TABLE 69-7 DRUGS COMMONLY USED FOR THE TREATMENT OF HYPERLIPIDEMIA

DRUG CLASS	LDL (% CHANGE)	HDL (% CHANGE)	TRIGLYCERIDES (% CHANGE)	SIDE EFFECTS
HMG-CoA inhibitors	↓ 20-60	↑ 5-10	↓ 10-30	Liver toxicity, myositis, rhabdomyolysis; enhanced warfarin effect
Cholesterol absorption inhibitors	↓ 17	No effect	↓ 7-8	Abnormal liver enzymes in combination with an HMG-CoA inhibitor, myalgia, hepatitis, rhabdomyolysis, pancreatitis, potential increase in cancer risk and cancer death
Bile acid sequestrants	↓ 15-30	Slight increase	No effect	Nausea, bloating, cramping, abnormal liver function; interferes with absorption of other drugs such as warfarin and thyroxine
Fibric acid	↓ 5-20	↑ 5-20	↓ 35-50	Nausea, cramping, myalgias, liver toxicity, enhanced warfarin effect
Nicotinic acid	↓ 10-25	↑ 15-35	↓ 25-30	Hepatotoxicity, hyperuricemia, hyperglycemia, flushing, pruritus, nausea, vomiting, diarrhea
Omega-3 fatty acids	↑ 4-49	↑ 5-9	↓ 23-45	Eructation, taste perversion, dyspepsia

HMG-CoA, Hydroxymethylglutaryl–coenzyme A reductase.

Lifestyle Modification

Lifestyle modification should be the initial step in the management of hyperlipidemia (see Table 69-6). Restricting the dietary intake of fat lowers total cholesterol by approximately 15% and LDL cholesterol by 25%. Low-fat diets that limit saturated fat content promote LDL receptor expression and increase the uptake of LDL-cholesterol from the circulation. By contrast, saturated fat downregulates hepatic LDL receptors and increases circulating LDL. Because unsaturated fats (polyunsaturated and monounsaturated) generally do not have this effect, they are the preferred form of fat intake. However, polyunsaturated fats containing fatty acids with a *trans* rather than *cis* double bond configuration (*trans*-fatty acids) increase plasma cholesterol levels similarly to saturated fat.

Limiting the intake of saturated and *trans*-unsaturated fatty acids requires appropriate calorie substitutions. Increasing carbohydrate content to achieve this goal can increase the hepatic synthesis of triglyceride. Dietary substitution with soluble fibers (e.g., oat bran) has been recommended, because these fibers have a limited effect on triglyceride levels. They also bind bile acids in the gut and thereby decrease cholesterol levels. Other polyunsaturated fats, such as omega-3 fatty acids, are cardioprotective. They are abundant in fatty fish, flaxseed oil, canola oil, and nuts. They reduce VLDL production, inhibit platelet aggregation, and decrease CHD. Even two servings per week of fatty fish such as salmon can be beneficial.

Dietary restriction of fat (<10%) is essential for the treatment of marked hypertriglyceridemia. Other factors such as carbohydrate and alcohol intake can also increase the synthesis of triglyceride. Restriction of alcohol intake to 1 or 2 servings per week and adherence to a low-fat, high-fiber diet will improve hypertriglyceridemia.

Exercise has been shown to increase LPL activity. Even a single exercise session can reduce triglycerides and increase HDL. The impact of exercise on LDL is less clear. With low- to moderate-intensity exercise regimens, clearance of VLDL particles increases LDL production. However, this effect is not seen with high-intensity exercise programs. A decrease in LDL-cholesterol occurs with high-intensity exercise, and this effect is independent of weight loss.

Pharmacotherapy

If diet and exercise modifications do not sustain a normal lipid profile, then drug therapy is appropriate (see Table 69-7). Likely benefit needs to be balanced against potential adverse effects when determining drug therapy. Many patients require two or three agents to achieve adequate control.

HMG-CoA reductase is the rate-limiting enzyme involved in cholesterol biosynthesis. Inhibition of this enzyme decreases intracellular cholesterol pools and subsequently increases uptake of LDL cholesterol from the circulation. HMG-CoA reductase inhibitors (e.g., lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin) increase cholesterol utilization, decrease VLDL synthesis, and increase HDL synthesis. As a result, lower LDL and triglyceride levels and higher HDL levels are observed with treatment. Meta-analysis of primary and secondary CHD prevention trials found reductions in all-cause and cardiovascular mortality rates with statin therapy. These agents limit progression and may even cause regression of coronary atherosclerosis. Therefore, they represent first-line therapy in the management of abnormal LDL-cholesterol levels. Elevated liver enzymes and muscle toxicity are potential dose-related complications. Myositis can occur with statins alone, but the risk is higher when statins are used in combination with nicotinic acid or fibric acid derivatives. Some of these agents can also potentiate the effect of warfarin.

Cholesterol absorption inhibitors (e.g., ezetimibe) function by interfering with the transport of cholesterol at the intestinal brush border. They increase cholesterol utilization and decrease LDL-cholesterol levels. Despite reductions in LDL-cholesterol, improvements in cardiovascular events and mortality have not been reported with treatment. Ezetimibe may be used as a single agent or in combination with an HMG-CoA reductase inhibitor to lower LDL-cholesterol levels. In combination, this agent can increase serum transaminase levels and potentially increase the risk of cancer and cancer death.

Drugs that interfere with the absorption of cholesterol from the intestinal lumen increase cholesterol utilization and decrease circulating levels of cholesterol. Bile acid sequestrants (e.g., cholestyramine, colestipol, and colesevelam) bind bile acids in the intestinal lumen and increase fecal excretion. Subsequently, more LDL-cholesterol is used by the liver to synthesis bile acids. The decrease in cellular cholesterol pools upregulates LDL receptors and decreases the amount of LDL-cholesterol in the circulation. Mild increases in HDL-cholesterol are also seen with this agent as a result of increased intestinal HDL formation. Treatment is associated with a reduction in the incidence of CHD. Bile acid sequestrants may be used alone for mild lipid dysfunction or in