

Fibrates

PPAR-alpha agonists that accelerate lipoprotein lipase-mediated lipolysis, used mainly for hypertriglyceridaemia, and defined clinically by gallstone risk and by myopathy when combined with a statin.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/fibrates>

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Quick revision

One Liner: Fibrates activate peroxisome proliferator-activated receptor alpha, which raises lipoprotein lipase activity and downregulates apolipoprotein C-III - a triglyceride-directed mechanism, which is why they sit beside rather than instead of a statin.

1. Mechanism: activation of transcription factors for peroxisome proliferator-activated receptors, increasing lipoprotein lipase-mediated lipolysis. [2]
2. PPAR-alpha activation also downregulates apolipoprotein C-III, an inhibitor of triglyceride clearance. [4]
3. They reduce the substrate available for hepatic triglyceride synthesis and promote receptor-mediated clearance of LDL. [2]
4. HDL rises because production of apolipoprotein A-I and A-II in the liver is upregulated. [2]
5. Fibrates are used primarily to lower triglycerides, with a more modest effect on atherosclerotic cardiovascular risk than statins. [4]
6. Approved for primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet, and for severe hypertriglyceridaemia of Fredrickson types IV and V. [2]
7. Combination with a statin raises the risk of myopathy, particularly in older adults and in renal impairment. [2][4]
8. Gemfibrozil is the member specifically described as unsafe for that interaction, while bezafibrate and fenofibrate remain options. [2]
9. Active gallbladder disease is a contraindication, because PPAR-alpha-mediated downregulation of bile acids increases gallstone risk. [2]

Overview

1. Fibrates work through the peroxisome proliferator-activated receptors. Activating these transcription factors increases lipoprotein lipase-mediated lipolysis, so triglyceride-rich particles are broken down faster; PPAR-alpha activation also downregulates apolipoprotein C-III, which normally restrains that lipolysis. At the same time the drugs reduce the substrate available for hepatic triglyceride synthesis, promote receptor-mediated clearance of LDL, and raise HDL by upregulating hepatic production of apolipoprotein A-I and A-II. [2][4]
2. The clinical position that follows is a triglyceride-directed one. Approved indications cover primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet, and severe hypertriglyceridaemia of Fredrickson types IV and V, with primary biliary cholangitis recorded as an off-label use. Gemfibrozil is also indicated where very high triglycerides represent a risk factor for acute pancreatitis. Three agents have been used in the United States - gemfibrozil, fenofibrate and clofibrate - and clofibrate has been withdrawn. [2][3][5]
3. Two safety themes shape prescribing. The first is muscle: fibrates can inhibit statin metabolism and increase myopathy risk, so the combination is generally avoided, and the risk is highest in older adults and in renal impairment. The second is the biliary tract, since PPAR-alpha-mediated downregulation of bile acids increases gallstone risk. Hepatotoxicity sits behind both, with fenofibrate the member most convincingly associated with clinically apparent liver injury. [2][4][5]

Classification and drug examples

Intro: A small class whose members share one mechanism but differ sharply in whether they can safely accompany a statin. That single distinction, rather than potency, is what separates them in practice.

1. Name: The fibrate to keep away from statins

1. Note: Described as having proved unsafe in combination with a statin, and carrying transporter- and enzyme-level interactions that explain why.

Name: Gemfibrozil

Route: Oral

Note: Upregulates lipoprotein lipase and inhibits synthesis while increasing clearance of VLDL, reducing triglycerides by 30% to 60%; inhibits OATP1B1 and represses CYP2C8. [3] [2]

2. Name: Fibrates that remain options alongside a statin

2. Note: Still carry a myopathy risk in combination, particularly in older adults and in renal impairment, but are not described as unsafe in the way gemfibrozil is.

1. Name: Fenofibrate

1. Route: Oral

1. Note: Approved in the United States since 1993; the member most frequently and convincingly linked to clinically apparent liver injury. [5][2]

2. Name: Bezafibrate

2. Route: Oral

2. Note: Named alongside fenofibrate as a fibrate that remains an option where a statin is also required. [2] [2][4]

3. Name: Withdrawn member

3. Note: Retained here for context only, because its withdrawal is a recurring examination point rather than a live prescribing choice.

Name: Clofibrate

Route: Oral

Note: Withdrawn from use, largely because of concerns regarding an increased risk of cancer. [5] [5]

Mechanism of action

Summary: Fibrates activate peroxisome proliferator-activated receptors, chiefly PPAR-alpha, which increases lipoprotein lipase-mediated lipolysis of triglyceride-rich particles, downregulates apolipoprotein C-III, limits hepatic triglyceride synthesis and raises hepatic production of the structural apolipoproteins of HDL.

Target: Peroxisome proliferator-activated receptor alpha (PPAR-alpha)

Cidal Static: not applicable

Kill Kinetics: not applicable

1. Step: 1

1. Title: The drug activates PPAR transcription factors

1. Detail: Fibrates increase lipoprotein lipase-mediated lipolysis by activating transcription factors for peroxisome proliferator-activated receptors. [2]

2. Step: 2

2. Title: Apolipoprotein C-III is downregulated

2. Detail: PPAR-alpha activation reduces apolipoprotein C-III, removing a brake on the clearance of triglyceride-rich lipoproteins. [4]

3. Step: 3

3. Title: Triglyceride-rich particles are cleared faster

3. Detail: Increased lipoprotein lipase activity accelerates lipolysis, and gemfibrozil is additionally described as inhibiting the synthesis of very-low-density lipoprotein while increasing its clearance. [2][3]

4. Step: 4

4. Title: Hepatic triglyceride synthesis is limited

4. Detail: The drugs reduce the availability of substrates for triglyceride synthesis in the liver, so less is produced as well as more being removed. [2]

5. Step: 5

5. Title: LDL clearance rises and HDL increases

5. Detail: Receptor-mediated clearance of LDL is promoted, and HDL rises through upregulated hepatic production of apolipoprotein A-I and apolipoprotein A-II. [2]

Major clinical uses

1. Drug: Fibrates as a class

1. Organism: Not applicable

1. Indication: Severe hypertriglyceridaemia of Fredrickson types IV and V

1. Line: first-line

1. Note: The indication that follows most directly from the mechanism, since the class is primarily triglyceride-lowering. [2][4]

2. Drug: Fibrates as a class

2. Organism: Not applicable

2. Indication: Primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet

2. Line: adjunct

2. Note: An approved role, though statins remain first-line where LDL cholesterol is the dominant abnormality. [2][4]

3. Drug: Gemfibrozil

3. Organism: Not applicable

3. Indication: Very high triglycerides representing a risk factor for acute pancreatitis

3. Line: targeted

3. Note: Triglyceride reduction of 30% to 60% is described for this agent, alongside a rise in HDL. [3]

4. Drug: Gemfibrozil

4. Organism: Not applicable

4. Indication: Reduction of coronary heart disease risk in type IIb hyperlipidaemia

4. Line: targeted

4. Note: Described particularly in patients without a history of existing coronary heart disease symptoms. [3]

5. Drug: Fibrates as a class

5. Organism: Not applicable

5. Indication: Primary biliary cholangitis (off-label)

5. Line: adjunct

5. Note: A recorded off-label use, and a specialist decision rather than routine practice. [2]

Pharmacokinetics

1. Drug: Gemfibrozil

1. Route: Oral

1. Absorption: Oral administration as an adjunct to diet

1. Csf Penetration: Not clinically relevant

1. Metabolism: Represses CYP2C8 activity and inhibits the OATP1B1 transporter

1. Elimination: See prescribing reference

1. Half Life: See prescribing reference

1. Dose Adjust: Contraindicated in hepatic or severe renal dysfunction [3][2]

2. Drug: Fenofibrate

- 2. Route: Oral
- 2. Absorption: Oral administration as an adjunct to diet
- 2. Csf Penetration: Not clinically relevant
- 2. Metabolism: See prescribing reference
- 2. Elimination: See prescribing reference
- 2. Half Life: See prescribing reference
- 2. Dose Adjust: Contraindicated in active liver disease and in severe renal dysfunction [2]
- 1. Interaction risk in this class is not confined to drug-metabolising enzymes. Gemfibrozil inhibits the OATP1B1 uptake transporter, which raises the exposure of statins that depend on it, and that transporter effect is a large part of why the combination is dangerous. [3]
- 2. Monitoring includes serum creatine phosphokinase where a statin is co-administered, renal function, serum transaminases, and gallbladder studies where clinically indicated. [2]
- 3. Where a coumarin anticoagulant is co-prescribed, prothrombin time and INR require frequent monitoring during the early period of combined therapy. [2]
- 4. This page gives no dose regimens by design. Doses depend on the individual agent, renal and hepatic function and concurrent therapy, and belong in a prescribing reference used by the treating clinician.

Adverse effects

- 1. Effect: Deranged aminotransferases
 - 1. Detail: Raised AST and ALT are the most common laboratory abnormality on fibrate therapy, and elevations are typically transient and asymptomatic, sometimes resolving without discontinuation. [2][5]
- 2. Effect: Gastrointestinal upset
 - 2. Detail: Abdominal pain is described for the class, and dyspepsia was reported in approximately 20% of patients taking gemfibrozil, along with nausea, vomiting, diarrhoea and constipation. [2][3]
- 3. Effect: Reversible rise in serum creatinine and homocysteine
 - 3. Detail: A documented class effect, and reversible, so a modest creatinine rise is not necessarily evidence of new renal injury. [2]
- 4. Effect: Leg cramps
 - 4. Detail: Listed among the recognised adverse effects of fibrate therapy. [2]
- 1. Effect: Myopathy and rhabdomyolysis
 - 1. Detail: Myopathy carries a risk under 1% on its own, but the probability of myopathy or rhabdomyolysis rises when a fibrate is combined with a statin, particularly in older adults and in renal impairment.
 - 1. Action: Creatine phosphokinase is monitored where the combination is used, and muscle symptoms prompt reassessment of the whole regimen. [2][3][4]
- 2. Effect: Venous thromboembolism
 - 2. Detail: Pulmonary embolism and deep vein thrombosis occurred more often on fibrate than on placebo in the FIELD trial of fenofibrate, and a comparable excess was seen with clofibrate in the Coronary Drug Project, so the risk is recognised across the class rather than confined to one agent.
 - 2. Action: New leg swelling, pleuritic chest pain or breathlessness prompts assessment for thromboembolism by the treating clinician. [2][1]
- 3. Effect: Cholelithiasis
 - 3. Detail: Gallstone formation carries a risk of a similar order to myopathy, and gemfibrozil is described as enhancing cholesterol elimination into bile.
 - 3. Action: Gallbladder studies where symptoms suggest biliary disease; active gallbladder disease contraindicates the class. [2][3]
- 4. Effect: Clinically apparent liver injury
 - 4. Detail: All three fibrates used in the United States have been linked to acute liver injury, fenofibrate most frequently

and convincingly, and the injury can be severe and progress to chronic hepatitis with fibrosis and cirrhosis.

4. Action: Serum transaminases are followed during therapy, and active liver disease is a contraindication. [5][2]

1. Drug: Gemfibrozil

1. Effect: Simultaneous use with a statin enhances the probability of rhabdomyolysis or myopathy; combination with simvastatin, repaglinide or dasabuvir is contraindicated. [3]

2. Drug: Fenofibrate and bezafibrate

2. Effect: Remain options where a statin is also needed, unlike gemfibrozil, though the combination still carries myopathy risk. [2]

3. Drug: Clofibrate

3. Effect: Withdrawn from use, largely because of concerns about an increased risk of cancer. [5]

Contraindications, precautions and interactions

1. Known hypersensitivity to the drug. [2]

2. Active liver disease, given the hepatotoxic potential of the class. [2]

3. Active gallbladder disease, because PPAR-alpha-mediated downregulation of bile acids increases gallstone risk. [2]

4. Severe renal dysfunction, including patients on dialysis. [2]

5. For gemfibrozil specifically: combined use with simvastatin, repaglinide or dasabuvir. [3]

1. Older age and renal impairment, both of which increase the myopathy risk when a fibrate accompanies a statin. [4]

2. Any existing muscle symptoms, since creatine phosphokinase elevation and myopathy are recognised effects of the class. [2]

3. Concurrent anticoagulation, which requires frequent coagulation monitoring rather than a simple dose adjustment. [2]

1. With: Statins

1. Effect: Fibrates can inhibit statin metabolism and increase myopathy risk, so the combination is generally avoided; gemfibrozil has proved unsafe for it while bezafibrate and fenofibrate remain options. [2]

2. With: OATP1B1 substrates such as atorvastatin and rosuvastatin

2. Effect: Gemfibrozil inhibits the OATP1B1 transporter and can therefore increase the exposure of these medicines. [3]

3. With: Coumarin anticoagulants

3. Effect: Interaction requires frequent monitoring of prothrombin time and INR, with anticoagulant dose reduction described for gemfibrozil. [2][3]

4. With: CYP2C8 substrates

4. Effect: Gemfibrozil represses CYP2C8 activity and may increase the exposure of drugs handled by that enzyme. [3]

Comparison tables

Title: Fibrates compared with statins

Caption: The two classes are complementary in target but awkward in combination. Any decision to combine them belongs to the treating clinician working from a current prescribing reference.

1. Key: feature

1. Label: Feature

1. Is Row Header: true

2. Key: fibrate

2. Label: Fibrates

3. Key: statin

3. Label: Statins

1. Feature: Molecular target

1. Fibrate: Peroxisome proliferator-activated receptor alpha

1. Statin: HMG-CoA reductase [2][4]

2. Feature: Principal lipid effect
2. Fibrate: Lowering of triglycerides, with a rise in HDL
2. Statin: Lowering of LDL cholesterol [2][4]
3. Feature: Position in therapy
3. Fibrate: Primarily for hypertriglyceridaemia, with modest atherosclerotic benefit
3. Statin: First-line for hypercholesterolaemia [4]
4. Feature: Characteristic non-muscle risk
4. Fibrate: Gallstones, through downregulation of bile acids
4. Statin: New-onset diabetes and transaminase elevation [2][4]
5. Feature: Behaviour in combination
5. Fibrate: Raises statin exposure and myopathy risk; gemfibrozil is the unsafe member
5. Statin: Tolerates ezetimibe well; fibrate pairing needs care [2][3]

High-yield exam pearls

1. Pearl: Fibrates are the triglyceride drugs; statins are the LDL drugs.
1. Why: Their primary use is lowering triglycerides, with modest atherosclerotic benefit, whereas statins are described as the first-line lipid-lowering drugs for hypercholesterolaemia. Knowing which lipid fraction is the target answers most selection questions. [4]
2. Pearl: Not all fibrates are equally dangerous with a statin.
2. Why: Gemfibrozil has proved unsafe in combination with a statin, while bezafibrate and fenofibrate remain usable options - a within-class distinction that matters far more here than it does in most drug classes. [2]
3. Pearl: Gemfibrozil raises statin exposure through a transporter, not only through metabolism.
3. Why: It inhibits the OATP1B1 transporter and so increases exposure to OATP1B1 substrates including atorvastatin and rosuvastatin, and it also represses CYP2C8. [3]
4. Pearl: The gallstones are mechanistically predictable.
4. Why: PPAR-alpha-mediated downregulation of bile acids increases gallstone risk, and gemfibrozil is separately described as enhancing cholesterol elimination into bile - which is why active gallbladder disease is a contraindication. [2][3]
5. Pearl: A rise in creatinine on a fibrate is usually reversible.
5. Why: Reversible elevation of serum creatinine and homocysteine is a documented effect of the class, so a small rise is not automatically evidence of new renal disease. [2]
6. Pearl: Fenofibrate is the fibrate most convincingly linked to liver injury.
6. Why: All three agents used in the United States have been linked to clinically apparent acute liver injury, but fenofibrate most frequently and most convincingly, and the injury can evolve into chronic hepatitis with fibrosis and cirrhosis. [5]

Common exam traps

1. Trap: "Fibrates lower LDL cholesterol as effectively as statins."
1. Correction: Their main effect is on triglycerides. They do promote receptor-mediated clearance of LDL, but the atherosclerotic benefit is described as modest compared with the statins that remain first-line for hypercholesterolaemia. [2][4]
2. Trap: "Fibrate plus statin is simply an additive combination."
2. Correction: Fibrates can inhibit statin metabolism and increase myopathy risk, so the combination is generally avoided; gemfibrozil in particular has proved unsafe, and simvastatin is a contraindicated partner for it. [2][3]
3. Trap: "Clofibrate is still a standard fibrate."
3. Correction: It has been withdrawn from use, largely because of concerns about an increased risk of cancer. Gemfibrozil and fenofibrate are the members that remain in use in the United States. [5]

4. Trap: "Renal impairment merely calls for closer monitoring on a fibrate."

4. Correction: Severe renal dysfunction, including dialysis, is listed as a contraindication rather than a caution, and renal impairment also raises the myopathy risk when a fibrate is combined with a statin. [2][4]

Self-test questions

1. Question: Through which nuclear receptor do fibrates act?

1. The mineralocorticoid receptor
2. Peroxisome proliferator-activated receptor alpha
3. The farnesoid X receptor
4. The glucocorticoid receptor

1. Explanation: Fibrates activate transcription factors for peroxisome proliferator-activated receptors, and PPAR-alpha activation downregulates apolipoprotein C-III. The downstream result is increased lipoprotein lipase-mediated lipolysis of triglyceride-rich particles. [2][4]

2. Question: Which lipid abnormality are fibrates primarily used to treat?

1. Isolated low HDL cholesterol
2. Isolated elevated lipoprotein(a)
3. Hypertriglyceridaemia
4. Isolated elevated LDL cholesterol

2. Explanation: Fibrates are primarily used to lower triglycerides, and severe hypertriglyceridaemia of Fredrickson types IV and V is among their approved indications. Statins remain the first-line drugs where LDL cholesterol is the problem. [2][4]

3. Question: Why does HDL cholesterol rise on fibrate therapy?

1. Because hepatic production of apolipoprotein A-I and A-II is upregulated
2. Because cholesteryl ester transfer protein is inhibited
3. Because HDL particles are no longer filtered by the kidney
4. Because bile acid synthesis is blocked

3. Explanation: Fibrates increase HDL levels by upregulating hepatic production of apolipoprotein A-I and apolipoprotein A-II, which are the principal structural apolipoproteins of HDL. [2]

4. Question: Why is gemfibrozil singled out among fibrates for combination risk with statins?

1. It is the only fibrate that is renally excreted
2. It inhibits the OATP1B1 transporter and represses CYP2C8, raising statin exposure, and has proved unsafe in this combination
3. It is the only fibrate that activates PPAR-alpha
4. It has no effect on triglycerides and so adds nothing

4. Explanation: Gemfibrozil inhibits OATP1B1 and so increases exposure to substrates of that transporter, and it also represses CYP2C8. It has proved unsafe in combination with a statin, whereas bezafibrate and fenofibrate remain options. [2][3]

5. Question: Which condition is a contraindication to fibrate therapy?

1. Active gallbladder disease
2. Hypothyroidism
3. Well-controlled hypertension
4. Iron-deficiency anaemia

5. Explanation: Active gallbladder disease is a contraindication because PPAR-alpha-mediated downregulation of bile acids increases gallstone risk. Active liver disease and severe renal dysfunction are the other recorded contraindications. [2]

6. Question: Which fibrate has been withdrawn from use, and why?

1. Fenofibrate, because of chronic hepatitis

2. Gemfibrozil, because of rhabdomyolysis
3. Clofibrate, largely because of concerns about an increased risk of cancer
4. Bezafibrate, because of renal failure
6. Explanation: Clofibrate has been withdrawn from use, largely over concerns regarding an increased risk of cancer. Gemfibrozil and fenofibrate remain the fibrates used in the United States. [5]
7. Question: A patient on warfarin is started on a fibrate. What is the specific monitoring requirement?
1. No additional monitoring is required
2. Coagulation testing, with prothrombin time and INR followed frequently
3. Weekly full blood counts only
4. Serial echocardiography
7. Explanation: Fibrates interact with coumarin anticoagulants, and frequent monitoring of prothrombin time and INR is required. With gemfibrozil specifically, reduction of the anticoagulant dose and monitoring of the coagulation cascade is described. [2][3]

Frequently asked questions

1. Question: When is a fibrate preferred over a statin?
1. Answer: When triglycerides rather than LDL cholesterol are the problem. Fibrates are used primarily to lower triglycerides and are approved for severe hypertriglyceridaemia, whereas statins are the first-line drugs for hypercholesterolaemia. [2][4]
2. Question: Can a fibrate and a statin be taken together?
2. Answer: The combination is generally avoided because fibrates can inhibit statin metabolism and increase myopathy risk, and that risk is greater in older adults and in renal impairment. Gemfibrozil has proved unsafe for this pairing, while bezafibrate and fenofibrate remain options. [2][4]
3. Question: Why do fibrates cause gallstones?
3. Answer: Because PPAR-alpha-mediated downregulation of bile acids alters bile composition and increases the risk of stone formation. Gemfibrozil is separately described as enhancing the elimination of cholesterol into bile. [2][3]
4. Question: How much do fibrates lower triglycerides?
4. Answer: For gemfibrozil, a reduction of roughly 30% to 60% is described, achieved by upregulating lipoprotein lipase and by inhibiting the synthesis while increasing the clearance of very-low-density lipoprotein. [3]
5. Question: Are fibrates hard on the liver?
5. Answer: Mild to moderate transaminase elevations are common and often transient, but all three fibrates used in the United States have been linked to clinically apparent acute liver injury, fenofibrate most convincingly, and that injury can progress to chronic hepatitis. [5]

References

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