*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# Fenofibrate

**Evidence Summary**

Fenofibrate lowers blood lipids and may mitigate diabetic complications driven by vascular pathology. Neuroprotective benefits may be limited to males and those at early/preclinical stages.

**Neuroprotective Benefit:** Fenofibrate has anti-inflammatory, antioxidant, and vascular barrier protective properties through the activation of PPARα, but often requires pre-treatment for efficacy due to low BBB penetrance, and shows a strong sex effect.

**Aging and related health concerns:** Fenofibrate lowers blood lipid levels, but its ability to reduce cardiovascular risk may depend on genetics. It may reduce progression of diabetic retinopathy and diabetic neuropathy.

**Safety:** Fenofibrate is associated with liver enzyme elevations, with increased potential for hepatic toxicity when used with statins. Kidney dysfunction and muscle diseases have also been documented as rare, but serious adverse events.

**What is it?**

Fenofibrate is in a fibric acid derivative and belongs to the class of drugs known as fibrates (Rxlist). In the body it is rapidly metabolized into fenofibric acid, which is an activator of peroxisome proliferator-activated receptor alpha (PPARα), which is the primary mediator of its therapeutic activity. It is approved for primary hypercholesterolemia, mixed dyslipidemia, and severe hypertriglyceridemia to reduce elevated triglycerides, total cholesterol, LDL-c, and apolipoprotein B. Fenofibrate reduces lipids through activation of lipoprotein lipase, and inhibiting the lipase inhibitor, apoprotein-C-III. Fenofibrate is manufactured by AbbVie under the brand name TriCor®, but is also widely available as a generic medication. TriCor® is the original, but other branded formulations are also available including, Lofibra tablets, Fenoglide, Lipofen, and Triglide.

**Neuroprotective Benefit:** Fenofibrate has anti-inflammatory, antioxidant, and vascular barrier protective properties through the activation of PPARα, but often requires pre-treatment for efficacy due to low BBB penetrance, and shows a strong sex effect.

*Types of evidence:*

- 1 clinical trial for fenofibrate in NFLE
- 1 clinical trial for gemfibrozil in AD
- 2 observational studies for fibrates/lipid-lowering agent use and dementia risk
- Numerous laboratory studies

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function***:

The evidence regarding the role of lipid-lowering agents in reducing dementia risk has been mixed. While most studies have focused on statins, some have also examined fibrates as part of a broader analysis of lipid-lowering agents. Most studies have failed to find that the use of fibrates significantly affects dementia risk [1]. One observational study (n=342) found that Alzheimer's disease (AD) patients treated with lipid-lowering agents had a lower rate of cognitive decline in the Mini-Mental State Examination (MMSE) [2]. However, the effect attributable to fibrates is unclear since the cohort included patients treated with statins, fibrates, and other lipid-lowering agents (2:2:1, respectively). A study including 6,830 community-dwelling residents in France (≥65 years old) found that fibrate use was associated with an increased risk of decline in visual memory over 7 years in women (Hazard ratio [HR]:1.29, 95%CI 1.09 to 1.54, p=0.004), though there was no significant effect on incident dementia risk

[3]. The effect was driven by women with treatment resistant LDL-c that had received fibrates. It is unclear if having treatment resistant elevated LDL-c itself confers risk, or the fibrates play an active role in the visual memory decline. That the effect was only seen in women suggests that it may be tied to the fibrates. Preclinical studies in rodent models have clearly demonstrated a sex effect for fibrate use, and in some cases treatment with fenofibrate exacerbated inflammatory processes in females [4].

***Human research to suggest benefits to patients with dementia***:

Fenofibrate has not been tested as an intervention for dementia, however, a related fibrate,

gemfibrozil was recently tested in a Phase 1 clinical trial in patients with preclinical Alzheimer's disease and mild cognitive impairment (MCI) (n=72) (NCT02045056). Like fenofibrate, gemfibrozil exerts its lipid-lowering effects primarily through the activation of PPARα. The results of the study were presented at the 2019 CTAD conference which showed that over the one-year study, gemfibrozil lowered plasma levels of miR-107 (Alzforum.org). miR-107 is reduced in the AD brain, which may lead to increased BACE-1 expression, and plasma miR-107 is a candidate biomarker for cognitive impairment in AD. Preclinical studies suggest that fibrates increase levels of miR-107, thus the decrease in the clinical study was unexpected, and the clinical implications are unclear. There were also trends toward normalization of CSF Aβ42, p-tau, and p-tau/Aβ42 ratio, as well as trends toward reduced brain atrophy, reduced plasma TNFα, and better performance on memory tests. The lipid-lowering capacity has been shown to be more potent for fenofibrate than for gemfibrozil, but it is unclear how the efficacy of fenofibrate would compare to gemfibrozil in the context of neurogenerative disease. Larger confirmatory trials are needed.

***Mechanisms of action for neuroprotection identified from laboratory and clinical research***:

The neuroprotective activity of fenofibrate is largely derived from its ability to activate PPARα, which has roles in the regulation of mitochondria energetics, metabolism, inflammation, and oxidative stress responses [5]. However, fenofibrate and its active metabolite fenofibric acid have low capacity to cross the blood-brain-barrier (BBB), and do so slowly. As a result, many studies require pre-treatment with fenofibrate for several days or weeks to effectively activate protective pathways in the brain prior to the insult in order to confer resiliency. As a result, the clinical relevance in the context of established pathology/disease is questionable. In some cases, such as acute injuries involving inflammatory damage, the benefits may be more apparent, as preclinical studies suggest that many of its immune regulating properties occur in the periphery. Preclinical studies also show clear evidence of a sex effect for fenofibrate, with neuroprotective benefits primarily, or exclusively, seen in male animals.

**Alzheimer's disease:** POTENTIAL BENEFIT FOR ACTIVE METABOLITE AT PRECLINICAL STAGES (Shown in rodents)

Fenofibrate affects processes involved in Aβ generation and clearance. ***In vivo*, fenofibrate is rapidly metabolized, and effects are primarily mediated by its active metabolite, fenofibric acid, which is a PPARα agonist.** However, fenofibrate itself has additional activities, such that its effects *in vitro* do not necessarily replicate, and in some cases are antagonistic, to its reported effects *in vivo*. This suggests that the ability to metabolize fenofibrate could have an important impact on its therapeutic profile. Fenofibrate acts as an inverse gamma-secretase modulator, such that it promotes the amyloidogenic processing of amyloid precursor protein (APP) to favor production of Aβ42 over Aβ38, *in vitro* [6; 7; 8]. Additionally, fenofibrate inhibits the proteolytic degradation of Aβ42 in cell culture [9]. In contrast, fenofibric acid acts in the opposite manner, and leads to the enhancement of Aβ42 clearance in cell culture [9].

In AD rodent models, the biological effects of fenofibrate are mediated by its active metabolite fenofibric acid [8]. Fenofibrate has been shown to increase expression and activity of PPARα, mitigate impairments on memory tests, and in some models, reduce Aβ42 levels [10; 11]. However, the paradigms used are more consistent with a pretreatment approach, involving intervention at preclinical stages, which may not necessarily translate to clinical AD. In general, PPARα is considered a promising therapeutic target for neurodegenerative disease, primarily due to its effects on mitochondria, metabolism, oxidative stress, and inflammation [12]. Additionally, PPARα has been shown to play a role in cholinergic neurotransmission, and on synaptic plasticity through the regulation of brain derived neurotrophic factor (BDNF).

**Parkinson's disease**: POTENTIAL BENEFIT AT PRECLINICAL STAGES IN MALES (Shown in rats)

Fenofibrate (100 mg/kg) was shown to be neuroprotective in the MPTP model of PD in male rats, however, the clinical relevance of these findings is unclear. When administered as a pre-treatment starting five days before MPTP, fenofibrate treatment reduced oxidative stress, inflammation, dopaminergic loss, and spatial memory impairments [13]. When administered one hour after MPTP, fenofibrate similarly reduced oxidative stress and preserved dopamine levels, but did not prevent learning and memory impairments [14]. It has not been shown whether fenofibrate is protective in the context of chronic disease or in females.

**Amyotrophic lateral sclerosis:** POTENTIAL BENEFIT AT PRECLINICAL STAGES (Shown in mice)

In the SOD1$^{G93A}$ mouse model of ALS, treatment with fenofibrate (200 mg/kg/day i.p.) starting at postnatal day 40, which is prior to the onset of symptoms, delayed symptom onset from 85-88 days of age to 100 days of age [15]. This was related to attenuated loss of motor neurons in the spinal cord. This delay extended survival accordingly, to138 ± 5 days, as compared to 127 ± 3.4 days. The neuroprotection was associated with preservation of mitochondria, likely stemming from peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) activation, and a reduction in pro-inflammatory microglial activation. Unlike the vast majority of rodent studies assessing the neuroprotective effects of fenofibrate, this study used both male and female animals, though it was not reported whether there was a preferential effect in one sex.

**Stroke**: POTENTIAL BENEFIT AS PRETREATMENT ONLY IN MALES (Shown in rodents)

Fenofibrate has been shown to protect against cerebral ischemic injuries in stroke models in male rodents [12]. Fenofibrate was associated with reduced cell loss, inflammation, oxidative stress markers, and neurobehavioral deficits. The protective effects generally stem from pre-treatment with fenofibrate. Neuroprotective effects, particularly with respect to inflammation, have also been shown when administered close to the time of ischemic injury [4; 16; 17; 18]. Although some studies have shown benefits with post-treatment, others have failed to show an effect [19; 20; 21]. It is not clear how well this will translate to clinical practice if pre-treatment is needed for benefit. Fenofibrate and its metabolite fenofibric acid cross the BBB at a slow rate, and it is thought that many of the anti-inflammatory effects are mediated in the periphery through modulation of peripheral immune cells, which may subsequently migrate into the CNS and/or produce secreted factors that alter inflammatory phenotypes in the CNS [4]. The neuroprotective effects are only seen in males**.** Females have lower expression of PPARα and respond differently to PPARα activation. In rodent models, males and females treated with fenofibrate had differential immune activation, with females showing a more pro-inflammatory profile [4].

**Traumatic brain injury:** POTENTIAL BENEFIT IN MALES (Shown in rats)

Male rats treated with fenofibrate (50 mg/kg) at 1 or 6 hours following traumatic brain injury in the lateral fluid percussion model showed reduced brain edema and neurological deficits at 24 hours after injury [22]. The improved neurological recovery at 7 days was associated with reduced inflammation and oxidative stress [23]. Similar improvement was seen with fenofibrate and statins, though the combination was more effective than either one alone, in this model [24].

**Post-operative cognitive dysfunction:** POTENTIAL BENEFIT IN MALES (Shown in rats)

Pre-treatment with a fenofibrate-enriched diet (200 mg/kg) for 14 days prior to cardiopulmonary bypass surgery reduced neuronal loss, and memory impairments on the Y maze and passive avoidances tests 24 hours after the cardiac surgery in male rats [16]. Fenofibrate prevented surgery related endothelial dysfunction, and expression of inflammatory mediators, which may underlie the neuroprotective effect. The effect appears to be mediated by the upregulation of PPARα, as simvastatin, which has also been shown to exert anti-inflammatory effects in preclinical models of neurological injury through PPARα, showed similar neuroprotective benefits in this study. Due to the lower expression and potentially differential regulation of PPARα in females, they may not experience comparable benefit, though further testing is needed.

**Depression:** EXERTS ANTI-DEPRESSANT ACTIVITY IN MICE

Fenofibrate was shown to have antidepressant effects in rodent models through the activation of PPARα. Chronic stress decreases PPARα levels in the hippocampus, leading to reduced levels of PPARα at the CREB promoter, and a reduction in CREB-mediated production of BDNF [25]. Genetic overexpression of PPARα in the hippocampus has antidepressant-like activity, and the antidepressant fluoxetine increases expression of hippocampal PPARα, in mice. Treatment of male mice with fenofibrate inhibited depression-like phenotypes in mice to a similar degree as fluoxetine [26]. The protective effect was associated with the activation of PPARα and increased expression of BDNF.

**Epilepsy**: REDUCES SEIZURES IN NFLE

Fenofibrate, through activation of PPARα, inhibits β2-containing nicotinic acetylcholine receptors, and has been shown to protect against nicotine-induced seizures in mice [27]. Nocturnal frontal lobe epilepsy (NFLE) is an autosomal dominantly inherited form of epilepsy caused by mutations to nicotinic acetylcholine receptor subunits. In a clinical study, 11 individuals with pharmacoresistant NFLE were treated with fenofibrate (600 mg/day) for six months as an adjunctive therapy [27]. By the end of the study 8/11 were seizure free and the remaining individuals reduced epileptic episodes by >75%.

***APOE4 interactions***: Studies assessing whether ApoE variants have an impact on fenofibrate lipid-lowering capacity have been mixed, and inconclusive [28].

**Aging and related health concerns:** Fenofibrate lowers blood lipid levels, but its ability to reduce cardiovascular risk may depend on genetics. It may reduce progression of diabetic retinopathy and diabetic neuropathy.

*Types of evidence:*

- 8 meta-analyses and 2 systematic reviews
- 1 case-control study for fenofibrate use and retinal degeneration
- 3 gene association studies for fenofibrate response
- Numerous laboratory studies

**Lifespan**: EXTENDS LIFESPAN IN C. ELEGANS

In N2 strain *C. elegans*, the fibrates bezafibrate, clofibrate, and fenofibrate all extended lifespan (at 10 uM), with a mean increase of 2.1 days [29]. Fenofibrate extended the maximum lifespan by 6.5 days at 0.1 uM. The effect was dependent on PPARα, as extension of lifespan was not seen in strains lacking the PPARα ortholog nhr-49.

**Dyslipidemia/Hyperlipidemia:** BENEFIT, BUT GENETICS INFLUENCE EFFICACY

Fenofibrate is FDA approved for adults with severe hypertriglyceridemia, primary hypercholesterolemia, and mixed lipidemia. Meta-analyses and systematic reviews indicate that fenofibrate significantly decreases triglyceride and cholesterol levels, however, it tends to have a worse therapeutic profile relative to statins, which inhibit HMG-CoA reductase to lower cholesterol and can also engage PPARγ, and PPARα. In a meta-analysis of ten RCTs (n=477), fenofibrate decreased apolipoprotein C-III (apo C-III), a regulator of triglyceride metabolism, relative to placebo (weighted mean difference [WMD]: −4.78 mg/dL, 95% CI −6.95 to –2.61, p<0.001) [30]. In a systematic review of RCTs for fibrates, including seven RCTs for fenofibrate (n=12,398), fenofibrate decreased total cholesterol by 31.1 mg/dL, LDL by 24.7 mg/dL, and triglycerides by 23.5 mg/dL, and increased HDL by 1.1 mg/dL [31]. One area where fibrates may have an advantage over statins is in the reduction of Lp(a) in those with elevated Lp(a) at baseline. A meta-analysis of 16 head-to-head RCTs (n=1388) found that fibrates had a significantly greater reduction of Lp(a) than statins (WMD: –2.70 mg/dL, 95% CI –4.56 to –0.84; *P* = 0.004) [32]. Approximately half of the trials involved fenofibrate.

The greater heterogeneity in response to fenofibrate, relative to statins, likely stems from the findings that response to fenofibrate is influenced by genetics. The rs964184 polymorphism near APOA1 was found to be significantly associated with fenofibrate response for triglycerides and HDL in the GOLDN

(n=861) and HyperTG (n=267) cohorts [33]. Individuals with the rs964184 (G) polymorphism had higher HDL and triglyceride levels in response to fenofibrate. There was also an epistatic interaction between the rs10401969 variant near CILP2 and the rs4420638 variant in the APOE-APOC1-APOC4-APOC2 cluster with LDL-c and total cholesterol response to fenofibrate. A genome association study based on Caucasians in the GOLDN (n=813) and ACCORD (n=781) cohorts found that the locus near the pre-B-cell leukemia homeobox 4 (PBX4) gene on chromosome 19 is important for LDL-c response to fenofibrate ($p = 1.5\times10^{-8}$) [34].

Fenofibrate is also associated with systemic effects that may account for its worse safety profile, relative to statins. A meta-analysis of nine clinical trials (n= 2195) for fibrates found that fibrate therapy significantly increased circulating levels of cystatin C (WMD: 0.07 mg/dL, 95% CI 0.04 to 0.10, $p < .001$), and the effect was primarily attributed to fenofibrate, though it is unclear whether this increase is clinically meaningful [35]. Cystatin C levels are associated with worse kidney function, higher plasma homocysteine, and increased risk for cardiovascular disease. In a meta-analysis of 16 trials (n=6203) including fenofibrate or statins, plasma homocysteine levels were unchanged with statins, but increased with fenofibrate [36].

**Cardiovascular disease**: BENEFIT ONLY IN GENETICALLY DEFINED SUBSETS

There is heterogeneity in the reported effect of fenofibrate on cardiovascular disease, which may stem from genetic heterogeneity in different populations with respect to gene variants that influence fenofibrate efficacy and outcomes. The addition of fenofibrate to statin therapy was found to increase the risk of adverse events, without meaningfully improving patient outcomes relative to statin monotherapy, for the majority of patients [37]. As a result, the addition of fenofibrate to statin therapy is not generally recommended by the FDA or medical advisory groups. However, subgroup analyses indicate that certain subsets of patients may preferentially benefit from fenofibrate use [38].

A Cochrane review of 13 trials (n= 16,112), found that the use of currently available fibrates to prevent adverse cardiovascular events in individuals with pre-existing circulatory disease was not supported by the evidence [39]. A moderate quality of evidence in a separate Cochrane review involving six trials (n= 16,135) supports the use of fibrates for primary prevention of cardiovascular events in those without pre-existing disease [40]. The absolute risk reduction ranged from 5.0% to 4.3% over five years. In a systematic review of RCTs for fibrate therapy, fenofibrate randomized individuals had significantly fewer nonfatal myocardial infarctions relative to those randomized to placebo (158 vs 207). However, there was no significant effect for fibrate treatment on all-cause mortality (Odds ratio [OR]: 1.05; 95% CI 0.95 to 1.15). In a meta-analysis of trials involving statins with lipid-lowering agents, the inclusion of

fenofibrate did not significantly affect the risk for major adverse cardiovascular events, non-fatal myocardial infarctions, coronary heart disease, stroke, or all-cause mortality, relative to statins alone [41].

In a gene-association study derived from the ACCORD-Lipid trial including 3,065 white participants, a common variant at the PPARα locus (rs6008845, C/T) showed a significant influence on the effect of fenofibrate with respect to major cardiovascular events [42]. T/T homozygotes (36% of participants) had a 51% reduction in major cardiovascular events with fenofibrate treatment (HR: 0.49, 95% CI 0.34 to 0.72), while other genotypes (i.e., those with the C allele), did not show benefit ($P= 3.7 \times 10^{-4}$). This interaction was subsequently confirmed in an African American cohort (n=3059). Notably, the protective effect was seen even in participants without atherogenic dyslipidemia. The rs6008845 T variant is associated with lower expression of PPARα in the blood, and exerts its cardioprotective effect by enhancing the anti-inflammatory activity of fenofibrate. T/T individuals showed lower circulating levels of the proinflammatory and atherogenic chemokine CCL11/eotaxin. The rs6008845 variant could serve as stratification metric to identify individuals (T/T) who are most likely to derive therapeutic benefit from fenofibrate.

Fenofibrate has been shown to have beneficial effects on vascular endothelial cell function in preclinical models and some clinical studies. In a meta-analysis of RCTs involving fibrates, including 10 RCTs for fenofibrate, fenofibrate treatment was associated with increased flow-mediated dilation of the brachial artery (WMD:1.58%, 95% CI: 1.28, 1.88, $p < 0.001$), which is a measure of endothelium-dependent vasodilator function [43]. Fenofibrate has endothelial protective properties via the activation of PPARα and PGC-1α [44]. However, PPARα is known to have tissue-specific effects, and its activity can be influenced by the presence of other PPAR subtypes [12]. Therefore, the therapeutic effect of PPARα activation may depend on the tissue and other contextual factors. This may explain why benefit is more readily seen in some tissues, such as the retina, than others.

**Type 2 diabetes complications**

While the cardioprotective effects of fenofibrate in patients with type 2 diabetes were not apparent in the total clinical populations assessed in clinical trials [37], certain subsets were found to show a favorable response depending on their genetic makeup. The beneficial effects of fenofibrate for diabetic retinopathy and diabetic neuropathy appear to be more widespread.

***Diabetic retinopathy:*** POTENTIAL BENEFIT

A systematic review of five studies found that in type 2 diabetic patients with pre-existing retinopathy at baseline, micronized fenofibrate slowed the progression of retinopathy by 30 to 40% within 4 to 5 years [45]. In the FIELD study (n=9795), fenofibrate treatment showed a 79% reduction in the need for laser treatment for retinopathy (HR: 0.21, 95% CI 0.08 to 0.54; p = 0.0004), and reduced retinopathy progression by 34%. In the ACCORD study (n=10,251), there was a 40% reduction in retinopathy progression (OR: 0.60, 95% CI 0.42 to 0.87; p = 0.006). In the MacuFen study (n=110), fenofibrate significantly reduced total macular volume within 12 months, in the most diseased eyes (from 8.54 to 8.19 $mm^3$). A case-control study (n=89) involving individuals with type 2 diabetes found that those who had used fenofibrate had significantly thicker retinal nerve fiber layer (RNFL) thickness of the superior quadrant of the right eye relative to those who had not used fenofibrate [46]. These effects were independent of the lipid lowering activity of fenofibrate, and the changes in RNFL were not associated with blood lipid levels. Similarly, a meta-analysis of seven studies found that serum triglyceride level was not associated with the presence of diabetic retinopathy, and that fenofibrate showed clinical benefit for diabetic retinopathy cases [47]. These studies suggest that fenofibrate treatment early in the disease course may slow progression. There are currently four active clinical trials testing fenofibrate for diabetic retinopathy (Clinicaltrials.gov).

Based on preclinical models, the protective effects appear to be related to the activation of PPARα in the retina, particularly in vascular endothelial cells and pericytes [48]. PPARα is downregulated in the diabetic retina, which can lead to the loss of vascular cells, resulting in disrupting barrier function, and ultimately leading to inflammation and neovascularization. The restoration of PPARα by fenofibrate strengthens the barrier and mitigates these deleterious effects.

***Diabetic neuropathy:*** POTENTIAL BENEFIT

Nerve damage stemming from high blood glucose levels can lead to pain and numbness, and in severe cases, it can result in amputation. In the FIELD trial (n=9795), fenofibrate reduced the incidence of new neuropathy by 18% and reversed baseline neuropathy by 23% [49]. Fenofibrate also reduced the risk of any amputation by 37% relative to placebo [45]. This effect was not influenced by the level of glycemic control or dyslipidemia. There is an active clinical trial testing fenofibrate for diabetic neuropathy (NCT03869931).

In preclinical models, fenofibrate protected against diabetic peripheral neuropathy via upregulation of the PPARα-AMPK-PGC-1α-eNOS pathway [44]. The protection involved a reduction of inflammation and oxidative stress, thereby reducing the progression of endothelial damage. It also had impacts on the neural tissue, through the reduction of nerve fibrosis.

**Cancer**: POTENTIAL BENEFIT AS AN ADJUNCT

A case report indicates that a 52-year-old woman with inflammatory hepatocellular adenoma received fenofibrate (400 mg/day), and by six months her biochemistry parameters had normalized and the lesion area was reduced by 50% [50]. Further tumor regression was apparent with continued treatment.

Fenofibrate has shown evidence of anti-cancer properties in preclinical models, particularly in tumor cells of neuroectodermal origin, such as in glioblastoma [51]. Unlike its activity in other conditions, the anti-tumor activity of fenofibrate in cancer cell lines is largely independent of PPARα [50]. Fenofibrate treatment leads to cell cycle arrest and the induction of cell death by a variety of mechanisms, including the induction of oxidative stress. One of the identified mechanisms involves the impairment of mitochondrial respiration leading to a depletion of ATP. This effect is mediated by fenofibrate itself, not by its active metabolite, fenofibric acid. The decreased ability of the cancer cells to metabolize fenofibrate to fenofibric acid appears to account for the increased sensitivity of cancer cells to this mitochondrial toxicity, which is not seen in healthy cells [51]. This suggests that the toxicity may occur under conditions where fenofibrate is not efficiently metabolized into fenofibric acid *in vivo*, and may explain why some individuals are more susceptible to adverse events, though this would need to be confirmed. Despite the promise in cell culture, fenofibrate crosses the BBB very poorly, making it ineffective for CNS cancers, such as glioblastoma, *in vivo*. Efforts are underway to develop chemically modified versions that have increased stability, solubility, and tissue penetrance [52]. These compounds also convert to fenofibric acid at a slower rate, which allows greater accumulation of the compound with potent anti-tumor activity within the tumor tissues. It is unclear whether these compounds have a higher potential for toxicity toward non-tumor tissues.

**Safety:** Fenofibrate is associated with liver enzyme elevations, with increased potential for hepatic toxicity when used with statins. Kidney dysfunction and muscle diseases have also been documented as rare, but serious adverse events.

*Types of evidence:*

- 1 meta-analysis of adverse events in 13 fenofibrate-statin RCTs
- FDA prescribing label of TriCor® (fenofibrate)
- 1 review of medical practice recommendations for fenofibrate use
- 1 systematic review of kidney-related outcomes in fenofibrate studies
- Numerous laboratory studies

The FDA label for fenofibrate (TriCor®) contains warnings for increases in liver enzymes (serum transaminases), increases in serum creatine, and increased risk for gallstones (cholelithiasis). These are consistent with the most common adverse events (>2%) that occurred with greater frequency than placebo in clinical trials, which include abnormal liver tests, increased aspartate transaminase (AST), increased alanine aminotransferase (ALT), increased creatine phosphokinase, and rhinitis. Based on this profile, it is contraindicated in those with severe kidney dysfunction, liver disease, or gallstones.

A medical summary for clinicians lists headache, dizziness, back pain, joint pain, diarrhea, dyspepsia, cough, wheezing, nasopharyngitis, and flu-like symptoms as the most common adverse events with fenofibrate [53]. Severe adverse events include elevated liver enzymes, elevated creatine phosphokinase, gallstone development, arrhythmia exacerbation, pulmonary embolism, pancreatitis, agranulocytosis, and myocardial infarction. Due to the risks involving the kidney and liver, it is **recommended that clinicians regularly monitor the kidney function and liver function of patients treated with fenofibrate**. Creatine phosphokinase levels should be monitored regarding potential risk for myopathy and rhabdomyolysis (the breakdown of damaged muscle), which are rare effects primarily associated with the use of fenofibrate in combination with statins.

Studies examining the effects of fenofibrate on kidney function markers and assessing its clinical relevance have been mixed. Fenofibrate has been found to increase the production of creatine, thus, in individuals with normal kidney function, the elevated creatine levels are generally not associated with changes in the glomerular filtration rate (eGFR) or indicative of impaired kidney function [54]. In contrast, fenofibrate is associated with kidney toxicity in those with severely impaired kidney function, which is why it is contraindicated in this population. The effect in those with mild kidney disease is unclear, as some benefits on microalbuminuria have been reported in the context of diabetic nephropathy. The outcome may be related to the dose, the presence of comorbidities, and sex. Higher doses of fenofibrate increase the risk of kidney toxicity, and the concomitant use of calcium channel blockers also increases risk. Women may be at higher risk for adverse outcomes, as case reports have linked fenofibrate use with renal failure in women.

The use of fenofibrate in combination with statins is generally not recommended, based on clinical trials reporting an increased incidence of side effects without an increase in therapeutic benefit. A meta-analysis of 13 RCTs (n= 7712) involving the use of statins with fenofibrate found that aminotransferase elevations were more common in the combination group relative to statins alone (OR:1.66; 95% CI 1.17 to 2.37; $P < 0.05$) [55]. The increased risk for hepatic toxicity was only apparent in trials shorter than 12 months, suggesting that the effect on the liver may be transient, and subsequently stabilize with continued treatment. While myopathy and rhabdomyolysis were reported with the use of fenofibrate

with statins, the incidence of muscle-related adverse events and elevation of creatine phosphokinase was not significantly different in the combination group relative to statins alone, in this meta-analysis.

*Sex effect*: Preclinical studies support a sex effect for fenofibrate, with females showing less therapeutic benefit and increased risk for adverse events.

***Drug interactions***: The FDA label for fenofibrate (TriCor®) lists drug interactions with coumarin anticoagulants, immunosuppressants, bile acid resins, and colchicine. The simultaneous use of fenofibrate with cholestyramine, colesevelam, or colestipol will decrease the efficacy of fenofibrate, so they should be taken at different times of day from one another (Drugs.com).

**Sources and dosing:**

Fenofibrate is available by prescription through the brand name TriCor® made by AbbVie, through other branded formulations Lofibra tablets, Fenoglide, Lipofen, and Triglide, or as a generic version. The exact dosing depends on the formulation, the range is 43-54mg to 120-200 mg. TriCor® is dosed at 48 mg to145 mg once per day, orally, and bioavailability is improved if it is taken with food. TriCor® is available as 48 mg or 145 mg tablets.

**Research underway:**

There are currently 10 active clinical trials testing fenofibrate on Clincaltrials.gov. The tested indications include, type 2 diabetes, diabetic retinopathy, diabetic neuropathy, metabolic syndrome, coronary artery disease (in combination with statins), and Covid-19.

**Search terms:**

Pubmed, Google:  Fenofibrate

- Alzheimer's disease, Parkinson's disease, neurodegeneration, stroke, cardiovascular, lifespan, diabetes, cancer, meta-analysis, systematic reviews, safety

Websites visited for Fenofibrate:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem

- DrugBank.ca

**References:**

1. Shepardson NE, Shankar GM, Selkoe DJ (2011) Cholesterol Level and Statin Use in Alzheimer Disease: II. Review of Human Trials and Recommendations. *Archives of Neurology* **68**, 1385-1392.https://doi.org/10.1001/archneurol.2011.242.

2. Masse I, Bordet R, Deplanque D *et al.* (2005) Lipid lowering agents are associated with a slower cognitive decline in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry* **76**, 1624-1629.https://jnnp.bmj.com/content/jnnp/76/12/1624.full.pdf.

3. Ancelin M-L, Carrière I, Barberger-Gateau P *et al.* (2012) Lipid lowering agents, cognitive decline, and dementia: the three-city study. *J Alzheimers Dis* **30**, 629-637.https://pubmed.ncbi.nlm.nih.gov/22451317 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3743740/.

4. Dotson AL, Wang J, Chen Y *et al.* (2016) Sex differences and the role of PPAR alpha in experimental stroke. *Metab Brain Dis* **31**, 539-547.https://pubmed.ncbi.nlm.nih.gov/26581674 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4864150/.

5. Sáez-Orellana F, Octave J-N, Pierrot N (2020) Alzheimer's Disease, a Lipid Story: Involvement of Peroxisome Proliferator-Activated Receptor $\alpha$. *Cells* **9**, 1215.https://pubmed.ncbi.nlm.nih.gov/32422896 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7290654/.

6. Isoo N, Sato C, Miyashita H *et al.* (2007) Ab42 Overproduction Associated with Structural Changes in the Catalytic Pore of Secretase: COMMON EFFECTS OF PEN-2 N-TERMINAL ELONGATION AND FENOFIBRATE. *Journal of Biological Chemistry* **282**, 12388-12396.https://doi.org/10.1074/jbc.M611549200.

7. Lessard CB, Cottrell BA, Maruyama H *et al.* (2015) $\gamma$-Secretase Modulators and APH1 Isoforms Modulate $\gamma$-Secretase Cleavage but Not Position of $\varepsilon$-Cleavage of the Amyloid Precursor Protein (APP). *PLOS ONE* **10**, e0144758.https://doi.org/10.1371/journal.pone.0144758.

8. Kukar T, Murphy MP, Eriksen JL *et al.* (2005) Diverse compounds mimic Alzheimer disease–causing mutations by augmenting A$\beta$42 production. *Nature Medicine* **11**, 545-550.https://doi.org/10.1038/nm1235.

9. Abdul-Hay SO, Edirisinghe P, Thatcher GRJ (2009) Selective modulation of amyloid-$\beta$ peptide degradation by flurbiprofen, fenofibrate, and related compounds regulates A$\beta$ levels. *Journal of Neurochemistry* **111**, 683-695.https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1471-4159.2009.06355.x.

10. Assaf N, El-Shamarka ME, Salem NA *et al.* (2020) Neuroprotective effect of PPAR alpha and gamma agonists in a mouse model of amyloidogenesis through modulation of the Wnt/beta catenin pathway via targeting alpha- and beta-secretases. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **97**, 109793.https://www.sciencedirect.com/science/article/pii/S0278584619305287.

11. Zhang H, Gao Y, Qiao P-f *et al.* (2014) Fenofibrate reduces amyloidogenic processing of APP in APP/PS1 transgenic mice via PPAR-$\alpha$/PI3-K pathway. *International Journal of Developmental Neuroscience* **38**, 223-231.https://onlinelibrary.wiley.com/doi/abs/10.1016/j.ijdevneu.2014.10.004.

12. Wójtowicz S, Strosznajder AK, Jeżyna M *et al.* (2020) The Novel Role of PPAR Alpha in the Brain: Promising Target in Therapy of Alzheimer's Disease and Other Neurodegenerative Disorders. *Neurochemical Research* **45**, 972-988.https://doi.org/10.1007/s11064-020-02993-5.

13. Uppalapati D, Das NR, Gangwal RP *et al.* (2014) Neuroprotective Potential of Peroxisome Proliferator Activated Receptor-$\alpha$ Agonist in Cognitive Impairment in Parkinson's Disease: Behavioral, Biochemical, and PBPK Profile. *PPAR Research* **2014**, 753587.https://doi.org/10.1155/2014/753587.

14. Barbiero JK, Santiago R, Tonin FS *et al.* (2014) PPAR-$\alpha$ agonist fenofibrate protects against the damaging effects of MPTP in a rat model of Parkinson's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **53**, 35-44.https://www.sciencedirect.com/science/article/pii/S0278584614000396.

15. Esmaeili MA, Yadav S, Gupta RK *et al.* (2015) Preferential PPAR-$\alpha$ activation reduces neuroinflammation, and blocks neurodegeneration in vivo. *Human Molecular Genetics* **25**, 317-327.https://doi.org/10.1093/hmg/ddv477.

16. Ouk T, Amr G, Azzaoui R *et al.* (2016) Lipid-lowering drugs prevent neurovascular and cognitive consequences of cardiopulmonary bypass. *Vascular Pharmacology* **80**, 59-66.https://www.sciencedirect.com/science/article/pii/S1537189116000033.

17. Altintas O, Altintas MO, Aydin MS *et al.* (2017) Neuroprotective Effects of Chronic Fenofibrate Treatment via Modulating the Immunoreactivity of Cleaved Caspase-3 in Stroke Induced by Transient Middle Cerebral Artery Occlusion Rat Model. *Turkish neurosurgery* **27**, 522-529

18. Shehata AHF, Ahmed A-SF, Abdelrehim AB *et al.* (2020) The impact of single and combined PPAR-$\alpha$ and PPAR-$\gamma$ activation on the neurological outcomes following cerebral ischemia reperfusion. *Life Sciences* **252**, 117679.https://www.sciencedirect.com/science/article/pii/S0024320520304276.

19. Xuan A-G, Chen Y, Long D-H *et al.* (2015) PPAR$\alpha$ Agonist Fenofibrate Ameliorates Learning and Memory Deficits in Rats Following Global Cerebral Ischemia. *Molecular Neurobiology* **52**, 601-609.https://doi.org/10.1007/s12035-014-8882-7.

20. Ouk T, Gautier S, Pétrault M *et al.* (2014) Effects of the PPAR-$\alpha$ agonist fenofibrate on acute and short-term consequences of brain ischemia. *J Cereb Blood Flow Metab* **34**, 542-551.https://pubmed.ncbi.nlm.nih.gov/24398933 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3948136/.

21. Deplanque D, Gelé P, Pétrault O *et al.* (2003) Peroxisome proliferator-activated receptor-alpha activation as a mechanism of preventive neuroprotection induced by chronic fenofibrate treatment. *J Neurosci* **23**, 6264-6271.https://pubmed.ncbi.nlm.nih.gov/12867511 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6740545/.

22. Besson VC, Chen XR, Plotkine M *et al.* (2005) Fenofibrate, a peroxisome proliferator-activated receptor $\alpha$ agonist, exerts neuroprotective effects in traumatic brain injury. *Neuroscience Letters* **388**, 7-12.https://www.sciencedirect.com/science/article/pii/S0304394005006907.

23. Chen XR, Besson VC, Palmier B *et al.* (2007) Neurological Recovery-Promoting, Anti-Inflammatory, and Anti-Oxidative Effects Afforded by Fenofibrate, a PPAR Alpha Agonist, in Traumatic Brain Injury. *Journal of Neurotrauma* **24**, 1119-1131.https://www.liebertpub.com/doi/abs/10.1089/neu.2006.0216.

24. Chen XR, Besson VC, Beziaud T *et al.* (2008) Combination Therapy with Fenofibrate, a Peroxisome Proliferator-Activated Receptor $\alpha$ Agonist, and Simvastatin, a 3-Hydroxy-3-methylglutaryl-Coenzyme A Reductase Inhibitor, on Experimental Traumatic Brain Injury. *Journal of Pharmacology and Experimental Therapeutics* **326**, 966-974.https://jpet.aspetjournals.org/content/jpet/326/3/966.full.pdf.

25. Song L, Wang H, Wang Y-J *et al.* (2018) Hippocampal PPAR $\alpha$ is a novel therapeutic target for depression and mediates the antidepressant actions of fluoxetine in mice. *British Journal of Pharmacology* **175**, 2968-2987.https://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/bph.14346.

26. Jiang B, Wang Y-J, Wang H *et al.* (2017) Antidepressant-like effects of fenofibrate in mice via the hippocampal brain-derived neurotrophic factor signalling pathway. *British Journal of Pharmacology* **174**, 177-194.https://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/bph.13668.

27. Puligheddu M, Melis M, Pillolla G *et al.* (2017) Rationale for an adjunctive therapy with fenofibrate in pharmacoresistant nocturnal frontal lobe epilepsy. *Epilepsia* **58**, 1762-1770.https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.13863.

28. Feitosa MF, An P, Ordovas JM *et al.* (2011) Association of gene variants with lipid levels in response to fenofibrate is influenced by metabolic syndrome status. *Atherosclerosis* **215**, 435-439.https://pubmed.ncbi.nlm.nih.gov/21324458 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3777277/.

29. Brandstädt S, Schmeisser K, Zarse K *et al.* (2013) Lipid-lowering fibrates extend C. elegans lifespan in a NHR-49/PPARalpha-dependent manner. *Aging (Albany NY)* **5**, 270-275.https://pubmed.ncbi.nlm.nih.gov/23603800 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3651519/.

30. Sahebkar A, Simental-Mendía LE, Katsiki N *et al.* (2018) Effect of fenofibrate on plasma apolipoprotein C-III levels: a systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open* **8**, e021508.https://bmjopen.bmj.com/content/bmjopen/8/11/e021508.full.pdf.

31. Abourbih S, Filion KB, Joseph L *et al.* (2009) Effect of Fibrates on Lipid Profiles and Cardiovascular Outcomes: A Systematic Review. *The American Journal of Medicine* **122**, 962.e961-962.e968.https://www.sciencedirect.com/science/article/pii/S0002934309004902.

32. Sahebkar A, Simental-Mendía LE, Watts GF *et al.* (2017) Comparison of the effects of fibrates versus statins on plasma lipoprotein(a) concentrations: a systematic review and meta-analysis of head-to-head randomized controlled trials. *BMC Med* **15**, 22-22.https://pubmed.ncbi.nlm.nih.gov/28153024 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5290642/.

33. Aslibekyan S, Goodarzi MO, Frazier-Wood AC *et al.* (2012) Variants Identified in a GWAS Meta-Analysis for Blood Lipids Are Associated with the Lipid Response to Fenofibrate. *PLOS ONE* **7**, e48663.https://doi.org/10.1371/journal.pone.0048663.

34. Irvin MR, Rotroff DM, Aslibekyan S *et al.* (2016) A genome-wide study of lipid response to fenofibrate in Caucasians: a combined analysis of the GOLDN and ACCORD studies. *Pharmacogenet Genomics* **26**, 324-333.https://pubmed.ncbi.nlm.nih.gov/27002377 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4986826/.

35. Sahebkar A, Simental-Mendía LE, Pirro M *et al.* (2018) Impact of fibrates on circulating cystatin C levels: a systematic review and meta-analysis of clinical trials. *Annals of Medicine* **50**, 485-493.https://doi.org/10.1080/07853890.2018.1495338.

36. Sahebkar A, Pirro M, Reiner Ž *et al.* (2016) A Systematic Review and Meta-Analysis of Controlled Trials on the Effects of Statin and Fibrate Therapies on Plasma Homocysteine Levels. *Current medicinal chemistry* **23**, 4490-4503

37. (2010) Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *New England Journal of Medicine* **362**, 1563-1574.https://www.nejm.org/doi/full/10.1056/NEJMoa1001282.

38. Elam M, Lovato L, Ginsberg H (2011) The ACCORD-Lipid study: implications for treatment of dyslipidemia in Type 2 diabetes mellitus. *Clin Lipidol* **6**, 9-20.https://pubmed.ncbi.nlm.nih.gov/26207146 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4509601/.

39. Wang D, Liu B, Tao W *et al.* (2015) Fibrates for secondary prevention of cardiovascular disease and stroke. *Cochrane Database of Systematic Reviews*.https://doi.org//10.1002/14651858.CD009580.pub2.

40. Jakob T, Nordmann AJ, Schandelmaier S *et al.* (2016) Fibrates for primary prevention of cardiovascular disease events. *Cochrane Database of Systematic Reviews*.https://doi.org//10.1002/14651858.CD009753.pub2.

41. Ip C-k, Jin D-m, Gao J-j *et al.* (2015) Effects of add-on lipid-modifying therapy on top of background statin treatment on major cardiovascular events: A meta-analysis of randomized controlled trials. *International Journal of Cardiology* **191**, 138-148.https://www.sciencedirect.com/science/article/pii/S0167527315009626.

42. Morieri ML, Shah HS, Sjaarda J *et al.* (2020) PPARA Polymorphism Influences the Cardiovascular Benefit of Fenofibrate in Type 2 Diabetes: Findings From ACCORD-Lipid. *Diabetes* **69**, 771-783.https://diabetes.diabetesjournals.org/content/diabetes/69/4/771.full.pdf.

43. Sahebkar A, Giua R, Pedone C *et al.* (2016) Fibrate therapy and flow-mediated dilation: A systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacological Research* **111**, 163-179.https://www.sciencedirect.com/science/article/pii/S1043661816301530.

44. Cho YR, Lim JH, Kim MY *et al.* (2014) Therapeutic Effects of Fenofibrate on Diabetic Peripheral Neuropathy by Improving Endothelial and Neural Survival in db/db Mice. *PLOS ONE* **9**, e83204.https://doi.org/10.1371/journal.pone.0083204.

45. Czupryniak L, Joshi SR, Gogtay JA *et al.* (2016) Effect of micronized fenofibrate on microvascular complications of type 2 diabetes: a systematic review. *Expert Opinion on Pharmacotherapy* **17**, 1463-1473.https://doi.org/10.1080/14656566.2016.1195811.

46. Liu X, Machado GC, Eyles JP *et al.* (2018) Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. *British Journal of Sports Medicine* **52**, 167-175.https://bjsm.bmj.com/content/bjsports/52/3/167.full.pdf.

47. Zhou Y, Wang C, Shi K *et al.* (2018) Relationship between dyslipidemia and diabetic retinopathy: A systematic review and meta-analysis. *Medicine (Baltimore)* **97**, e12283-e12283.https://pubmed.ncbi.nlm.nih.gov/30200172 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6133445/.

48. Stewart S, Lois N (2018) Fenofibrate for Diabetic Retinopathy. *The Asia-Pacific Journal of Ophthalmology* **7**, 422-426.https://journals.lww.com/apjoo/Fulltext/2018/11000/Fenofibrate_for_Diabetic_Retinopathy.8.aspx.

49. Rajamani K, Donoghoe M, Li L *et al.* (2010) Abstract 18987: Fenofibrate Reduces Peripheral Neuropathy in Type 2 Diabetes: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Circulation* **122**, A18987-A18987.https://www.ahajournals.org/doi/abs/10.1161/circ.122.suppl_21.A18987

50. Lian X, Wang G, Zhou H *et al.* (2018) Anticancer Properties of Fenofibrate: A Repurposing Use. *J Cancer* **9**, 1527-1537.https://pubmed.ncbi.nlm.nih.gov/29760790 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5950581/.

51. Wilk A, Wyczechowska D, Zapata A *et al.* (2015) Molecular mechanisms of fenofibrate-induced metabolic catastrophe and glioblastoma cell death. *Mol Cell Biol* **35**, 182-198.https://pubmed.ncbi.nlm.nih.gov/25332241 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4295376/.

52. Stalinska J, Zimolag E, Pianovich NA *et al.* (2019) Chemically Modified Variants of Fenofibrate with Antiglioblastoma Potential. *Translational Oncology* **12**, 895-907.https://www.sciencedirect.com/science/article/pii/S1936523319300361.

53. Sidhu G, J T (Updated 2020 Jun 25. ) Fenofibrate. *In: StatPearls [Internet]* **Treasure Island (FL): StatPearls Publishing**.https://www.ncbi.nlm.nih.gov/books/NBK559219/.

54. Emami F, Hariri A, Matinfar M *et al.* (2020) Fenofibrate-induced renal dysfunction, yes or no? *J Res Med Sci* **25**, 39-39.https://pubmed.ncbi.nlm.nih.gov/32582345 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7306240/.

55. Geng Q, Ren J, Chen H *et al.* (2013) Adverse events following statin–fenofibrate therapy versus statin alone: A meta-analysis of randomized controlled trials. *Clinical and Experimental Pharmacology and Physiology* **40**, 219-226.https://onlinelibrary.wiley.com/doi/abs/10.1111/1440-1681.12053.