Antihyperlipidemic Drugs

Drug	MOA	Effects	Side Effects	Notes
Niacin	▫In adipose tissue: **inhibits** the lipolysis of triglycerides by **inhibiting adipocyte adenylyl cyclase**, which reduces transport of free fatty acids to the liver and decreases hepatic triglyceride synthesis. ▫May **inhibit** a rate –limiting enzyme of triglyceride synthesis, **diacylglycerol acetyltransferase 2**. ▫**Reduction** of triglyceride **synthesis reduces** hepatic VLDL &consequently LDL. ▫**Inhibits** intracellular **lipase** in adipose tissues leading to decreased FFA flux to the liver.	▫Hypolipidemic effects only in **large** doses (has low potency) ▫Affects all lipid parameters: -Best agent to **increase** HDL-C -**Lowers** triglycerides -**Decreases** LDL-C production ▫**Reduces** fibrinogen levels ▫**Increases** plasminogen activator	▫Toxicity: -Harmless cutaneous vasodilation and sensation of warmth, can be **prevented** by NSAIDS -Pruritus, rashes, dry skin and mucus membranes (acanthosis nigricans: black discoloration) -Nausea, vomiting, abdominal discomfort, diarrhea -Elevations in transaminases and possible hepatotoxicity -Insulin resistance &hyperglycemia -Hyperuricemia and gout -Cardiac arrhythmias -Amblyopia, blurring of vision	- Nicotinic Acid or Vitamin B3 - Water-soluble B-complex vitamin, functions only after conversion to NAD+ or NADP+ nicotinamide - Completely absorbed, peaks within 1hr, half-life is about 1 hr, so needs to be given twice or thrice daily (inconvenient) -Generally: all anti-hyperlipidemic drugs cause myopathy **except for Niacin**
Fibrates (Fibric Acid Derivatives): PPARs Activators				
▫Clofibrate **▫Gemfibrozil** **▫Fenofibrate** **▫Bezafibrate**	▫Activate PPAR- α (Peroxisome Proliferator Activated Receptor- α) which stimulates fatty acid oxidation, increases LPL synthesis, and reduces expression of apoC-III, and increases apoA-I and apoA-II expression (the major apolipoproteins in HDL)	▫**Drugs of choice** in severe hypertriglyceridemia ▫Lipid parameter affected: -**Increase** lipolysis of lipoprotein triglyceride via LPL -**Decrease** levels of VLDL and LDL -Moderately **increase** HDL ▫Have **anticoagulant** and **fibrinolytic** activities	-Rashes, urticaria, hair loss, headache, GIT symptoms, impotence, and anemia. -Myalgia, fatigue, myopathy and rhabdomyolysis (breakdown of muscle fibers resulting in the release of muscle fiber contents (myoglobin) into the blood) -Risk of cholesterol gallstones -Elevated transaminases or alkaline phosphatase	-The first drug was Clofibrate in 1962 but it was discontinued in 1987 -Interact with **statins, levels of both drugs will increase** ***Used with caution in renal failure**
Bile Acid –Binding Resins				
▫Colestipol **▫Cholestyramine** **▫Colesevelam**	-Large polymeric anionic- exchange resins, insoluble in water, which bind the negatively charged bile acids in the intestinal lumen and **prevent their reabsorption** leading to depletion of bile acid pool and increased hepatic synthesis →	✵**Indications:** -Lower LDL as much as 25%, but will cause GI side effects -Relieve pruritus in cholestasis (abnormal bile flow) -**Digitalis toxicity**, can bind digitoxin and enhance its excretion	-Gritty sensation is unpleasant but can be tolerated -Constipation, bloating & gallstones -Malabsorption of Vitamin K -Gall stones & Heartburn -Impaired absorption of drugs	-Probably the **safest drugs**, since they are not absorbed from the intestine because of their large size -Maximal doses are effective but cause side effects -May increase triglyceride levels

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Bild Acid Binding Resins (Cont.)	→ Hepatic cholesterol content is **decreased**, stimulating the production of LDL receptors → **increased** LDL **clearance** and lowered LDL-C levels (this effect is partially offset by the enhanced cholesterol synthesis caused by upregulation of HMG-CoA reductase)			
Statins				
▫**Mevastatin** ▫**Simvastatin** ▫**Lovastatin** ▫**Pravastatin** ▫**Fluvastatin** ▫**Atorvastatin** ▫ **Rosuvastatin**	▫Competitive Inhibitors of HMG-CoA Reductase (the early rate-limiting enzyme in de novo synthesis of cholesterol)	▫**Most effective** drugs in lowering LDL ▫**Major effect:** Reduced free cholesterol in hepatocytes activates a protease which will cleave membrane-bound SREBP → will be translocated to the nucleus to stimulate transcription of LDL receptors → Increased removal of LDL-C from the blood → **lowering blood LDL-C levels and preventing CHD.** ▫**Minor effect: r**educe LDL levels by enhancing the **removal** of LDL precursors (VLDL and IDL) and by **decreasing** hepatic VLDL production ▫**Higher doses** can reduce triglyceride levels caused by elevated VLDL levels ▫Some (simvastatin and rosuvastatin) can **raise HDL-C levels** ▫**Decrease** oxidative stress and vascular inflammation by **enhancing NO production** ▫**Reduce** platelet aggregation	▫Important side effects: -**Elevation of transaminases**, this is intermittent and not associated with strong evidence of liver failure -**Elevation of creatine kinase** (CK) activity -**Rhabdomyolysis**, causing myoglobinuria and renal injury and failure or even death (extremely rare) -**Lupus-like disorder and peripheral neuropathy** ▫Less important side effects: -Headache, Difficulty sleeping, Flushing of the skin, Muscle aches, tenderness, or weakness (myalgia) -Drowsiness, Dizziness, Nausea and/or vomiting -Abdominal cramping and/or pain, Bloating and/or gas, Diarrhea, Constipation, Rash *__Memory loss, mental confusion, high blood sugar, and type 2 diabetes are possible side effects__	-Most commonly prescribed drugs worldwide -Isolated from a mold called Penicillium Citrinum, in 1976 -Toxicity is dose-related, associated with advanced age, hepatic or renal dysfunction, small body size, associated diseases, hypothyroidism and concomitant drugs -Statins may interact with other medications -Statins are metabolized by the **CYP450** enzyme system, which is a subject to **individual genetic differences**. These differences will be exhibited for their: therapeutic response & side effects.

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Inhibitors of Sterol Absorption				
Ezetimibe	▫Inhibitor of NPC1L1, a protein in jejunal brush border, essential for cholesterol absorption	-**Reduces** cholesterol **absorption and reabsorption** by 54%, precipitating a compensatory increase in cholesterol synthesis -**Reduces** cholesterol **delivery** to the liver by the chylomicron remnants →This will stimulate the expression of the hepatic genes regulating the LDL receptor expression leading to enhanced LDL-C clearance from the plasma (15- 20%) *Action is **complementary to statins** (together they cause 60% reduction in LDL-C)	-Can cause allergic reactions, reversible impairment of liver function tests and myopathy.	
Inhibitors of Cholesteryl Ester Transfer Protein				
▫Torcetrapib ▫Anacetrapib ▫Dalcetrapib	▫Inhibitors of cholesteryl ester transfer protein (CETP) → resulting in increased levels of HDL	-Can **increase HDL levels** by 45-106% in humans → effective in patients whose main problem is **low levels of HDL.**		-CETP is a plasma glycoprotein synthesized by the liver that mediates the transfer of cholesteryl esters from HDL to triglyceride-rich lipoproteins and LDL in exchange for a molecule of triglyceride -Torcetrapib was **withdrawn**

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