mg - 35 mg iron
  Ferrous sulphate 300 mg - 60 mg iron
  Ferrous sulphate, dried 200 mg - 65 mg iron

- ***Parenteral iron - iron dextran, iron sucrose, ferric carboxymaltose.***
- ***Folic acid - Folinic acid***
- ***vitamin B preparations - Hydroxocobalamin , cyanocobalamin***
- ***Erythropoietins*** ***Epoetins (recombinant human erythropoietins)***
  Darbepoetin(hyperglycosylated derivative)
  Methoxy polyethylene glycol-epoetin beta

Clinical uses

- Ferrous sulphate , For treatment of iron-deficiency anaemia in children and for prophylaxis of iron-deficiency anaemia in babies of low birth weight,
- Compound preparations containing iron and folic acid are used during pregnancy in women who are at high risk of developing iron and folic acid deficiency.
- Parenteral iron is generally reserved for use when oral therapy is unsuccessful because the patient cannot tolerate oral iron, or if there is continuing blood loss, or in malabsorption. Parenteral iron may also have a role in the management of chemotherapy induced anaemia, when given with erythropoietins, in specific patient groups.
- Folic acid is used for the treatment of folate-deficient megaloblastic anaemia (e.g. because of poor nutrition, pregnancy, or antiepileptic drugs).
- Folic acid supplements taken before and during pregnancy can reduce the occurrence of neural tube defects.
- Folic acid Prophylaxis in chronic haemolytic states.
- Folinic acid is also effective in the treatment of folate deficient megaloblastic anaemia but it is generally used in association with cytotoxic drugs.
- Vitamin B is also needed in the treatment of megaloblastosis.
- Vitamin B should be given prophylactically after total gastrectomy or total ileal resection.

- Epoetins are used to treat symptomatic anaemia associated with erythropoietin deficiency in chronic renal failure.
- Erythropoietins licensed for the treatment of symptomatic anaemia associated with cancer, are licensed only for patients who are receiving chemotherapy.

***Cautions and contraindications*:**

- Oral iron, particularly modified-release preparations, can exacerbate diarrhoea in patients with inflammatory bowel disease; care is also needed in patients with intestinal strictures and diverticular disease.
- C.I with parenteral administration in history of allergic disorders including asthma, eczema and anaphylaxis.
- Folic acid should never be given alone for pernicious anaemia and other vitamin-B deficiency states (may precipitate subacute combined degeneration of the spinal cord).

- Side-effect:
- Gastro-intestinal irritation can occur with iron salts.
- Iron preparations taken orally can be constipating, particularly in older patients and occasionally lead to faecal impaction. If side-effects occur, the dose may be reduced; alternatively, another iron salt may be used of a lower content of elemental iron.They may be taken after food to reduce gastro-intestinal side-effects; they may discolour stools.
- Anaphylactoid reactions can occur with parenteral administration of iron complexes.

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