DYSLIPIDEMIAS DRUGS, ANTI-OBESITY DRUGS, and THYROID DRUGS (HYPER- & HYPOTHYROID)

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Blok Pencernaan 2

Mei/2023

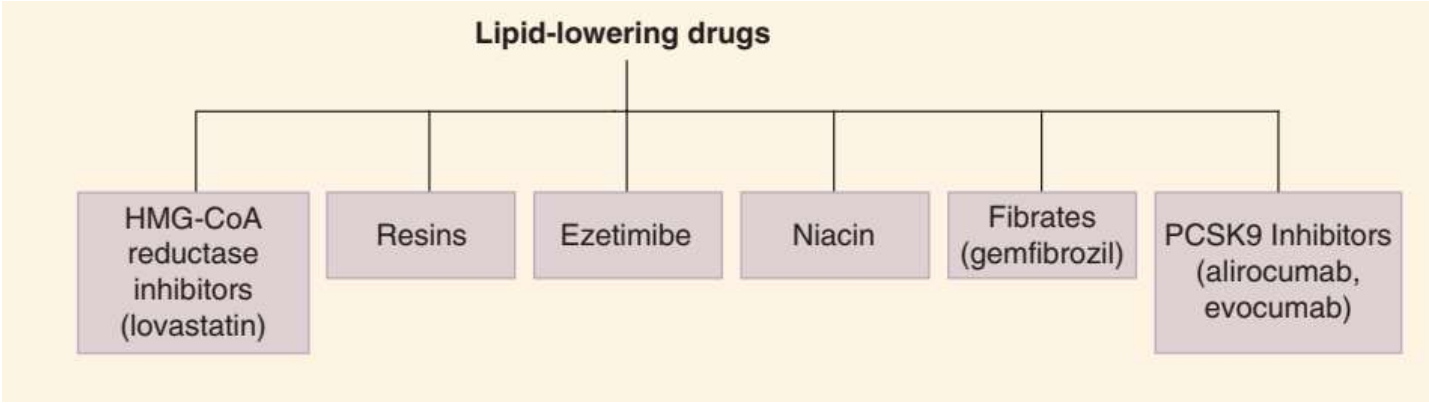
Topics

- Dyslipidemias Drugs
- Anti-Obesity Drugs
- Thyroid Drugs
  - Hyperthyroid Drugs
  - Hypothyroid Drugs

DYSLIPIDEMIAS

- Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency

https://www.skedoc.com/health-topics/dyslipidemia/dyslipidemia



Katzung, 2019

HMG-CoA REDUCTASE INHIBITORS: STATIN

- Patients aged 40 to 75 years with a known history of clinical ASCVD or diabetes mellitus and those with elevated LDL-C greater than or equal to 190 mg/dL should be offered statins regardless of their ASCVD risk scor

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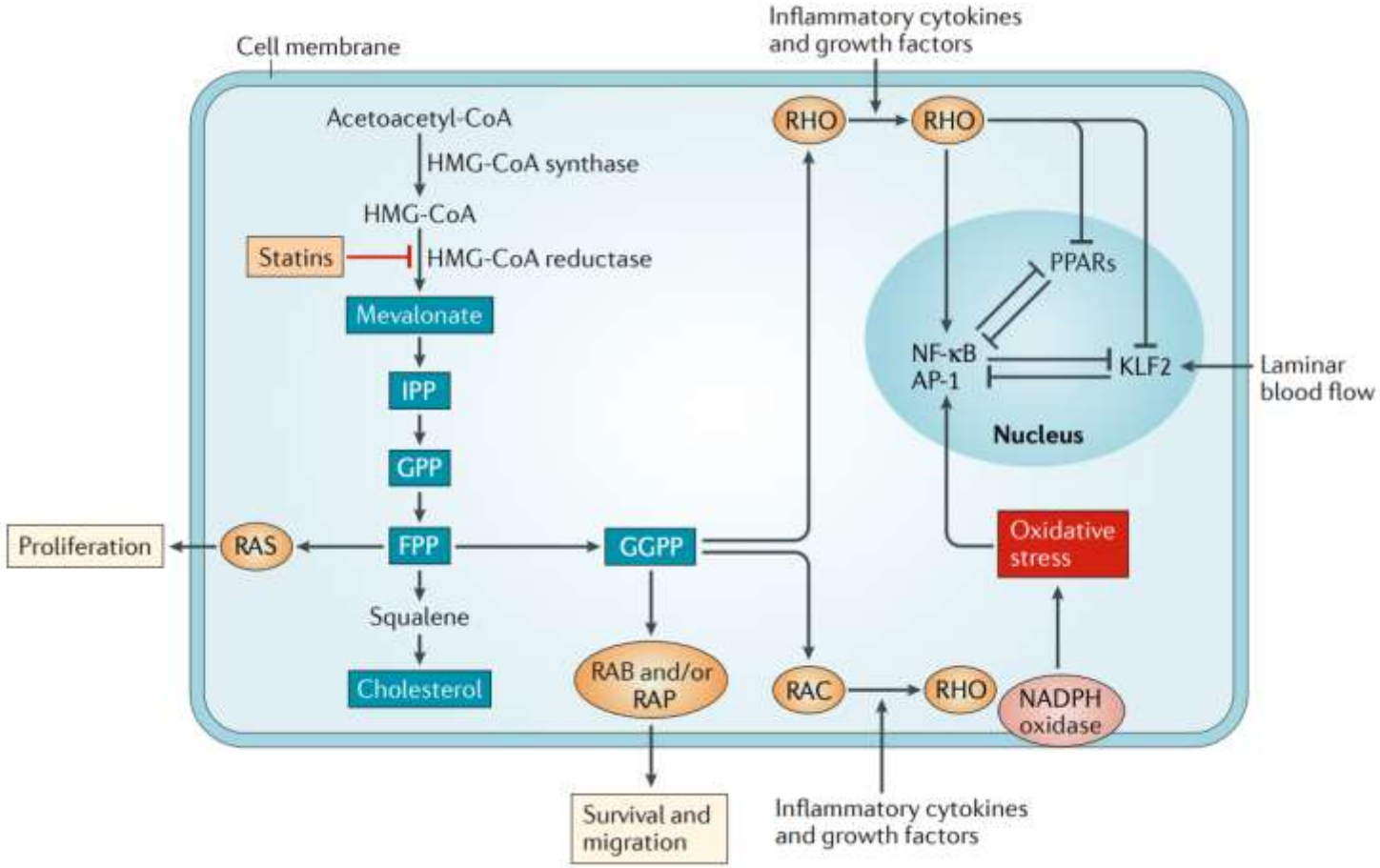

Parihar SP, Guler R, and Brombacher F. 2019. *Statins: a viable candidate for host-directed therapy against infectious disease. Nature Reviews*: Immunology, Vol 19; pg 104-117

STATIN

- **ADME:**
- All statins, except simvastatin and lovastatin, are administered in the β-hydroxy acid form, which is the form that inhibits HMG-CoA reductase
- Simvastatin and lovastatin are administered as inactive lactones that must be transformed in the liver to their respective β-hydroxy acids, simvastatin acid and lovastatin acid
- Statins t1/2 of 4 h or less (all but atorvastatin and rosuvastatin) should be taken in the evening.
- Atorvastatin and rosuvastatin both have longer half-lives and may be taken at other times of day to optimize adherence.
- Rosuvastatin, atorvastatin, pitavastatin, and simvastatin have greater maximal efficacy than the other HMG-CoA reductase inhibitors. These drugs also reduce triglycerides and increase HDL cholesterol in patients with triglyceride levels that are higher than 250 mg/dL and with reduced HDL cholesterol levels.

SECONDARY CAUSE	ELEVATED LDL-C	ELEVATED TRIGLYCERIDES
Disorders and Conditions		
Diabetes mellitus		+
Nephrotic syndrome	+	+
Excess alcohol use		+
Pregnancy	+	+
Menopause transition (declining estrogen levels)	+	+
Chronic kidney disease	+	+
Hypothyroidism	+	+
Obstructive liver disease	+	
Metabolic syndrome		+
HIV infection	+	+
Autoimmune disorders	+	+
Polycystic ovary syndrome	+	+
Drug Therapies		
Oral estrogens		+
Some progestins	+	
Glucocorticoids	+	+
Immunosuppressive drugs	+	+
Thiazide diuretics	+	+
Anabolic steroids	+	
Thiazolidinediones	+	
Rosiglitazone		+
β Blockers (especially non-β_1 selective)		+
Fibric acids (in severe hypertriglyceridemia)	+	
Bile acid sequestrants		+
Amiodarone	+	
Danazol	+	
Isotretinoin	+	
Long-chain ω-3 fatty acids (in severe hypertriglyceridemia) with docosahexanoate	+	
Tamoxifen		+
Raloxifene		+
Interferon		+
Atypical antipsychotic drugs (clozapine, olanzapine)		+
Protease inhibitors		+
L-Asparaginase		+
Cyclophosphamide		+

Source: Data from 2015 National Lipid Association recommendations, part 1 (Jacobson et al., 2015).

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STATIN

- All statins possess very low systemic bioavailability → extensive first-pass effect.
- Atorvastatin, lovastatin, and simvastatin are primarily metabolized by CYPs 3A4 and 3A5.
- Pravastatin has the lowest protein-binding (around 50%) when compared to other statins (>90%)
- In the case of hypercholesterolemia, the recommended dose is 10–20 mg/day administered in a single dose in the evening; patients requiring a large reduction in LDL-C (greater than 45%) may start with 20–40 mg/day administered in a single dose in the evening
- Only rosuvastatin should be initiated with a dosage of 5–10 mg/day, reaching maximum doses of up to 40 mg/day only in patients who have not reached the therapeutic goals established with the lowest doses
- In the case of homozygous familial hypercholesterolemia, the recommended dose is 40 mg/day in the evening
- In the case of cardiovascular prevention, the usual dose ranges from 20 to 40 mg/day administered in single dose at night, while for atorvastatin, a dose of 10 mg/day is used, although it may be increased as needed

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STATIN: Therapeutic Effect

HIGH-INTENSITY STATINS	MODERATE-INTENSITY STATINS	LOW-INTENSITY STATINS
Lower LDL-C by ≥50%	Lower LDL-C by 30% to <50%	Lower LDL-C, on average, by <30%
Atorvastatin 40–80 mg **Rosuvastatin 20–40 mg**	**Atorvastatin 10 mg** (to 20 mg) **Fluvastatin 40 mg twice daily** Fluvastatin XL 80 mg **Lovastatin 40 mg** (to 80 mg) Pitavastatin 1–4 mg **Pravastatin 40 mg** (to 80 mg) **Rosuvastatin** (5 mg) to **10 mg** **Simvastatin 20–40 mg**	Fluvastatin 20–40 mg **Lovastatin 20 mg** **Pravastatin 10–20 mg** Simvastatin 10 mg

Bold type signifies statin doses used in randomized controlled trials demonstrating a reduction in major cardiovascular events.
Source: Data from *Table* 3 in 2018 AHA/ACC guidelines (Grundy et al., 2019).

- Effects of Statins on LDL-C Levels
  - LDL-C is reduced by about 6% (from baseline) with each doubling of the dose. Maximal effects on plasma cholesterol levels are achieved within 7 to 10 days. The statins are effective in almost all patients with high LDL-C levels.
- TG Reduction by Statins
  - Triglyceride levels greater than 250 mg/dL are reduced substantially by statins, and the percent reduction achieved is similar to the percent reduction of LDL-C
- Effect of Statins on HDL-C Levels
  - Most studies of patients treated with statins have systematically excluded patients with low HDL-C levels.
- Adverse Effects and Drug Interactions
  - Myopathy
  - Hepatotoxicity
- Drug Interactions: Coadministration of gemfibrozil nearly doubles the plasma concentration of statin hydroxy acids. When statins are administered with niacin, the myopathy is likely caused by an enhanced inhibition of skeletal muscle cholesterol synthesis (a pharmacodynamic interaction)

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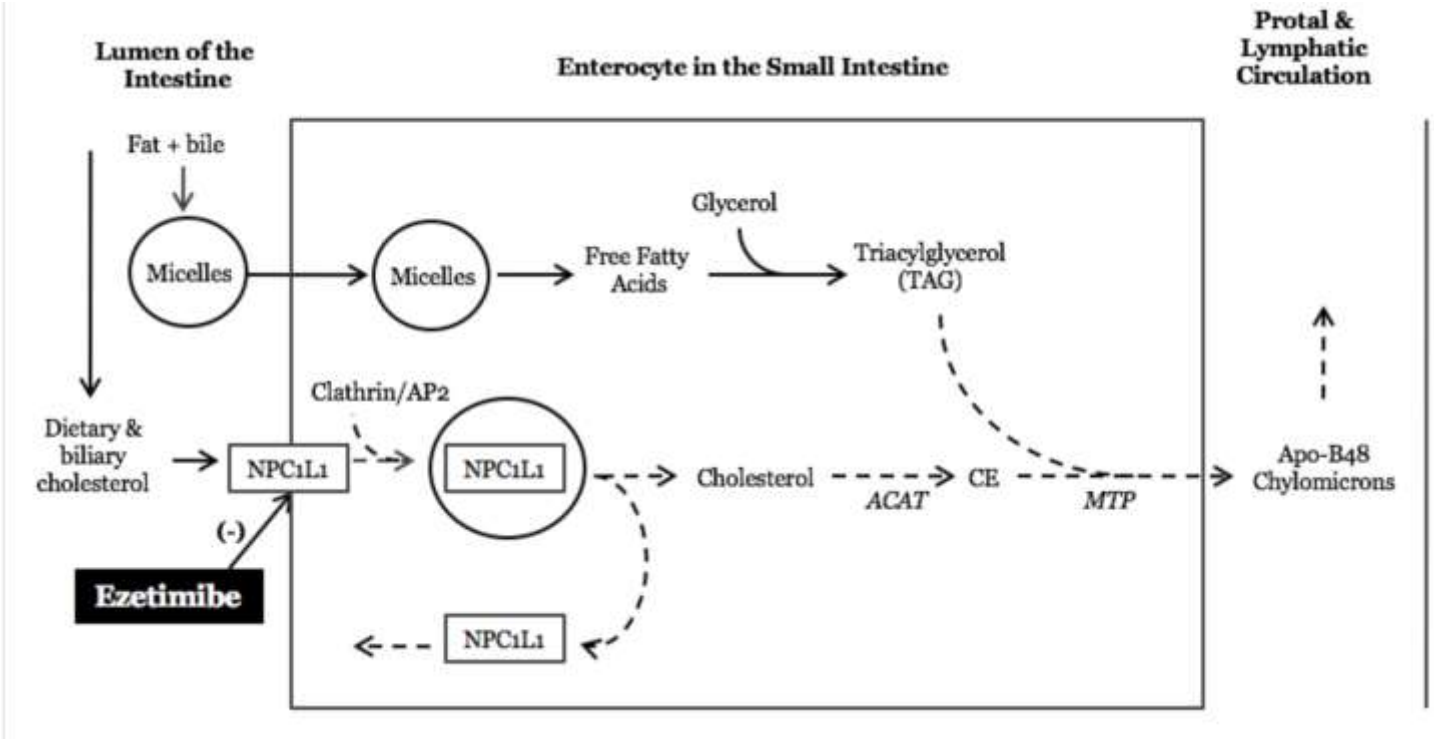
Cholesterol Absorption Inhibitor

EZETIMIBE

- Ezetimibe is a prodrug that is converted in the liver to the active glucuronide form
- Ezetimibe is the first compound approved for lowering total cholesterol and LDL-C levels that acts by inhibiting cholesterol absorption by enterocytes in the small intestine. It lowers LDL-C levels by about 20% and may be used as adjunctive therapy with statins.



https://www.ebmconsult.com/articles/ezetimibe-mechanism-action-inhibit-cholesterol-absorption-intestine

Cholesterol Absorption Inhibitor

EZETIMIBE

- ADME:
  - Ezetimibe is highly water insoluble, precluding studies of its bioavailability. After ingestion, it is absorbed and glucuronidated in the intestinal epithelium and then enters an enterohepatic recirculation.
  - Pharmacokinetic studies indicated that about 70% is excreted in the feces and about 10% in the urine (as a glucuronide conjugate). Bile acid sequestrants inhibit absorption of ezetimibe, and the two classes of agents should not be administered together.
- Therapeutic Effects
  - The role of ezetimibe as monotherapy of patients with elevated LDL-C levels is generally limited to the small group of statin-intolerant patien
  - When combined with an HMG-CoA reductase inhibitor, it is even more effective.
- Adverse Effects and Drug Interactions
  - Specific adverse effects have not been observed in patients taking ezetimibe.

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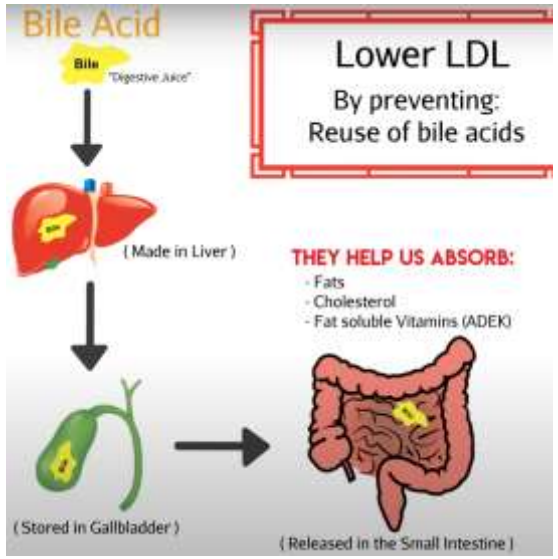
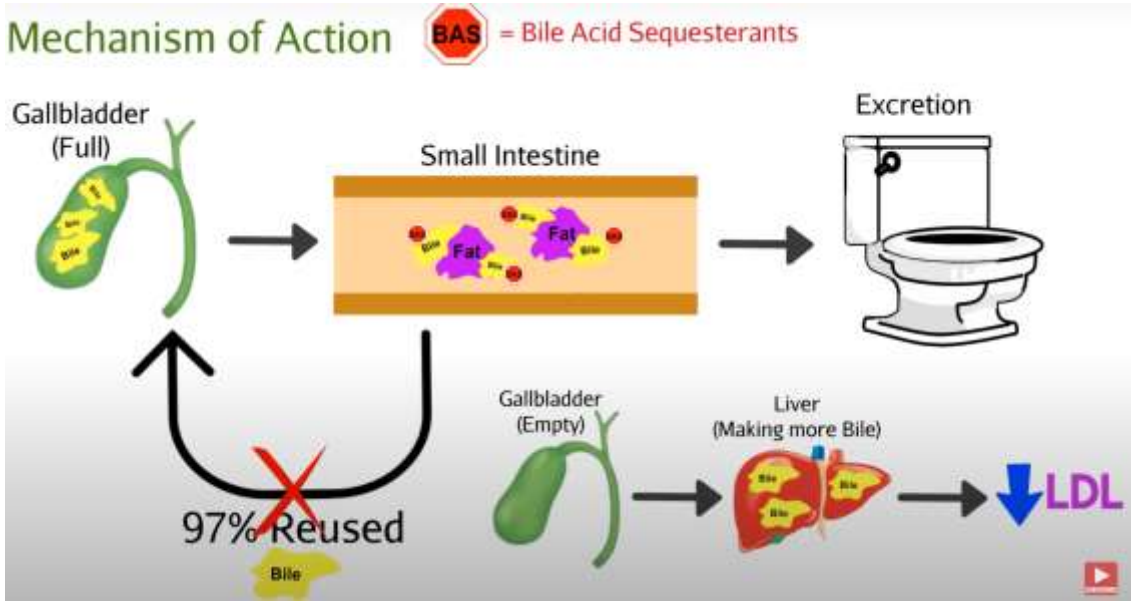
Bile Acid Sequestrants/
Bile acid-binding resins

Cholestyramine, Colestipol, Colesevelam

- Are large nonabsorbable polymers that bind bile acids and similar steroids in the intestine and prevent their absorption
- These resins also are recommended for patients 11 to 20 years of age. Although statins are remarkably effective as monotherapy, the resins could be utilized as a second-line agent if statin therapy does not lower LDL-C levels sufficiently or in cases of statin intolerance





https://www.youtube.com/watch?v=Hk3X2m7f7gI&t=381s

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Bile Acid Sequestrants

Cholestyramine, Colestipol, Colesevelam

- Therapeutic Effects
  - Doses of 8 to 12 g of cholestyramine or 10 to 15 g of colestipol are associated with a 12% to 18% reduction in LDL-C.
  - Colesevelam lowers LDL-C by 18% at its maximum dose. Maximal doses (24 g of cholestyramine, 30 g of colestipol) may reduce LDL-C by as much as 25% but will cause GI side effects, which are often intolerable.
- Preparations and Use
  - The powdered forms of cholestyramine (4 g/dose) and colestipol (5 g/dose) are either mixed with a fluid (water or juice) and swallowed as a slurry or mixed with crushed ice in a blender. Ideally, patients should take the resins before breakfast and before supper.
- Adverse Effects and Drug Interactions
  - The resins are generally safe, as they are not systemically absorbed.
  - Severe hypertriglyceridemia → contraindication to the use of cholestyramine and colestipol because these resins increase triglyceride levels.

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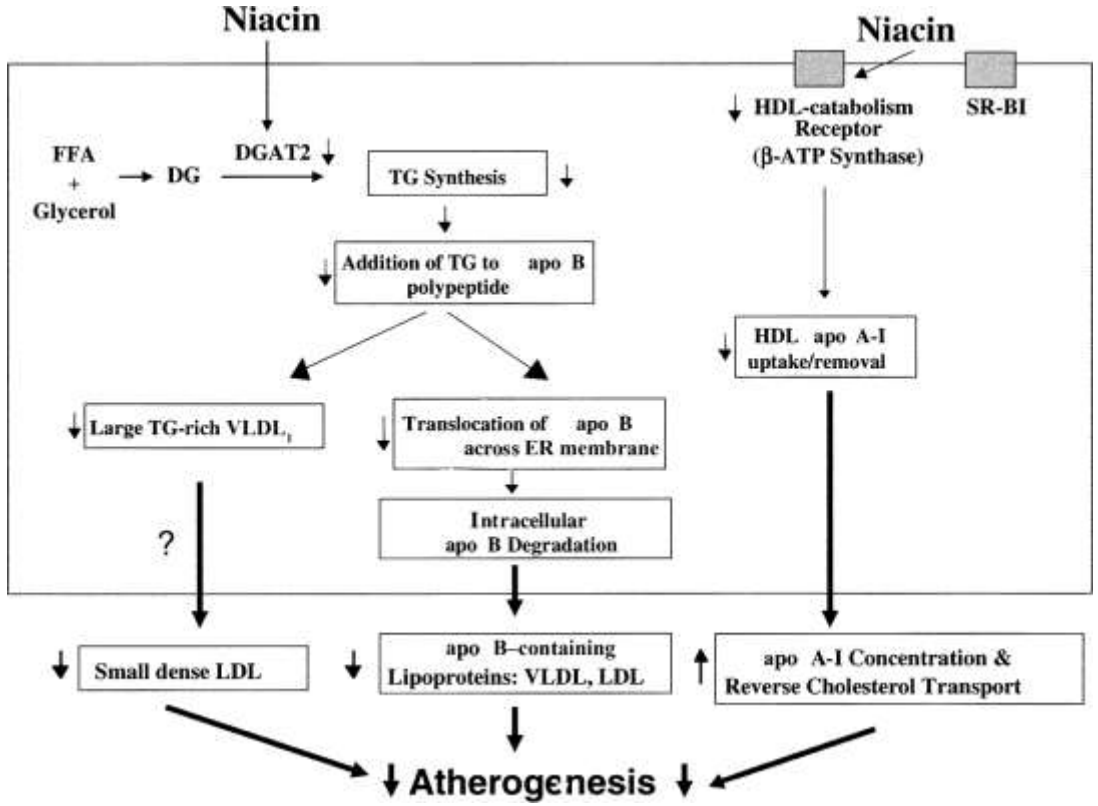
Niacin (Nicotinic Acid)

Niacin (Nicotinic Acid)

- Niacin is a water-soluble B-complex vitamin that functions as a vitamin only after conversion to nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP).
- Both niacin and its amide may be given orally as a source of niacin for its functions as a vitamin, but only niacin affects lipid levels



https://www.sciencedirect.com/science/article/pii/S1933287419302909

Niacin (Nicotinic Acid)

Niacin (Nicotinic Acid)

- ADME
  - Crystalline niacin (immediate or regular, IR) refers to niacin tablets that dissolve quickly after ingestion, are almost completely absorbed, and lead to peak serum concentrations within 30 to 60 min. Because the t 1/2 for nicotinic acid is about 20 to 48 min, crystalline niacin necessitates dosing two to three times daily.
- Therapeutic Effects
  - Niacin is indicated for the treatment of hypertriglyceridemia and elevated LDL-C
  - Regular or crystalline niacin in doses of 2 to 6 g/day reduces triglycerides by 35% to 50% (as effectively as fibrates and statins); the maximal effect occurs within 4 to 7 days. Reductions of 25% in LDL-C levels are possible with doses of 4.5 to 6 g/day; 3 to 6 weeks are required for maximal effect. Niacin is the most effective agent available for increasing HDL-C (30%–40%), but the effect is less in patients with HDL-C levels less than 35 mg/dL
- Preparations and use
  - Crystalline niacin tablets are available without a prescription in a variety of strengths, from 50- to 500-mg tablets, and with a prescription in 500-mg tablets. Niacin ER is available with a prescription as 500-, 750-, and 1000-mg ER tablets.
- Adverse Effects and Drug Interactions
  - Two of niacin's side effects, flushing and dyspepsia, limit patient compliance
  - The most common, medically serious side effects are hepatotoxicity, manifested as elevated serum transaminases, and hyperglycemia. Both IR (crystalline) and ER niacin have been reported to cause severe liver toxicity, particularly in doses above 2 g/day.
  - In patients with diabetes mellitus, niacin should be used cautiously because niacin-induced insulin resistance can cause severe hyperglycemia
  - Concurrent use of niacin and a statin can cause myopathy
  - Should not be taken by pregnant women → birth defects

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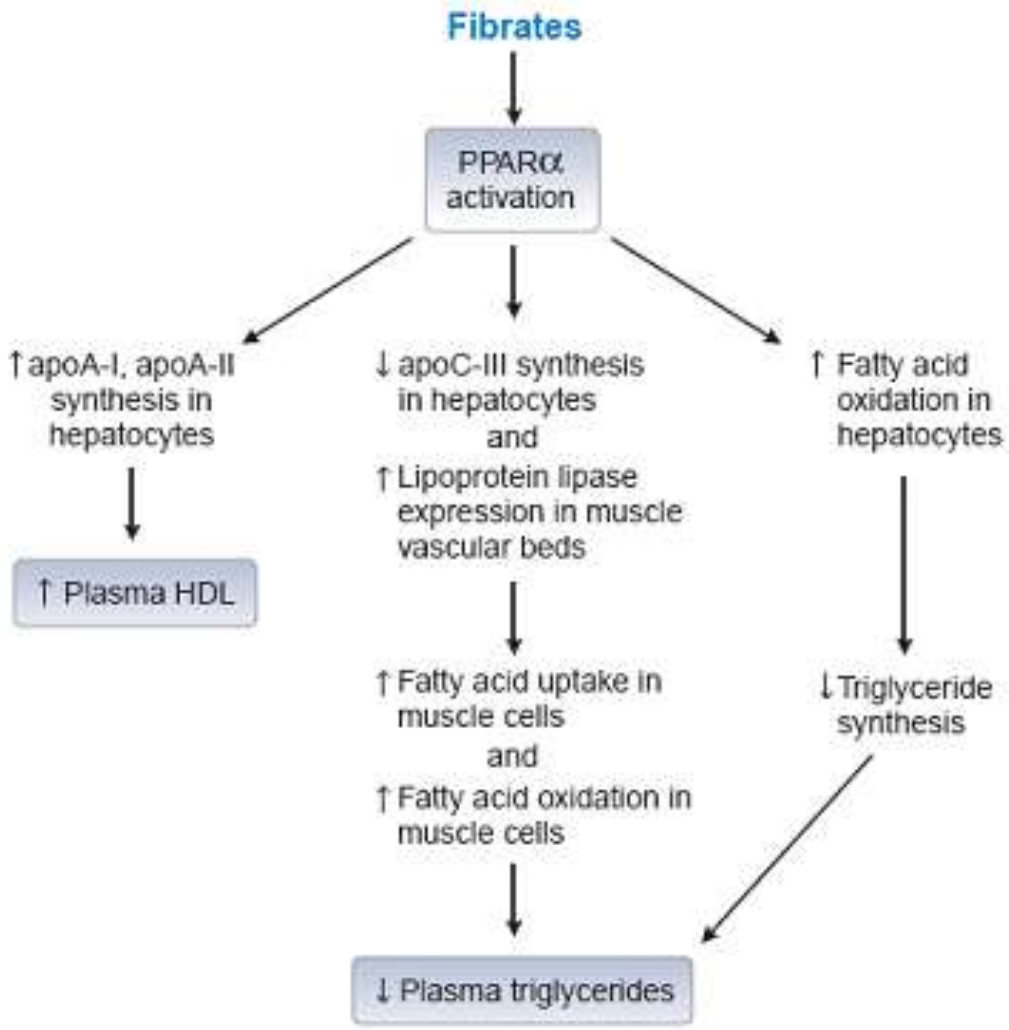
Fibric Acid Derivatives

Clofibrate, Gemfibrozil, Fenofibrate, Bezafibrate, Ciprofibrate

- Fibrates (fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil) are a class of lipid-lowering drugs and exert their effects mainly by activating the peroxisome proliferator-activated receptor-alpha (PPAR-alpha)



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Fibric Acid Derivatives

Clofibrate, Gemfibrozil, Fenofibrate, Bezafibrate, Ciprofibrate

- ADME
  - Fibrates are absorbed rapidly and efficiently (>90%) when given with a meal but less efficiently when taken on an empty stomach. Peak plasma concentrations are attained within 1 to 4 h. More than 95% of these drugs in plasma are bound to protein, nearly exclusively to albumin. The t1/2 of fibrates range from 1.1 h (gemfibrozil) to 20 h (fenofibrate).
- Therapeutic Effects
  - In patients with mild hypertriglyceridemia (e.g., triglycerides <400 mg/dL), fibrate treatment decreases triglyceride levels by up to 50% and increases HDL-C concentrations by about 15%; LDL-C levels may be unchanged or increase.
  - Fibrates usually are the drugs of choice for treating severe hypertriglyceridemia and the chylomicronemia syndrome.
- Preparations and Use
  - Gemfibrozil usually is administered as a 600-mg dose taken twice daily, 30 min before the morning and evening meals. Fenofibrate is available in tablets of 48 and 145 mg or capsules containing 67, 134, or 200 mg
- Adverse Effects and Drug Interactions
  - GI side effects occur in up to 5% of patients. Infrequent side effects include rash, urticaria, hair loss, myalgias, fatigue, headache, impotence, and anemia. Minor increases in liver transaminases and alkaline phosphatase have been reported. Clofibrate, bezafibrate, and fenofibrate reportedly potentiate the action of warfarin.

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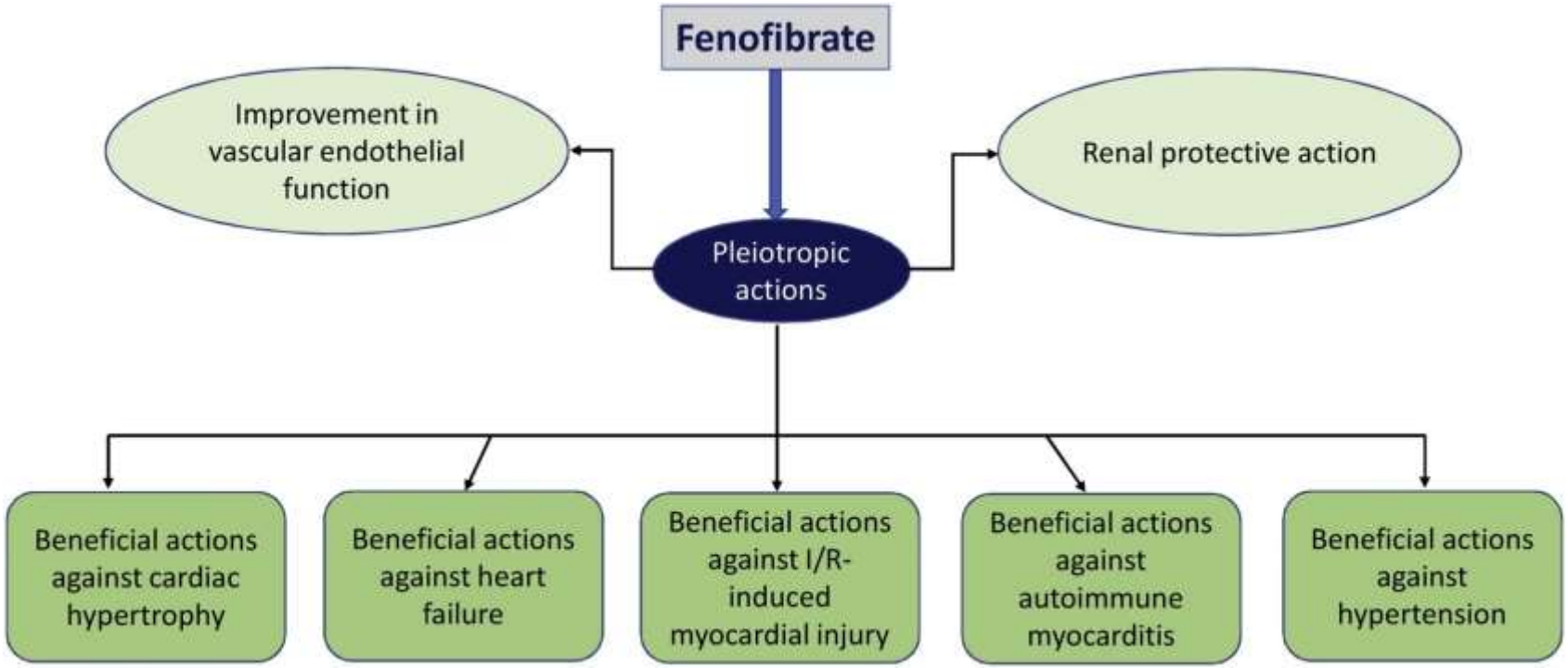
Fibric Acid Derivatives



https://www.sciencedirect.com/science/article/abs/pii/S1043661819302762

Omega-3 Fatty Acid Ethyl Esters

ICOSAPENT ETHYL

- MOA:
- Omega-3 fatty acids, commonly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) ethyl esters, reduce VLDL triglycerides and are used as an adjunct to diet for treatment of adult patients with severe hypertriglyceridemia.
- The recommended daily oral dose for patients with severe hypertriglyceridemia is 3 to 4 g/day administered with food
- ADME:
- The small intestine absorbs EPA and DHA, which are mainly oxidized in the liver, similar to fatty acids derived from dietary sources. The t1/2 of elimination is approximately 50 to 80 h
- Therapeutic Effects:
- **M**ost common over-the-counter (OTC) herbal, vitamin, or nutritional supplements
- The AHA recommends that consumers eat a variety of fish at least twice a week and that fish oil supplements should only be considered for individuals with heart disease or high triglyceride levels
- Adverse Effects and Drug Interactions
- Arthralgia, nausea, fishy burps, dyspepsia, and increased LDL-C levels. Because omega-3 fatty acids may prolong bleeding time, patients taking anticoagulants should be monitored. Icosapent ethyl may also increase the risk of atrial fibrillation and flutter.

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PCSK9 Inhibitors

ALIROCUMAB AND EVOLOCUMAB

- MOA
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protease that binds to the LDL receptor on the surface of hepatocytes and enhances lysosomal degradation of the LDL receptor, resulting in higher plasma LDL-C concentrations. Loss-of-function mutations of PCSK9 are associated with reduced LDL-C and lowered risk of ASCVD.
- ADME
- The PCSK9 antibody inhibitors are administered as subcutaneous injections either every 2 weeks or once monthly, depending on the dose and indication.
- Evolocumab is administered as a 140-mg injection every 2 weeks or as a 420-mg injection once a month. Similarly, alirocumab is administered as a 75-mg injection every 2 weeks or as a 300-mg injection once a month.
- Therapeutic Effects
- CSK9 antibody inhibitors reduce LDL-C in a dose-dependent manner by as much as 70% when used as monotherapy or by as much as 60% in patients already on statin therapy.
- Adverse Effects and Drug Interactions
- Several clinical trials have identified a small (<1%) risk of neurocognitive effects in patients treated with PCSK9 antibody inhibitors compared to placebo.

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Inhibitor of Microsomal Triglyceride Transfer

LOMITAPIDE

- MOA
- Lomitapide mesylate is the first drug that acts by inhibiting MTP, which is essential for the intracellular transfer of triglycerides into triglyceride-rich lipoproteins, thus inhibiting the formation of VLDLs in hepatocytes and chylomicrons in intestinal epithelial cells.
- ADME
- Lomitapide is administered with water and without food (or at least 2 h after the evening meal) because administration with food may increase risk of GI adverse effects. The drug is metabolized by CYP3A4 and is contraindicated with inhibitors of CYP3A4.
- Therapeutic Effects
- Lomitapide reduces LDL-C by up to 50% and should be used in combination with maximally tolerated statin therapy. The recommended starting oral dose (5 mg/day) is titrated upward at 4-week intervals to a maximum dose of 60 mg daily.
- Adverse Effects and Drug Interactions
- Significant diarrhea, vomiting, and abdominal pain in most patients. Serious concerns also exist regarding hepatotoxicity and liver steatosis

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ATP-Citrate Lyase Inhibitor

Bempedoic Acid

- A dicarboxylic acid, is a new class of cholesterol-lowering drugs approved by the FDA in 2020 that act by inhibiting de novo hepatocyte cholesterol biosynthesis. Its mechanism of action complements statins and other agents that lower LDL-C.
- ADME
- Bempedoic acid is administered orally once daily (180 mg), as is the combination of bempedoic acid and ezetimibe (180 mg and 10 mg, respectively).
- Elimination t1/2 is 21 ± 11 h, and steadystate concentrations are reached after 7 days of therapy
- Therapeutic Effects
- Bempedoic acid is FDA-approved for the treatment of adults with either HeFH or established ASCVD who need additional LDL-C lowering. Monotherapy with bempedoic acid results in a 15% to 25% reduction in LDL-C, less than with statins. In combination with ezetimibe, the reduction in LDL-C is around 30%, and triple therapy with a statin reduces LDL-C by 65%. Reduction in HDL-C by bempedoic acid is typically around 5%.
- Adverse Effects and Drug Interactions
- Therapy with bempedoic acid is associated with hyperuricemia (thought to be due to competition for OAT2 in the kidney) that can increase the risk of gout. Due to drug interactions that may increase the risk of myopathy, bempedoic acid is not used with simvastatin doses of greater than 20 mg/day or rosuvastatin doses of greater than 40 mg/day.
- Harm to the fetus.

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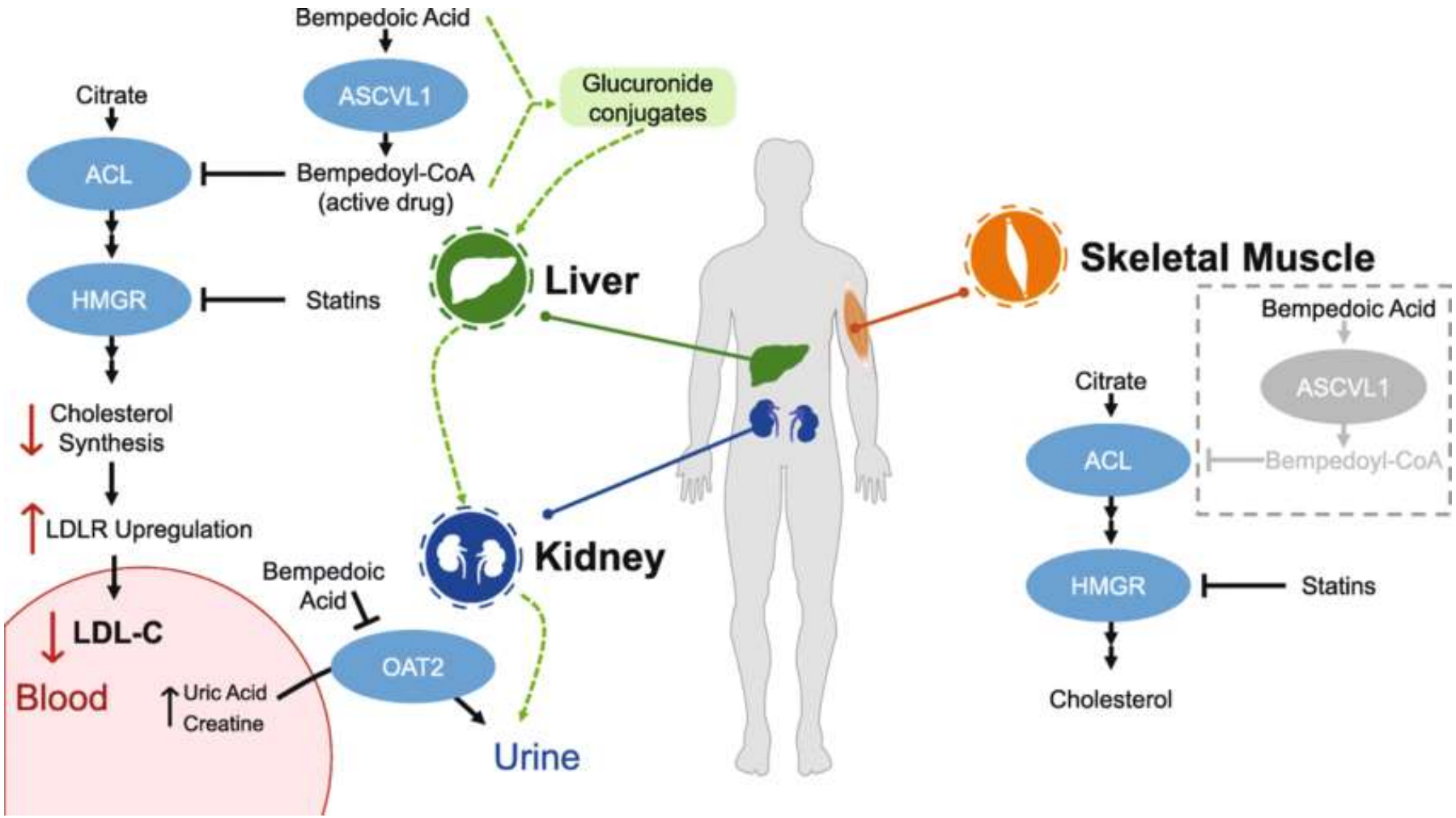
Bempedoic Acid



Drug Facts for Your Personal Formulary:
Therapy for Dyslipidemias

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Omega-3 Fatty Acid Ethyl Esters		

Omega-3 fatty acids (EPA, DHA, and icosapent ethyl)	• Adjunct for treating severe hypertriglyceridemia (triglycerides >1000 mg/dL)
	• *Icosapent ethyl*
	  • Adjunct to maximally tolerated statin therapy to reduce risk of cardiovascular events in adults with triglyceride levels ≥150 mg/dL
	  • Adjunct to diet in adults with severe hypertriglyceridemia (triglycerides ≥500 mg/dL)
		• Adverse effects may include arthralgia, nausea, fishy burps, dyspepsia, and increased LDL
		• Since omega-3 fatty acids may prolong bleeding time, patients taking anticoagulants should be monitored

PCSK9 Inhibitors (mAbs)		
Alirocumab Evolocumab	• To ↓risk of myocardial infarction, stroke and unstable angina requiring hospitalization in patients with established cardiovascular disease • To ↓LDL-C as adjunctive therapy alone or in combination with other LDL-C-lowering medication in adults with HeFH • To ↓LDL-C as adjunctive therapy in combination with other LDL-C-lowering medications in adult with HoFH	• Hypersensitivity or injection site reactions are possible • Most effective agents at reducing LDL-C • As with other mAbs, influenza-like symptoms, nasopharyngitis, upper respiratory infections may occur • Used in addition to maximally tolerated statin doses (complementary mechanism; see Figure 37–5) • Diabetes mellitus is associated with evolocumab (9%); large LDL-C reductions (to <25 mg/dL) are associated with alirocumab
PCSK9 Inhibitor (siRNA)		
Inclisiran	• To ↓LDL-C as adjunctive therapy with diet and maximally tolerated statin therapy for treatment of adults with HeFH who require additional lowering of LDL-C • To ↓LDL-C as adjunctive therapy with diet and maximally tolerated statin therapy for treatment of adults with clinical ASCVD who require additional lowering of LDL-C	• Injection site reactions are possible • Used in addition to maximally tolerated statin doses (complementary mechanism) • Long-lasting effects on lowering PCSK9 serum levels and LDL-C (dosing every 6 months at steady-sate) • Contraindicated in pregnancy
Liver Microsomal Triglyceride Transfer Protein Inhibitor		
Lomitapide	• Used as an adjunct to diet for lowering LDL-C, total cholesterol, apo B, and non–HDL-C in patients with HoFH	• In patients with HoFH, LDL-C reduction by 40%–50% • Adverse effects include GI symptoms, elevation of serum liver enzymes, and increased liver fat • The agent is used under an FDA Risk Evaluation and Mitigation Strategy due to hepatotoxicity (i.e., elevated transaminases and hepatic steatosis) • Patients should take daily supplements containing 400 IU vitamin E, 200 mg linoleic acid, 210 mg α-linoleic acid, 110 mg EPA, and 80 mg DHA
ATP-Citrate Lyase Inhibitor		
Bempedoic acid	• Used in patients who are statin intolerant or those who do not achieve desired LDL-C levels with statins • Monotherapy in statin-intolerant patients • Combination therapy with statins and fixed-dose combination with ezetimibe	• Low rates of adverse effects in clinical trials • May increase blood uric acid levels, leading to risk of gout
Angiopoietin-Like Protein 3 Inhibitor (Monoclonal Antibody)		
Evinacumab-dgnb	• Used as an adjunct to lipid-lowering agents and diet in patients with HoFH	• In patients with HoFH on lipid-lowering agents, LDL-C reduction by 50% • Severe hypersensitive reactions possible; contraindicated in pregnancy

Drug Facts for Your Personal Formulary: Therapy for Dyslipidemias (Continued)

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Liver Microsomal Triglyceride Transfer Protein Inhibitor		
Lomitapide	• Used as an adjunct to diet for lowering LDL-C, total cholesterol, apo B, and non–HDL-C in patients with HoFH	• In patients with HoFH, LDL-C reduction by 40%–50% • Adverse effects include GI symptoms, elevation of serum liver enzymes, and increased liver fat • The agent is used under an FDA Risk Evaluation and Mitigation Strategy due to hepatotoxicity (i.e., elevated transaminases and hepatic steatosis) • Patients should take daily supplements containing 400 IU vitamin E, 200 mg linoleic acid, 210 mg α-linoleic acid, 110 mg EPA, and 80 mg DHA
ATP-Citrate Lyase Inhibitor		
Bempedoic acid	• Used in patients who are statin intolerant or those who do not achieve desired LDL-C levels with statins • Monotherapy in statin-intolerant patients • Combination therapy with statins and fixed-dose combination with ezetimibe	• Low rates of adverse effects in clinical trials • May increase blood uric acid levels, leading to risk of gout
Angiopoietin-Like Protein 3 Inhibitor (Monoclonal Antibody)		
Evinacumab-dgnb	• Used as an adjunct to lipid-lowering agents and diet in patients with HoFH	• In patients with HoFH on lipid-lowering agents, LDL-C reduction by 50% • Severe hypersensitive reactions possible; contraindicated in pregnancy

Lipid-modifying effects of antihyperlipidemic drugs

Drug or Drug Group	LDL Cholesterol	HDL Cholesterol	Triglycerides
Statins			
Atorvastatin, rosuvastatin, simvastatin	–25 to –50%	+5 to +15%	↓↓
Lovastatin, pravastatin	–25 to –40%	+5 to +10%	↓
Fluvastatin	–20 to –30%	+5 to +10%	↓
Resins	–15 to –25%	+5 to +10%	±[a]
Ezetimibe	–20%	+5%	±
Niacin	–15 to –25%	+25 to +35%	↓↓
Gemfibrozil	–10 to –15%[b]	+15 to +20%	↓↓
PCSK9 inhibitors	–50 to –60 %	+4 to +8%	↓

LDL, low-density lipoprotein; HDL, high-density lipoprotein; ±, variable, if any.

[a]Resins can increase triglycerides in some patients with combined hyperlipidemia.

[b]Gemfibrozil and other fibrates can increase LDL cholesterol in patients with combined hyperlipidemia.

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Primary Hyperlipoproteinemias and Their Drug Treatment

Condition/Cause	Manifestations, Cause	Single Drug	Drug Combination
Primary chylomicronemia	Chylomicrons, VLDL increased; deficiency in LPL or apoC-II	Dietary management (+ omega-3 fatty acids, niacin, or fibrate)	Niacin plus fibrate[a]
Familial hypertriglyceridemia			
Severe	VLDL, chylomicrons increased; decreased clearance of VLDL	Omega-3 fatty acids, niacin or fibrate	Niacin plus fibrate
Moderate	VLDL increased, chylomicrons may be increased; increased production of VLDL	Omega-3 fatty acids, niacin or fibrate	Niacin plus fibrate
Familial combined hyperlipoproteinemia	Increased hepatic apoB and VLDL production		
	VLDL increased	Omega-3 fatty acids, niacin, fibrate, statin	Two or 3 of the individual drugs
	LDL increased	Niacin, statin, ezetimibe	Two or 3 of the individual drugs
	VLDL, LDL increased	Omega-3 fatty acids, niacin, statin	Statin plus niacin or fibrate
Familial dysbetalipoproteinemia	VLDL remnants, chylomicron remnants increased; deficiency in apoE	Omega-3 fatty acids, fibrate, statin, or niacin	Fibrate plus niacin, or either plus statin
Familial hypercholesterolemia	LDL increased; defect in LDL receptors		
Heterozygous		Statin, resin, niacin, ezetimibe	Two or 3 of the individual drugs
Homozygous		Niacin, atorvastatin, rosuvastatin, ezetimibe, mipomersen, or lomitapide, PCSK9 inhibitors (alirocumab, evolocumab	Niacin plus statin plus ezetimibe

[a]Single-drug therapy with marine omega-3 dietary supplement should be evaluated before drug combinations are used.

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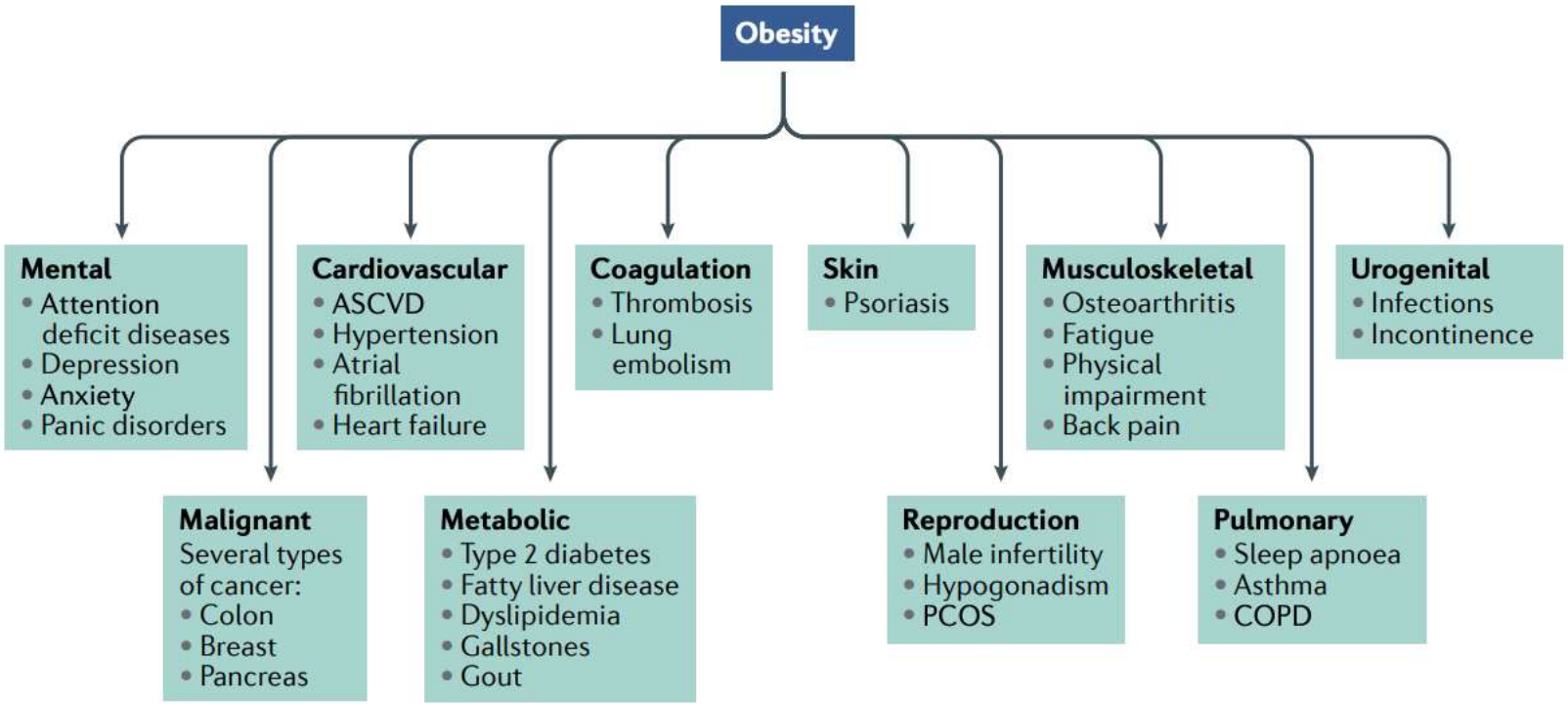
Non-Medical Treatments for Dyslipidemias

- Diet
- Low saturated fat (5-10% ↓ LDL-C); low cholesterol?
- Whole grains, fruits, vegetables
- Hard water ? (~5% ↓ LDL-C)
- Supplements
- Plant sterol/stanol ester margarine (5-10% ↓ LDL-C)
- Soluble fibers (~5% ↓ LDL-C)
- Niacin (Rx effective but AHA recommends against DS NA for lipids)
- Fish oil (Rx effective but AHA and FDA against DS w-3 at ↓TG doses anti-plt)
- Flaxseed oil (little conversion to EPA/DHA, few data. Ok for vegans)
- Phospholipids, garlic, biotin, etc. not well documented
- Folate, B6, B12 → ↓ Hcy but ↓ CVD not *seen* yet



TREATMENT OF OBESITY


Obesity
Mental
• Attention deficit diseases
• Depression
• Anxiety
• Panic disorders
Cardiovascular
• ASCVD
• Hypertension
• Atrial fibrillation
• Heart failure
Coagulation
• Thrombosis
• Lung embolism
Skin
• Psoriasis
Musculoskeletal
• Osteoarthritis
• Fatigue
• Physical impairment
• Back pain
Urogenital
• Infections
• Incontinence
Malignant
Several types of cancer:
• Colon
• Breast
• Pancreas
Metabolic
• Type 2 diabetes
• Fatty liver disease
• Dyslipidemia
• Gallstones
• Gout
Reproduction
• Male infertility
• Hypogonadism
• PCOS
Pulmonary
• Sleep apnoea
• Asthma
• COPD

Anti-obesity

Anti-obesity drugs and their effects

Drug or Drug Combination	Drug Group	Possible Mechanism of Action	Dosage	Toxicity
Orlistat	GI lipase inhibitor	Reduces lipid absorption	60–120 mg TID PO	Decreased absorption of fat-soluble vitamins, flatulence, fecal incontinence
Liraglutide	GLP-1 agonist	Decreases appetite	3 mg/d SC	Nausea, vomiting, pancreatitis
Lorcaserin	5-HT_{2c} agonist	Decreases appetite	10 mg PO BID	Headache, nausea, dry mouth, dizziness, constipation
Naltrexone/bupropion	Opioid antagonist + antidepressant	Unknown	32 mg/360 mg PO TID	Headache, nausea, dizziness, constipation
Phentermine	Sympathomimetic	Norepinephrine release in CNS	30–37.5 mg/d PO	Increased BP, HR; arrhythmias, insomnia, anxiety
Phentermine/topiramate	Sympathomimetic + antiseizure agent	Norepinephrine release plus unknown mechanism	3.75–15 mg/23–92 mg PO	Insomnia, dizziness, nausea, paresthesia, dysgeusia

BID, twice daily; BP, blood pressure; CNS, central nervous system; GI, gastrointestinal; HR, heart rate; PO, by mouth; SC, subcutaneously; TID, three times daily.

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History of weight loss drugs

Drug (full dose and administration)	Company	Approval	Weight loss (placebo/drug)	Side effects	Refs
Mitochondrial uncoupler					
DNP	Stanford University	1933–1938 (USA)	No data for controlled treatment ≥52 weeks	Hyperthermia, tachycardia, fever, tachypnoea, death	34
Sympathicomimetic					
Diethylpropion/afepramone	Merrell National Drug	1959–present (EU)	No controlled treatment ≥52 weeks	Nausea, constipation, insomnia, headache, tension and irritation, seizures	34
Methamphetamine	Abbott Laboratories	1947–1979 (USA)		Nigh risk for abusiveness and addiction	34
Phenmetrazine	Ciba-Geigy Corp	1956–present (USA)		Nausea, diarrhoea, dry mouth	34
Phendimetrazine	Carnick Laboratories	1959–present (USA)		Nausea, diarrhoea, dry mouth	34
Phenylpropanolamine	Thompson Medical	1960–2000 (USA)		Haemorrhagic stroke	
Fenfluramine and dexfenfluramine	Wyeth Ayerst	1973–1997 (USA)	−2.8%/−5.4%	Cardiac valvular insufficiency and pulmonary hypertension	285
Cathine (nor-pseudoephedrine) (53.3 mg, OD, oral)	Riemser Pharma	1975–present (EU, only for short-term use)	−2.4%/−6.6% to 9.9% (dose-dependent, short-term use only)	Tachycardia, increase in blood pressure, restlessness, sleep disorder, depression	32
Sibutramine (10 mg, OD)	Abbott Laboratories	1997–2010 (USA, EU)	+0.7%/−1.7%	Non-fatal myocardial infarction and stroke (in individuals with pre-existing CVD)	154
Phentermine (15–30 mg, OD, oral)	Teva Pharmaceuticals	1959–present (USA, only for short-term use)	−1.7%/−6.6% to −7.4% (dose-dependent)	Palpitations, elevated blood pressure	286
Polypharmacy					
Rainbow pills	Clark & Clark and others	1961–1968 (USA)	No controlled treatment ≥52 weeks	Insomnia, palpitations, anxiety, increase in heart rate and blood pressure, death	287
CB1 receptor blocker					
Rimonabant (20 mg, OD)	Sanofi SA	2006–2009 (EU)	−1.6%/−6.4%	Depression, suicidal ideation	288
Pancreatic lipase inhibitor					
Orlistat (120 mg TID, oral)	Roche Pharmaceuticals	1999–present (USA, EU)	−6.1%/−10.2%	Liver injury, gastrointestinal symptoms	289
5-HT$_{2C}$ serotonin agonist					
Lorcaserin (10 mg, BID, oral)	Arena Pharmaceuticals, Eisai	2012–2020 (USA)	−2.2%/−5.8%	Depression, suicidal ideation, palpitations, gastrointestinal symptoms, increased cancer risk	65

History of weight loss drugs

Drug (full dose and administration)	Company	Approval	Weight loss (placebo/drug)	Side effects	Refs
Sympathomimetic/anticonvulsant					
Phentermine/topiramate ER (with titration) (15 mg/92 mg, OD, oral)	Vivus	2012–present (USA)	−1.2%/−7.8% to 9.3% (dose-dependent)	Depression, suicidal ideation, cardiovascular events, memory loss, birth defects	290,291
Opioid receptor antagonist/dopamine and noradrenaline reuptake inhibitor					
Naltrexone SR/bupropion SR (with titration) (32 mg/360 mg, BID, oral)	Orexigen Therapeutics Inc.	2014–present (USA, EU)	−1.3%/−5.0% to −6.1% (dose-dependent)	Seizures, palpitations, transient blood pressure elevations	292
GLP1R agonists					
Liraglutide (with titration) (3.0 mg, OD, subcutaneous injection)	Novo Nordisk	2014–present (USA, EU)	−2.6%/−8%	Nausea/vomiting, diarrhoea, constipation, pancreatitis, gallstones	176
Semaglutide (2.4 mg, once weekly, subcutaneous injection)	Novo Nordisk	2021 (USA)	−2.4%/−14.9%	Nausea/vomiting, diarrhoea, constipation	38

BID, twice daily; CB1, cannabinoid receptor 1; CVD, cardiovascular disease; DNP, 2,4-dinitrophenol; ER, extended release; GLP1R, glucagon-like peptide 1 receptor; SR, sustained release; TID, three times daily; OD, once daily.

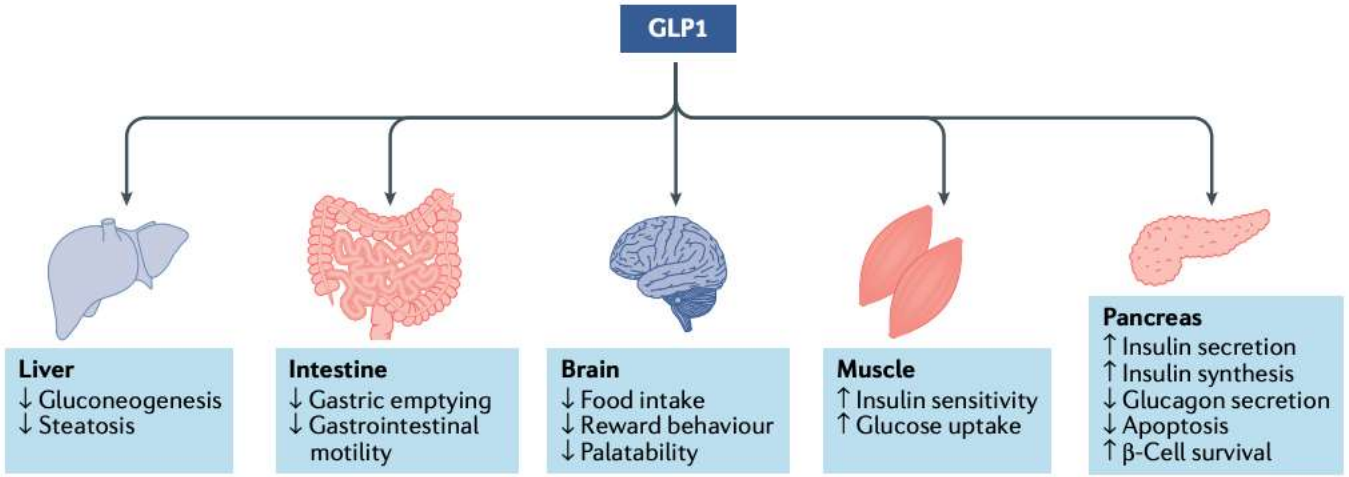
Weight loss drugs in clinical development

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
Leptin sensitizers				
Withaferin A	Academic, non-commercial	Phase I	Obesity, T2D	[293]
Celastrol	Academic, non-commercial	Preclinical	Obesity, T2D	[294]
Leptin/amylin	Amylin Pharmaceuticals	Discontinued	Obesity, T2D	See Related links
Y2R agonists				
PYY analogue	Eli Lilly	Phase I	T2D	See Related links
NN9748 (NN9747)	Novo Nordisk	Phase I	Obesity, T2D	NCT03574584
NNC0165-1875 + semaglutide	Novo Nordisk	Phase II	Obesity, T2D	NCT04969939
Amylin/calcitonin dual agonists				
KBP-089	Nordic Biosciences	Phase I	T2D	NCT03907202
KBP-042	Nordic Biosciences	Discontinued	T2D	NCT03230786
Davalintide	Amylin Pharmaceuticals	Discontinued	Obesity, T2D	See Related links
Amylin analogues				
Cagrilintide	Novo Nordisk	Phase II	Obesity, T2D	NCT04940078 NCT04982575
ZP 8396	Zealand Pharma	Preclinical	Obesity	See Related links

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
Drugs targeting the ghrelin pathway				
CYT009-GhrQb	Cytos Biotechnology	Phase I	Obesity	See Related links
Nox-B11	Noxxon Pharma	Preclinical	Obesity	See Related links
AZP-531	Millendo Therapeutics SAS	Discontinued	Hyperphagia in patients with Prader–Willi syndrome	NCT03790865
Mitochondrial uncoupler				
BAM15	Continuum Biosciences	Preclinical	Obesity, NASH	See Related links
Other appetite suppressants				
GDF15 (LA-GFD15)	Novo Nordisk	Phase I	Obesity	See Related links
LY-3463251 (GDF15 agonist)	Lilly	Phase I	T2D, obesity	NCT03764774
JNJ-9090/CIN-109 (GDF15 agonist)	Jansenn/CinFina Pharma	Phase I	Obesity	NA

GDF15, growth differentiation factor 15; GIP, glucose-dependent insulinotropic polypeptide; GLP1, glucagon-like peptide 1; GLP1R, GLP1 receptor; NA, not applicable; NASH, nonalcoholic steatohepatitis; OXM, oxyntomodulin; PYY, peptide tyrosine tyrosine; T2D, type 2 diabetes; Y2R, neuropeptide Y receptor type 2. [a]See Related links for further information.

Regulation of Body Weight and Glucose Metabolism by GLP1R Agonism



Muller, Timo D, et al., 2022. Anti-obesity Drug Discovery: Advances and Challenges. Nature Review: Drug Discovery: Vol. 21 pg. 201-223

Anti-Thyroid Agents

Thyroid and Antithyroid Drugs

THYROID HORMONE PREPARATIONS

- Levothyroxine
- Liothyronine
- T_4/T_3 Combination Preparations
- Therapeutic Uses of Thyroid Hormone
- Adverse Effects of Thyroid Hormone
- Drug Interactions
- Investigational Uses of Thyroid Hormone Analogues

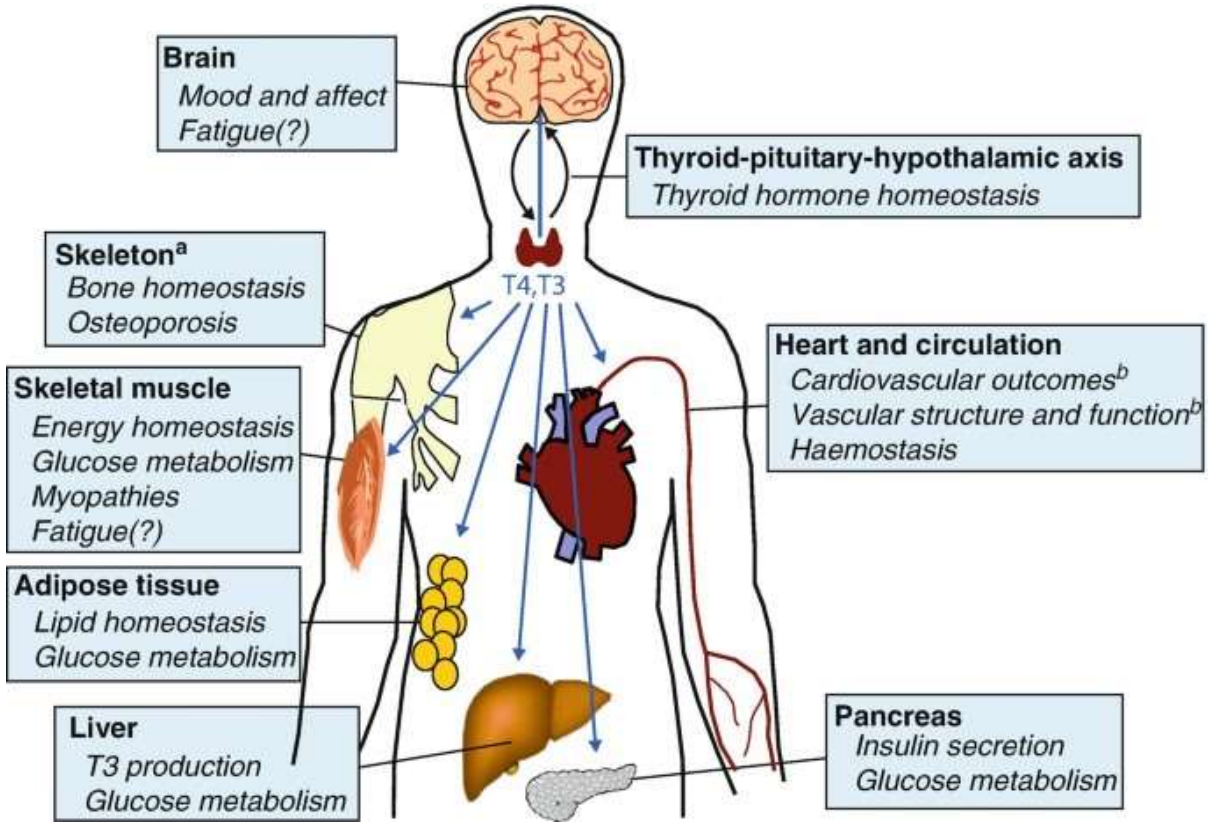
ANTITHYROID DRUGS AND OTHER THYROID INHIBITORS

- Antithyroid Drugs
- Ionic Inhibitors
- Iodine
- Radioactive Iodine

Thyroid Hormone Preparations

LEVOTHYROXINE

- **ADME**
- Levothyroxine sodium is available in tablets and liquid-filled capsules for oral administration and as a lyophilized powder for injection.
- Absorption of levothyroxine occurs in the stomach and small intestine and is incomplete (~80% of the tablet dose is absorbed).
- Absorption is slightly increased when the hormone is taken on an empty stomach



Thyroid Hormone Preparations

LIOTHYRONINE

- **ADME**
- Liothyronine sodium is the salt of T3 and is available in tablets and in an injectable form. Liothyronine absorption is nearly 100%, with peak serum levels 2 to 4 h following oral ingestion.
- Liothyronine may be used occasionally for thyroid hormone replacement when a rapid onset of action is desired, such as in the rare presentation of myxedema coma, or if rapid termination of action is desired, such as when preparing a patient with thyroid cancer for 131I therapy.
- Liothyronine is less desirable than levothyroxine for chronic replacement therapy due to the requirement for more-frequent dosing (plasma t1/2 is ~20 h), higher cost, and transient elevations of serum T3 concentrations above the normal range.

Therapeutic Uses of Thyroid Hormone

- **Thyroid Hormone Replacement Therapy in Hypothyroidism**
  - Levothyroxine is the hormone of choice for thyroid hormone replacement therapy due to its consistent potency and prolonged duration of action.
  - Dosing should generally be based on lean body mass.
  - The goal of therapy is to normalize the serum TSH (in primary hypothyroidism) or free T4 (in secondary or tertiary hypothyroidism) and to relieve symptoms of hypothyroidism.
- **Hypothyroidism During Pregnancy**
  - Due to the increased serum concentration of TBG induced by estrogen, the expression of Dio3 by the placenta, and the small amount of transplacental passage of T4 from mother to fetus, a higher dose of levothyroxine is usually required in pregnant patients.
- **Myxedema Coma**
  - Rare syndrome
  - Cardinal features of myxedema coma are hypothermia, respiratory depression, and decreased consciousness
  - Therapy with levothyroxine is begun with a loading dose of 200 to 400 µg followed by a daily full replacement dose or slightly less in the very elderly or in patients with cardiac disease (typically 50–100 µg/day intravenously). Some clinicians recommend adding liothyronine (10 µg intravenously followed by 2.5–10 µg every 8 h) until the patient is stable and conscious.

Therapeutic Uses of Thyroid Hormone

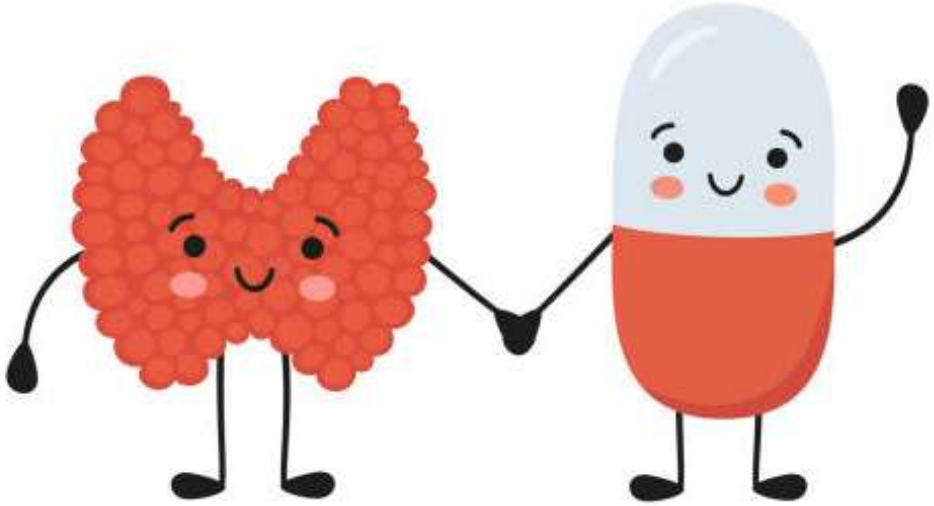
- **Congenital Hypothyroidism**
  - Success in the treatment of congenital hypothyroidism depends on the age at which therapy is started and the speed with which hypothyroidism is corrected.
  - To rapidly normalize the serum T4 concentration in the congenitally hypothyroid infant, an initial daily dose of levothyroxine of 10 to 15 μg/kg is recommended
  - The levothyroxine is administered orally as crushed tablets mixed with breast milk or water.
- **Thyroid Hormone Replacement in Thyroid Cancer**
  - The mainstays of therapy for well-differentiated thyroid cancer (papillary, follicular) are surgical thyroidectomy, radioiodine (discussed in material that follows), and levothyroxine to maintain a low TSH.
  - The rationale for TSH suppression is that TSH is a growth factor for thyroid cancer, but there are no randomized controlled trials that addressed the optimal TSH target range
  - The benefits of TSH suppression need to be weighed against the risks, including osteoporosis and atrial fibrillation.
- **Thyroid Nodules**
  - Nodular thyroid disease is the most common endocrinopathy
  - Most patients with thyroid nodules are euthyroid, which should be confirmed by TSH measurement.
  - The use of levothyroxine to suppress TSH in euthyroid individuals with thyroid nodules cannot be recommended as a general practice. However, if the TSH is elevated, it is appropriate to administer levothyroxine to bring the TSH into the lower portion of the reference range.

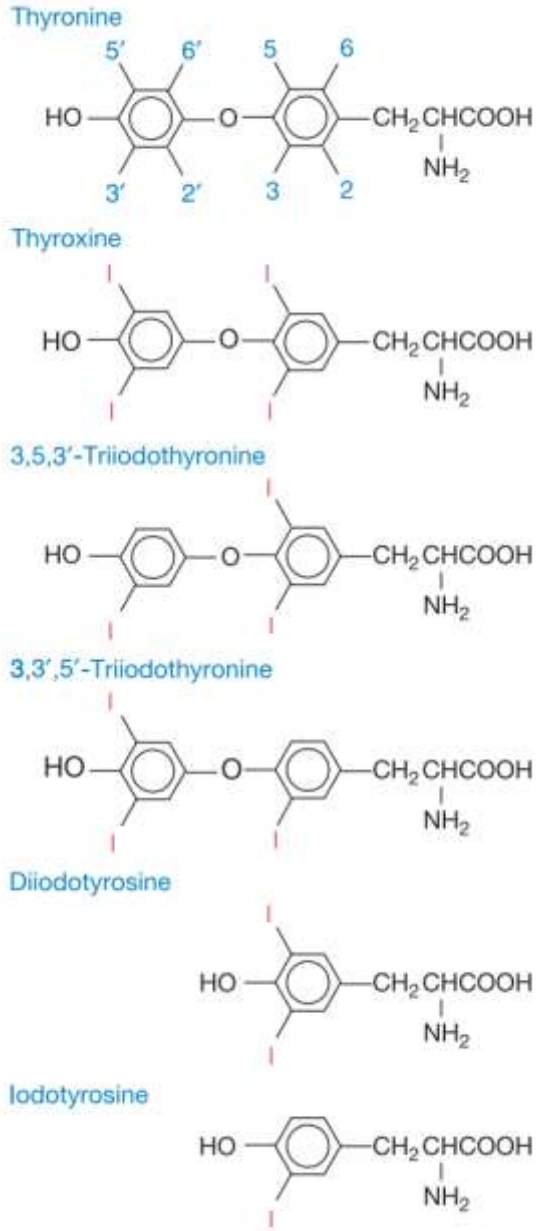
- **Adverse Effects of Thyroid Hormone**
- An excess of thyroid hormone can increase the risk of atrial fibrillation, especially in the elderly, and can increase the risk of osteoporosis, especially in postmenopausal women.

IMPORTANT FACTORS INFLUENCING ORAL LEVOTHYROXINE THERAPY

Drugs and other factors that may increase levothyroxine dosage requirements
Impaired levothyroxine absorption
Aluminum-containing antacids, proton pump inhibitors, sucralfate
Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
Calcium carbonate (effect generally small), phosphate binders (lanthanum carbonate, sevelamer)
Chromium picolinate, raloxifene, iron salts
Orlistat, kayexalate, simethicone
Food, soy products (effect generally very small), lactose intolerance (single case report)
Increased thyroxine metabolism, CYP3A4 induction
Rifampin, carbamazepine, phenytoin, sertraline, phenobarbital
Impaired $T_4 \rightarrow T_3$ conversion
Amiodarone, glucocorticoids, beta blockers
Mechanisms uncertain or multifactorial
Estrogen, pregnancy, lovastatin, simvastatin, ethionamide, Tyr kinase inhibitors
Drugs and other factors that may decrease levothyroxine dosage requirements
Advancing age (>65 years), androgen therapy in women
Drugs that may decrease TSH without changing free T_4 in levothyroxine-treated patients
Metformin

Antithyroid Drugs and Other Thyroid Inhibitors





Thyronine, thyroid hormones, and precursors

Antithyroid Drugs and Other Thyroid Inhibitors

- **Several types are clinically useful:**
  - Antithyroid drugs, which interfere directly with the synthesis of thyroid hormones
  - Ionic inhibitors, which block the iodide transport mechanism
  - High concentrations of iodine, which decrease release of thyroid hormones from the gland and also may decrease hormone synthesis
  - Radioactive iodine, which damages the thyroid gland with ionizing radiation

ANTITHYROID DRUGS

- **Thioamides**
  - Methimazole and propylthiouracil (PTU) are small sulfur-containing thioamides that inhibit thyroid hormone synthesis by blocking peroxidase-catalyzed reactions, iodination of the tyrosine residues of thyroglobulin, and coupling of DIT and MIT
  - The thioamides can be used by the oral route and are effective in young patients with small glands and mild disease
  - PTU is preferred in pregnancy and lactation because it is less likely than methimazole to cross the placenta and to enter breast milk.
- **Iodide Salts and Iodine**
  - Iodide salts inhibit iodination of tyrosine and thyroid hormone release, these salts also decrease the size and vascularity of the hyperplastic thyroid gland. Because iodide salts inhibit release as well as synthesis of the hormones, their onset of action occurs rapidly, within 2–7 d.
  - Iodide salts are used in the management of thyroid storm and to prepare patients for surgical resection of a hyperactive thyroid. The usual forms of this drug are Lugol's solution (iodine and potassium iodide) and saturated solution of potassium iodide. Adverse effects include rash, drug fever, metallic taste, bleeding disorders, and, rarely, anaphylactic reactions

ANTITHYROID DRUGS

- Radioactive Iodine
- Radioactive iodine (^{131}I) is taken up and concentrated in the thyroid gland so avidly that a dose large enough to severely damage the gland can be given without endangering other tissues. Unlike the thioamides and iodide salts, an effective dose of ^{131}I can produce a permanent cure of thyrotoxicosis without surgery. ^{131}I should not be used in pregnant or lactating women.
- Anion Inhibitors
- Anions such as thiocyanate (SCN–) and perchlorate (ClO4–) block the uptake of iodide by the thyroid gland through competitive inhibition of the iodide transporter. Their effectiveness is unpredictable and ClO4– can cause aplastic anemia, so these drugs are rarely used clinically
- Other Drugs
- An important class of drugs for the treatment of thyrotoxicosis is the β blockers. These agents are particularly useful in controlling the tachycardia and other cardiac abnormalities of severe thyrotoxicosis. Propranolol also inhibits the peripheral conversion of T4 to T3 at doses greater than 160 mg/d.
- The iodine-containing antiarrhythmic drug amiodarone (Chapter 14) can cause hypothyroidism through its ability to block the peripheral conversion of T4 to T3. It also can cause hyperthyroidism either through an iodine-induced mechanism in persons with an underlying thyroid disease such as multinodular goiter or through an inflammatory mechanism that causes leakage of thyroid hormone into the circulation.

Antithyroid Drugs

- The antithyroid drugs with clinical utility are the thioureylenes, which belong to the family of thioamides. Propylthiouracil is the prototype
- ADME
  - A small dose of methimazole, 0.5 mg, decreases the organification of iodine in the thyroid gland, but a single dose of 10 to 25 mg is needed to extend the inhibition to 24 h. Absorption of effective amounts of propylthiouracil occurs within 20 to 30 min of an oral dose; the duration of action is brief. he effect of a dose of 100 mg of propylthiouracil begins to wane in 2 to 3 h; even a 500-mg dose is completely inhibitory for only 6 to 8 h. The plasma t1/2 of methimazole is 4 to 6 h; the t1/2 of propylthiouracil is about 75 min

Antithyroid Drugs

- **Therapeutic Uses**
- The antithyroid drugs are used in the treatment of hyperthyroidism in the following ways:
  - As definitive treatment to control → spontaneous remission in Graves disease, or as long-term therapy in patients who do not undergo spontaneous remission and prefer medication rather than radioiodine treatment or surgery
  - In conjunction with radioactive iodine, to hasten recovery while awaiting the effects of radiation
  - To control the disorder in preparation for surgical treatment
- Methimazole is the drug of choice for Graves disease; it is effective when given as a single daily dose, has improved adherence, and is less toxic than propylthiouracil

Adjuvant Therapy

- Several drugs that have no intrinsic antithyroid activity are useful in the symptomatic treatment of thyrotoxicosis.
- The β adrenergic receptor antagonists are effective in antagonizing the sympathetic/adrenergic effects of thyrotoxicosis—thereby reducing the tachycardia, tremor, and stare—and relieving palpitations, anxiety, and tension. Either propranolol, 20 to 40 mg four times daily, or atenolol, 50 to 100 mg daily, is usually given initially
- The Ca2+ channel blockers (diltiazem, 60–120 mg four times daily) can be used to control tachycardia and decrease the incidence of supraventricular tachyarrhythmias.
- Immunotherapy has been used for Graves hyperthyroidism and ophthalmopathy.

Thyroid Storm

- Life-threatening complication of thyrotoxicosis
- Occurs in untreated or partially treated thyrotoxic patients
- Cardinal features include fever (temperature usually >38.5°C) and tachycardia out of proportion to the fever. Nausea, vomiting, diarrhea, agitation, and confusion are frequent presentations. Coma and death may ensue in up to 20% of patients. Thyroid function abnormalities are similar to those found in uncomplicated hyperthyroidism.
- Treatment includes supportive measures such as intravenous fluids, antipyretics, cooling blankets, and sedation. Antithyroid drugs are given in large doses.
- Propylthiouracil is preferred over methimazole because it also inhibits Dio1, thus impairing peripheral conversion of T4 to T3.

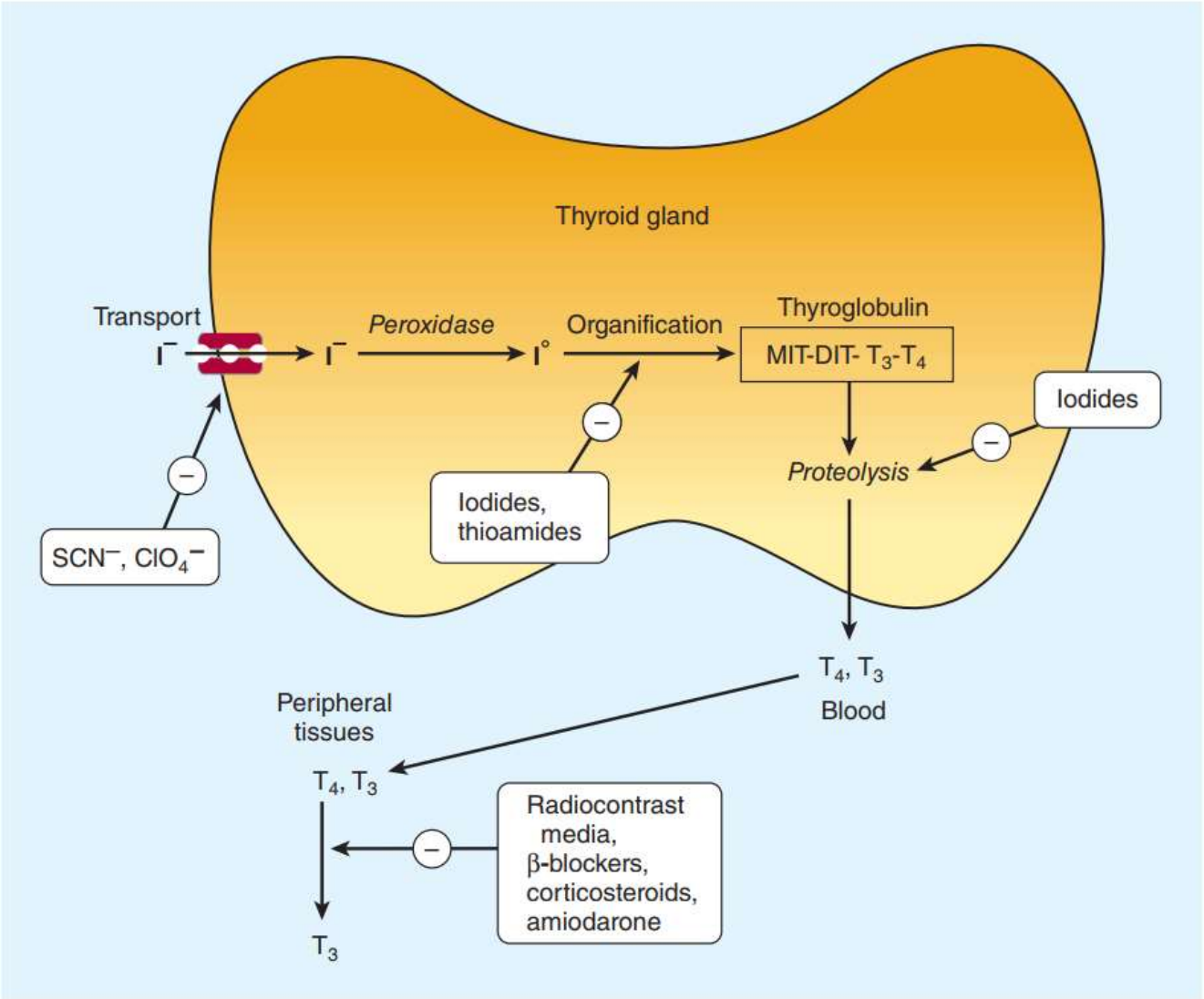
PHARMACOKINETIC FEATURES OF ANTITHYROID DRUGS

	PROPYLTHIOURACIL	METHIMAZOLE
Plasma protein binding	~75%	Nil
Plasma $t_{1/2}$	75 min	~4–6 h
Volume of distribution	~0.4 L/kg	~0.7 L/kg
Concentrated in thyroid	Yes	Yes
Metabolism of drug during illness		
Severe liver disease	Normal	Decreased
Severe kidney disease	Normal	Normal
Dosing frequency	1–4 times daily	Once or twice daily
Transplacental passage	Low	Low
Levels in breast milk	Low	Low

Drug	Therapeutic Uses	Clinical Pharmacology and Tips
Thyroid Hormone Preparations: Replace T_4 or T_3 normally produced by the thyroid		
Levothyroxine (T_4)	• Hypothyroidism • TSH suppression in thyroid cancer	• Plasma $t_{1/2}$ ~1 week • Deiodinases convert circulating T_4 to the bioactive hormone T_3 • Dosage generally needs to increase during pregnancy • Congenital hypothyroidism requires rapid diagnosis and correction to allow normal physical and mental development • Overtreatment can lead to osteoporosis and atrial fibrillation
Liothyronine (T_3)	• When rapid onset of action is desired (sometimes for myxedema coma) • When rapid termination of action is desired (preparing patients with thyroid cancer for radioiodine therapy)	• Plasma $t_{1/2}$ ~18–24 h • Multiple daily doses needed to achieve needed C_{Pss} • Levothyroxine generally preferred over liothyronine for the long-term therapy of hypothyroidism
Desiccated thyroid and T_4–T_3 mixtures	• Generally not a preferred therapy, although occasional hypothyroid patients say they feel better than when taking levothyroxine	• Mixture of levothyroxine and liothyronine (~4:1 by weight) • Supplies a relative excess of T_3 compared to normal thyroidal secretion, which is ~11:1 T_4 to T_3 by weight • No convincing evidence of greater efficacy than levothyroxine alone
Antithyroid Drugs: Thionamides: Interfere with incorporation of iodine into tyrosyl residues and inhibit iodotyrosyl-coupling reactions		
Methimazole	• Reduce thyroid hormone production	• Carbimazole (available in Europe) converted to methimazole after absorption • Long intrathyroidal $t_{1/2}$ allows once-daily dosing for most patients • Preferred antithyroid drug • Do not use in first trimester of pregnancy due to embryopathy
Propylthiouracil	• Reduce thyroid hormone production • At high doses, reduces T_4 to T_3 conversion	• Major concern is liver toxicity; rare but more commonly seen in children and pregnancy • Main indications are for thyroid storm due to action on reducing T_4 to T_3 conversion and in the first trimester of pregnancy, although it has been associated with congenital defects that are not initially detected at birth
Antithyroid Drugs: Ionic Inhibitors: Inhibit iodine uptake by antagonizing the NIS		
Perchlorate	• Primarily used to enhance the response to thioamides in refractory Graves disease (e.g., that associated with amiodarone)	• Not available commercially; must be specialty compounded

Drug	Therapeutic Uses	Clinical Pharmacology and Tips
Antithyroid Drugs: Iodide: Acute reduction in thyroid hormone		
Lugol solution	• Acutely reduces the secretion and synthesis of thyroid hormone	• "Escape" from thyroid inhibition after 7–10 days • Strictly contraindicated in pregnancy
KISS: potassium iodide saturated solution (or SSKI)	• Acutely reduces the secretion and synthesis of thyroid hormone	• "Escape" from thyroid inhibition after 7–10 days • Strictly contraindicated in pregnancy
Antithyroid Drugs: Radioactive Iodine: Used to destroy hyperfunctioning thyroid tissue		
^{131}I	• Effective for permanent treatment of Graves disease and toxic nodule or toxic goiter • Destruction of iodide-avid thyroid cancer	• Highly effective for permanent cure to hyperthyroidism • Effective treatment of hyperthyroidism usually results in permanent hypothyroidism and lifelong requirement for levothyroxine replacement • Absolutely contraindicated in pregnancy • Treatment of thyroid cancer requires TSH stimulation (endogenous or exogenous)
Recombinant Human TSH Agonist for the TSH Receptor		
Thyrotropin alpha	• Stimulates radioiodine uptake and thyroglobulin release in patients with thyroid cancer after thyroidectomy • Prepares patients for radioiodine ablation of thyroid remnants after thyroidectomy for thyroid cancer	• Allows assessment of residual or recurrent thyroid cancer without stopping levothyroxine and becoming clinically hypothyroid • Allows radioiodine therapy of thyroid remnants without stopping levothyroxine and becoming clinically hypothyroid
Thyroid Cancer Chemotherapeutics: TRK Inhibitors: Used when surgery, ^{131}I, TSH suppression, and external beam radiotherapy are inadequate		
Larotrectinib Entrectinib	• Systemic therapy of follicular cell–derived thyroid cancers with *NTRK* fusion gene driver mutations	• *NTRK* fusion genes are uncommon in thyroid cancer • Limited data suggest better tolerated and more efficacious than multikinase inhibitors when an *NTRK* fusion gene is present • See Chapter 71 for a more general discussion of these drugs

Drug	Therapeutic Uses	Clinical Pharmacology and Tips
Thyroid Cancer Chemotherapeutics: RET Inhibitors: Used when surgery, ^{131}I, TSH suppression, and external beam radiotherapy are inadequate		
Selpercatinib Pralsetinib	• Systemic therapy of thyroid cancers with *RET* driver mutations (papillary cancers with *RET* fusion genes and medullary cancers with *RET* point mutations)	• *RET* driver mutations (fusion genes) are uncommon in papillary thyroid cancer • *RET* driver mutations (point mutations) are common in sporadic medullary cancer and nearly universal in inherited medullary cancers (multiple endocrine neoplasia type 2) • Since medullary cancers are not derived from follicular cells, ^{131}I and TSH suppression are ineffective • Limited data suggest better tolerated and more efficacious than multikinase inhibitors when a *RET* driver mutation is present • See Chapter 71 for a more general discussion of these drugs
Thyroid Cancer Chemotherapeutics: *BRAF* V600E Inhibitors: Used when surgery, ^{131}I, TSH suppression, and external beam radiotherapy are inadequate		
Vemurafenib Dabrafenib	• Systemic therapy of thyroid cancers with *BRAF* V600E driver mutation • May be useful as redifferentiation therapy to induce radioiodine uptake in non–iodine-avid thyroid cancers with *BRAF* V600E	• Although *BRAF* V600E is the most common driver mutation in papillary cancer, BRAF inhibitors have not been shown to be clearly superior to multikinase inhibitors • The role of redifferentiation therapy is uncertain • See Chapter 71 for a more general discussion of these drugs
Thyroid Cancer Chemotherapeutics: Multikinase Inhibitors: Used when surgery, ^{131}I, TSH suppression, and external beam radiotherapy are inadequate		
Lenvatinib Sorafenib	• Systemic therapy of follicular cell–derived thyroid cancers without regard to driver mutation status	• Inhibit multiple kinases including vascular endothelial growth factor receptors • Although there are no head-to-head trials, existing data suggest lenvatinib is more efficacious • Toxicities are common and can limit drug dosage or usage • See Chapter 71 for a more general discussion of these drugs
Vandetanib Cabozantinib	• Systemic therapy of medullary thyroid cancer without regard to driver mutation status	• Inhibit multiple kinases including vascular endothelial growth factor receptors and RET • Since medullary cancers are not derived from follicular cells, ^{131}I and TSH suppression are ineffective • See Chapter 71 for a more general discussion of these drugs
Thyroid Cancer Chemotherapeutics: MEK Inhibitors		
Trametinib Selumetinib	• Trametinib is FDA-approved in combination with dabrafenib to treat anaplastic cancers containing *BRAF* V600E • May be useful as redifferentiation therapy (with or without BRAF inhibition) to induce radioiodine uptake in non–iodine-avid thyroid cancers	• The role of redifferentiation therapy and the effectiveness of MEK inhibitors are uncertain • See Chapter 71 for a more general discussion of these drugs


Thyroid gland
Transport
I⁻
I⁻
Peroxidase
I°
Organification
Thyroglobulin
MIT-DIT- T3-T4
Iodides
Proteolysis
Iodides, thioamides
SCN⁻, ClO4⁻
T4, T3
Blood
Peripheral tissues
T4, T3
Radiocontrast media, β-blockers, corticosteroids, amiodarone
T3

TERIMAKASIH