Drugs for Hyperlipidemias & Obesity

I. Overview

Coronary heart disease (CHD) is the cause of about half of all deaths in the world .

The incidence of CHD is correlated with elevated levels of low-density lipoprotein (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoprotein (HDL) cholesterol.

Causes of hyperlipidemia

1- **Life-style factors**

Cholesterol levels may be elevated as a result of an individual's lifestyle as :

cigarette smoking, hypertension, obesity, and diabetes, by lack of exercise and consumption of a diet containing excess saturated fatty acids).

2- Genetic factors or family history

Hyperlipidemias can also result from a single inherited gene defect in lipoprotein metabolism or

3- More commonly, from a combination of genetic and lifestyle factors.

Appropriate lifestyle changes in combination with drug therapy can lead to a decline in the progression of coronary plaque, regression of preexisting lesions, and reduction in mortality due to CHD by 30 to 40 percent.

Antihyperlipidemic drugs must be taken indefinitely; when therapy is terminated, plasma lipid levels return to pretreatment levels. The lipid-lowering drugs are listed in Figure 21.1.

Figure 21.2 illustrates the normal metabolism of serum lipoproteins and the characteristics of the major genetic hyperlipidemias.

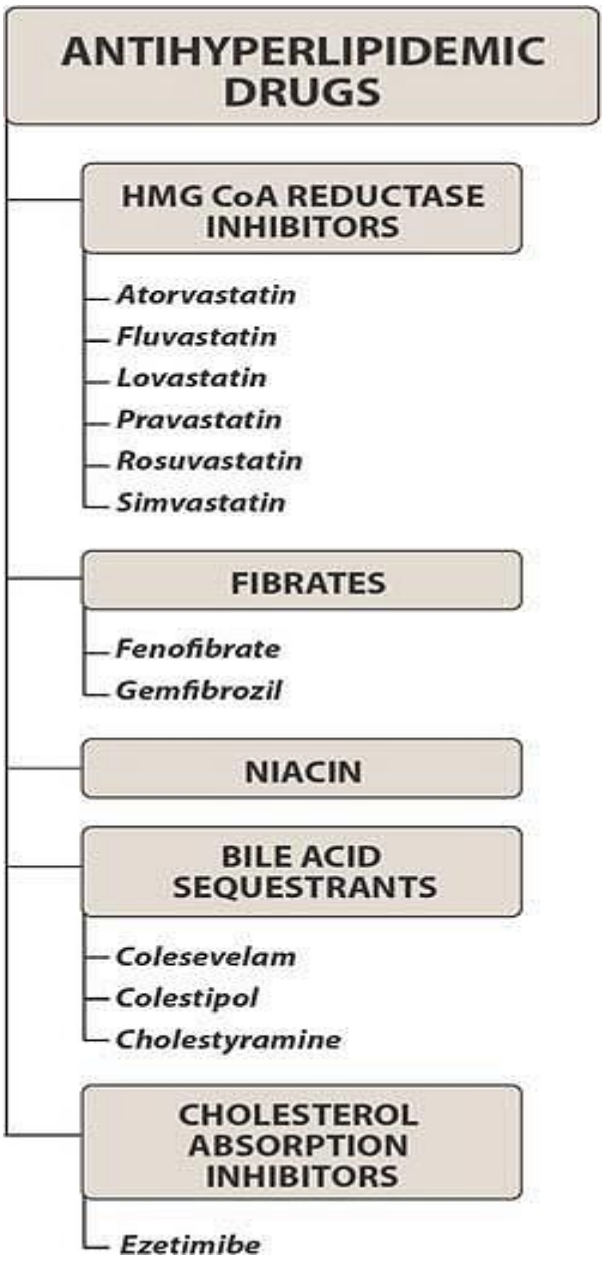


Figure 21.1 Summary of antihyperlipidemic drugs. HMG CoA = 3-hydroxy-3- methylglutaryl coenzyme A

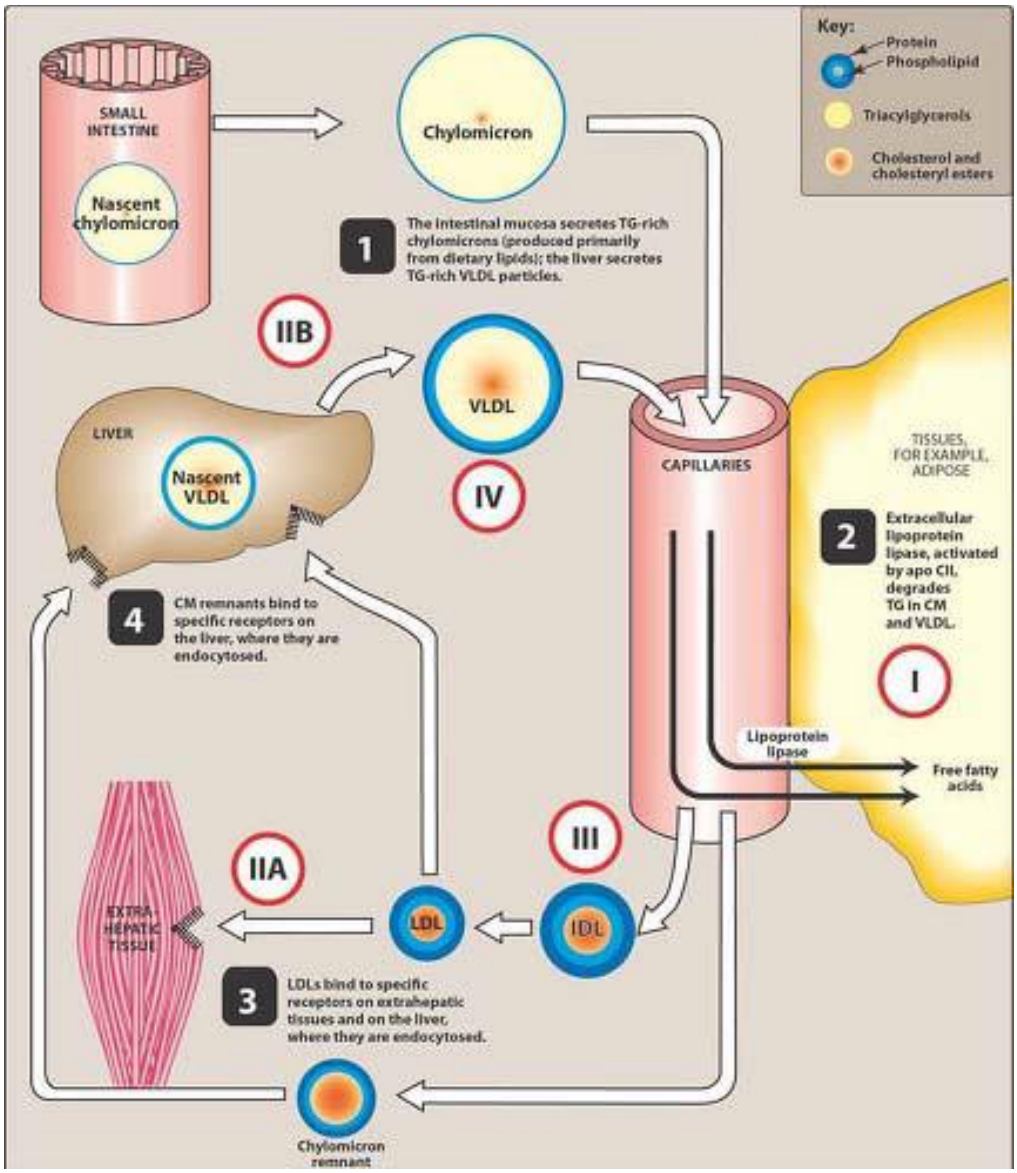
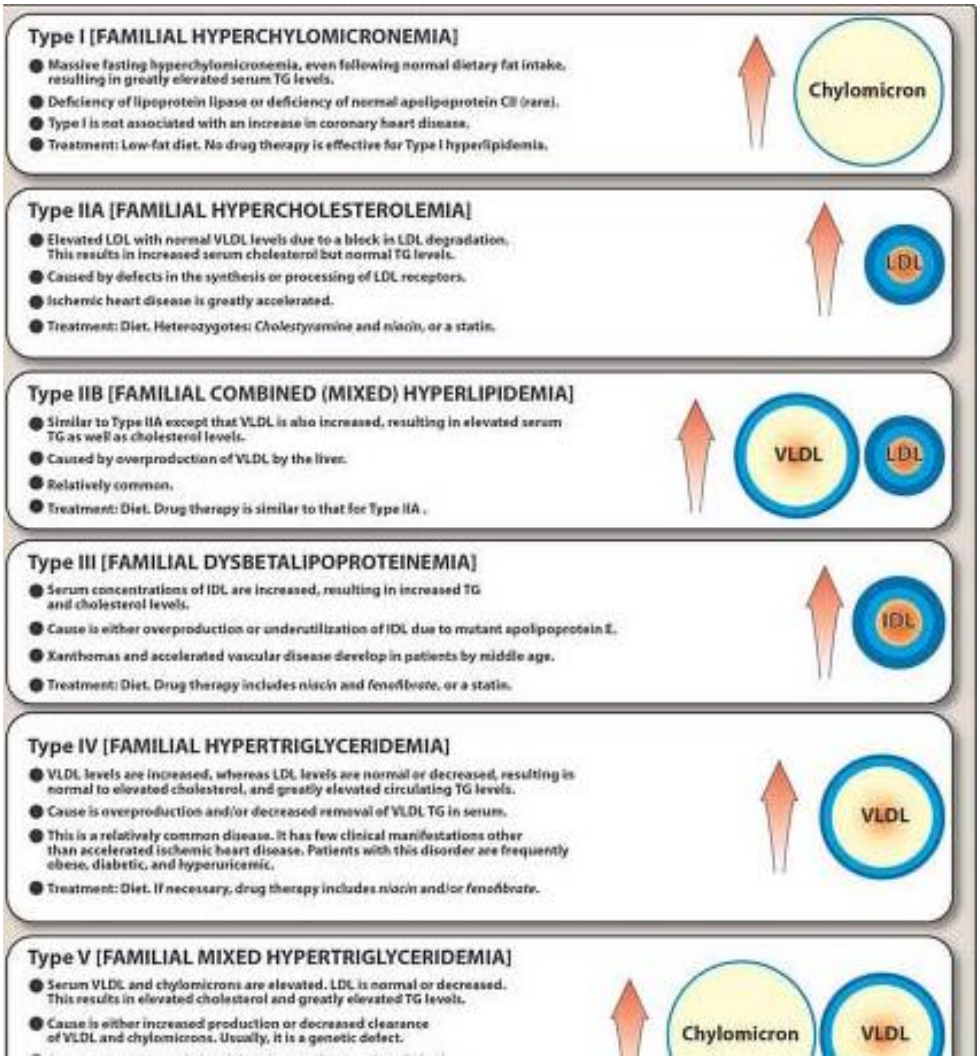


Figure 21.2 Metabolism of plasma lipoproteins and related genetic diseases. الرسم للاطلاع

Types of Hyperlipedemia للاطلاع



Types of Hyperlipedemia

A- Triglyceridemia(Elevated TG in the blood & tissues)

B- Hypercholesterolemia(Elevated cholesterol (LDL ,VLDL) inblood and tissues)

- **LDL- cholesterol** : major form of lipid **enter the liver** , carry high lipid content)
- **VLDL-Cholesterol : secreted by the liver transport cholesterol from the liver to blood**
- **HDL- Cholesterol : transport cholesterol from the blood to the liver**
- **Chylomicron : largest lipoprotein carry triglycerides and cholesterol ester from the gut to other tissues**

Treatment Goals

Plasma lipids consist mostly of **lipoproteins** "spherical macromolecular complexes of **lipids and specific proteins (Apolipoproteins).**

The clinically important lipoproteins, listed in **decreasing order of Atherogenicity, are LDL>very-low-density lipoprotein (VLDL) and chylomicrons, >> HDL.**

The SAFE (GOOD CHOLESTEROL) = HDL

The TOXIC (BAD CHOLESTEROL) =LDL

The occurrence of CHD is positively associated with :

- **High total cholesterol**, and even more strongly with **elevated LDL** cholesterol in the blood.
- **High levels of HDL cholesterol** have been associated with a **decreased risk for heart** disease (Figure 21.3).
- **Reduction of the LDL level is the primary goal of cholesterol-lowering therapy.**

Recommendations for the reduction of LDL cholesterol to specific target levels are influenced by the coexistence of CHD and the number of other cardiac risk factors. The higher the overallrisk of heart disease, the more aggressive the recommended LDL-lowering therapy.

Drugs for hyperlipidemia

A. HMG CoA reductase Inhibitors

A 3-Hydroxy-3-methylglutaryl (HMG) coenzyme A (COA) reductase inhibitors (commonly known as statins) lower elevated LDL cholesterol levels, resulting in a substantial reduction in coronary events and death from CHD.

This group of antihyperlipidemic agents inhibits the first committed enzymatic step of cholesterol synthesis, catalyzed by HMG CoA reductase enzyme and they are the first-line and more effective treatment for patients with elevated LDL cholesterol.

A-CLASS: Theses drugs called (STATINS GROUP) include : **Lovastatin , simvastatin , Atorvastatin , fluvastatin and Rosuvastatin**

B- Mechanism of action: statins assumed to act through **Inhibition of HMG CO A reductase** : Since statins are **analogs of HMG**, the precursor of cholesterol.

all compete effectively to **inhibit HMG CoA reductase, the rate-limiting step in cholesterol synthesis**. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol in the liver

Lovastatin and simvastatin are lactones that are hydrolyzed to the active drug. **Pravastatin and fluvastatin are active as such.**

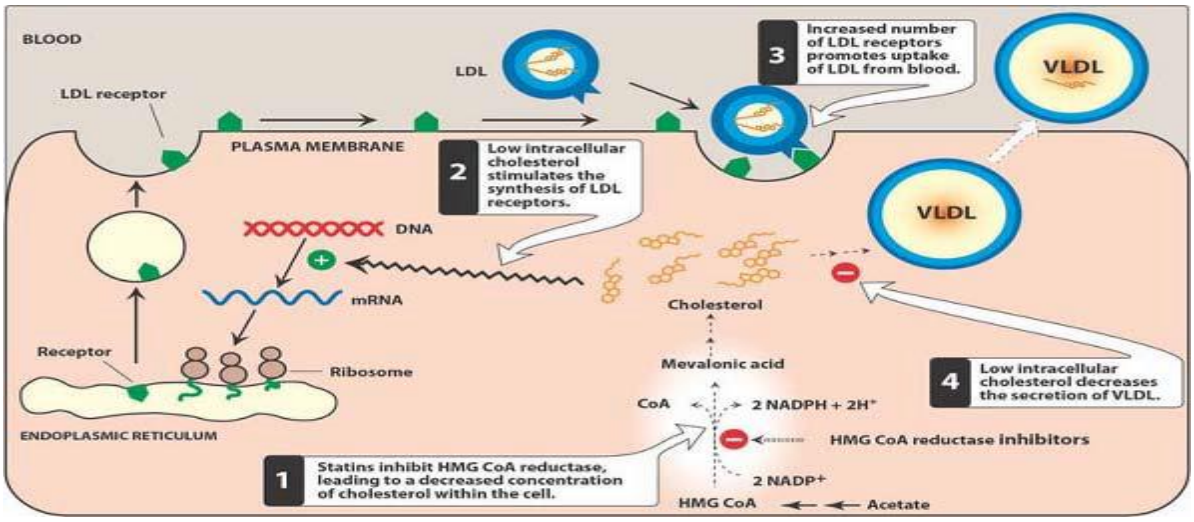


Figure 21.5 Inhibition of HMG CoA reductase by the statin drugs. للاطلاع

Adverse effects: few adverse effects, related to liver and muscle function, were reported

- **Liver**: Biochemical abnormalities in liver function ,Therefore, it is prudent to evaluate liver function and measure **serum transaminase levels periodically**.
- **Muscle**: Myopathy and rhabdomyolysis (disintegration or dissolution of muscle) h b. ave been reported only rarely.
- In most of these cases, patients usually suffered from **renal insufficiency or Renal functions parameters levels should be determined regularly**.

B. Niacin (Nicotinic acid)

Mechanism of action: At gram doses**, niacin strongly inhibits lipolysis in adipose tissue** "the primary producer of circulating free fatty acids , The liver normally utilizes these circulating fatty acids as a major **precursor for triacylglycerol synthesis**.

Adverse effects: The most common side effects of niacin therapy are

1- An intense cutaneous flush (accompaniedby an uncomfortable feeling of warmth) and pruritus. the flush, which is prostaglandin mediated.

2- Some patients also experience nausea andabdominal pain.

3- Niacin inhibits tubular secretion of uric acid and, thus, predisposes to hyperuricemia and gout.

4- Impaired glucose tolerance and hepatotoxicity have also been reported.

C. The fibrates: Fenofibrate and Gemfibrozil

Mechanism of action: The **Peroxisome Proliferator Activated Receptors (PPARs)** are members of the nuclearreceptor gene family that **regulates lipid metabolism**.

Act through two steps :

1-They then bind to peroxisome proliferator response elements within genethat regulates the **expression of proteins involved in lipoproteinSO Fibrates increase the level of HDL cholesterol by increasing the expression of apo proteins**

2- Leads to decreased triacylglycerolconcentrations by increasing the expression of **lipoprotein lipase** (Figure 22.11)

Adverse effects:

1-Gastrointestinal effects: The most common adverse effects are mild gastrointestinal disturbances. These lessen as the therapy progresses.

2-Lithiasis: Because these drugs increase biliary cholesterol excretion, there is a predisposition to theformation of **gallstones.**

3-Muscle: Myositis (inflammation of a voluntary muscle) can occur with both drugs; thus, muscle weakness ortenderness should be evaluated.

Patients with renal insufficiency may be at risk. Myopathy andrhabdomyolysis have been reported in a few patients taking gemfibrozil and lovastatin together.

D. Bile acid binding resins : Cholestyramine and Colestipol

Mechanism of action: these drugs are **anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine** (Figure 21.12). The resin/bile acid complex **is excreted in the feces**, thus preventing the bile acids from returning to the liver by the enterohepatic circulation.

Consequently, the intracellular cholesterol concentration decreases, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL.

The final outcome of this sequence of events is a decreased total plasma cholesterol concentration.

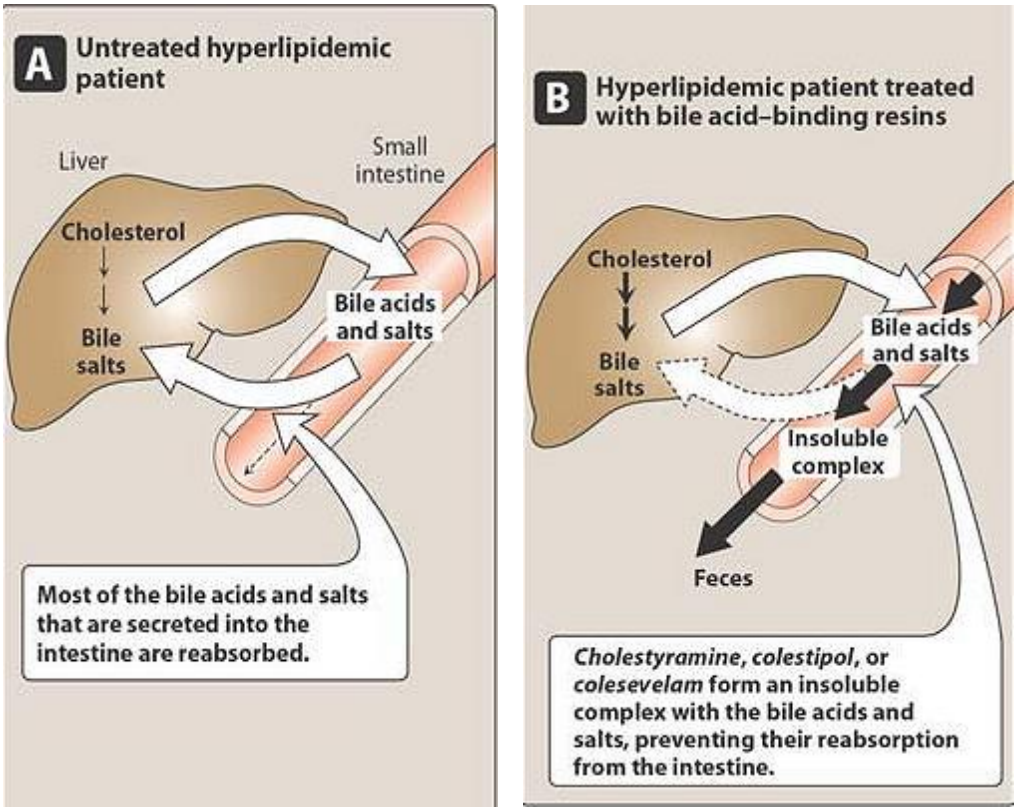


Figure 21.12 Mechanism of bile acidâ€“binding resins. للاطلاع

Adverse effects:

1-Gastrointestinal effects: The most common side effects are gastrointestinal disturbances, such asconstipation, nausea, and flatulence.

2-Impaired absorptions: At high doses, cholestyramine and colestipol (impair theabsorption of the fat-soluble vitamins (A, D, E, and K).

Drug interactions: Cholestyramine and colestipol interfere with the intestinal absorption of manydrugs"for example, tetracycline, phenobarbital, digoxin, warfarin, , fluvastatin, aspirin,and thiazide diuretics.

Therefore, drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after,the bile acid"binding resins.

E- Cholesterol absorption inhibitors: Ezetimibe

Ezetimibe selectively **inhibits intestinal absorption of dietary and biliary cholesterol in the smallintestine**, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an **increase in clearance of cholesterol from the blood.**

Ezetimibe lowers LDL cholesterol by 17 percent and triacylglycerols by 6 percent, and it increases HDL cholesterol

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronideconjugation with subsequent biliary and renal excretion.

[Note: A formulation of ezetimibe and simvastatin has been shown to lower LDL levels more effectively than the statin alone.]

SUMMARY :Figure 21.14 summarizes some actions of the Antihyperlipidemic drugs.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Drugs Used to Treat Obesity

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health, leading to reduced life expectancy and/or increased health problems

In Western countries, people are considered obese when their body mass index (BMI) a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m2, with the range 25–30 kg/m2 defined as overweight. Some East Asian countries use stricter criteria.

Obesity increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis

Obesity is most commonly caused by a combination of excessive food energy intake, lack of physical activity, and genetic susceptibility, although a few cases are caused primarily by genes, endocrine disorders, medications, or psychiatric illness. Evidence to support the view that some obese people eat little yet gain weight due to a slow metabolism is limited. On average, obese people have a greater energy expenditure than their thin counterparts due to the energy required to maintain an increased body mass.

CLASSES OF DRUGS FOR OBESITY

Two classes of drugs are used in treating obesity:

A- the Anorexiants(Appetite suppressants) Phentermineand Sibutramine,

B- Lipase inhibitor: Orlistat.

Sibutramine and orlistat have been approved for up to 2 and 4 years of use,

Figure 29.8 Effect of sibutramine treatment on body weight.

Phentermine [FEN-ter-meen]

A-CLASS :Anorexiant or Appetite inhibitor

B-Mechanism of action :exerts its pharmacologic action :

1- by **increasing release of norepinephrine and dopaminefrom the nerve terminals**

2- by**inhibiting reuptake of these neurotransmitters**, **thereby increasing levels ofneurotransmitters in the brain.**

C- Pharmacokinetics: Limited information is available regarding the pharmacokinetics of phentermine. Theduration of activity is dependent on the formulation, and the primary route of excretion is via the kidney.

D-Theraputic uses &advesrse effects

Phentermine indicatedfor short-term management of obesity.

Sibutramine [si-BYOO-tra-meen]

A-CLASS :**Anorexiant or Appetite inhibitor**

B-Mechanism of action :**inhibits central reuptake of serotonin, norepinephrine**, and to a lesser extent,dopamine. Unlike the other agents, sibutramine does not cause the release of neurotransmitters.

C-Pharmacokinetics :Sibutramine undergoes hepatic metabolism to active metabolites, which are primarilyresponsible for its pharmacologic effects. The active metabolites are biotransformed further in the liver andexcreted primarily in the urine. The half-life of the active metabolites is about 15 hours.

Adverse effects and contraindications of both phentermine &sibutramine

1-Dry mouth, headache, insomnia, and constipation are common problems.

2- All of the appetite suppressants have potential**for dependence or abuse**.

3- Heart rate and blood pressure may be increased with these agents, and they should be avoided in patients with ahistory of hypertension, CVD, arrhythmias, congestive heart failure, or stroke.

4- Sibutramine should also be avoided inpatients who are taking selective serotonin inhibitors such as fluoxetine, serotonin agonists for migraine

B. Orlistat

A-CLASS :Orlistat is the first drug in a class of antiobesity drugs known as **lipase inhibitors**.

B-Mechanism of action :Orlistat inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat intosmaller molecules that can be absorbed.

C-Pharmacokinetics :

D-Theraputic uses &Adverse effects

Orlistat is administeredthree times daily with meals.Fat absorption is decreased by about 30 percent. The loss of calories is the main cause of weight loss,

The most common adverse effectsassociated with orlistatare :

Gastrointestinal symptoms, : such as oily spotting, flatulence with discharge, fecalurgency, and increased defecation.

It interferes with the absorption of fat-soluble vitamins and B-carotene. Thus,patients should be advised to take a multivitamin supplement that contains vitamins A, D, E, and K and also B-carotene.

Orlistat is contraindicated inpatients with chronic malabsorption syndrome or cholestasis.