

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.

Pentoxifylline

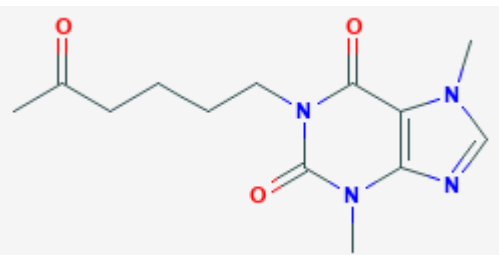
Evidence Summary

May help protect against vascular damage by reducing inflammation and blood viscosity. Has low potency as a monotherapy and its efficacy is enhanced when used in combination with other agents.

Neuroprotective Benefit: May help protect against cerebrovascular dysfunction by reducing inflammation and promoting blood flow.

Aging and related health concerns: May protect against minor inflammation or oxidative stress damage in the vasculature, kidney, and liver. May help mitigate cancer treatment-associated fibrosis. Benefits observed typically as combination rather than monotherapy.

Safety: Generally well-tolerated with mild nausea as the primary side effect. Associated with an increased risk for bleeding.

Availability: Rx, approved for intermittent claudication	Dose: 400 mg oral 3X daily for intermittent claudication	Chemical formula: C ₁₃ H ₁₈ N ₄ O ₃ MW: 278.312 g/mol  Source: PubChem
Half-life: 0.4-0.8 hours	BBB: Penetrant	
Clinical trials: Many RCTs, but majority <300 people. Multiple RCTs for: vascular dementia, stroke, intermittent claudication, venous leg ulcers, heart failure, kidney disease, liver disease, and cancer.	Observational studies: None	

What is it? Pentoxifylline, also known as oxpentifylline, is a methylxanthine that was approved for intermittent claudication in Europe in 1972 and in the US in 1985 [1]. It improves blood flow by decreasing blood viscosity. It reduces the aggregation and activation of blood cells, primarily erythrocytes and neutrophils, which improves their ability to flow through the vasculature. Its inhibition of blood cell activation also produces anti-inflammatory and antioxidant effects. Pentoxifylline is a non-selective phosphodiesterase (PDE) inhibitor, with similar affinity to PDE 1, 3, 4, and 5 subtypes, and generally has lower potency than more subtype selective inhibitors [2]. Its mechanisms of action *in vivo* are not completely understood because most *in vitro* mechanistic studies have used concentrations far higher than the levels found in human plasma after administration of the standard dose. Much of its biological activity is expected to come from its major metabolites, which are found in higher concentrations in the plasma than pentoxifylline itself [2]. While pentoxifylline has been tested in numerous clinical trials for a variety of indications, the majority of these trials were conducted outside of the US, and their interpretability is limited by small sample sizes and other methodological design flaws. Current development efforts are largely focused on its use as adjunct to mitigate side effects stemming from cancer therapies.

Neuroprotective Benefit: May help protect against cerebrovascular dysfunction by reducing inflammation and promoting blood flow.

Types of evidence:

- 1 systematic review for vascular dementia (n=4 RCT, n=469 patients)
- 5 RCT (Mental deterioration n=80, Parkinson's disease n=11, ALS n=400, Stroke prevention n=66, Major depressive disorder n=80)
- Numerous laboratory studies

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

Pentoxifylline has not been directly tested for its ability to improve cognitive function, but its projected mechanisms of action affect processes implicated in risk for cognitive decline. While this suggests that pentoxifylline may be useful for dementia prevention, long-term prospective or retrospective studies evaluating the ability of pentoxifylline to reduce dementia incidence in high-risk populations have not been conducted. Although most suffer from methodological design flaws, such as underpowering, the clinical trials that have been conducted thus far have been fairly consistent in showing that, as a monotherapy, pentoxifylline tends to have little or no clinically meaningful benefit, but **may improve outcomes when used as a part of a combination therapy**. This likely stems from weak *in vivo* biological activity on the relevant targets at the standard clinical dose.

Depression: Potential benefit (in combination with SSRI)

Some studies indicate that depression may be a risk factor for dementia [3]. In a 12-week, placebo-controlled, double-blind RCT of adults with major depressive disorder (n=80, age 24-53), the addition of pentoxifylline (400 mg TID) to selective serotonin reuptake inhibitor (SSRI) therapy (20 mg escitalopram), significantly improved depression, based on a reduction in the Hamilton Depression Rating Scale (HAM-D) (least squared mean difference=-3.49, P = 0.000) [4]. The benefits are thought to stem from the reduction of inflammation and oxidative stress. In a rat model of stress, pentoxifylline alleviated memory impairments, and restored levels of the antioxidant glutathione and brain derived neurotrophic factor (BDNF) [5]. Similarly, in the RCT, there was a positive correlation between the reduction of the HAM-D score with the reduction of serum biomarkers of inflammation and oxidative stress (TNF α , IL-6, 8-OHdG), and an inverse correlation between HAM-D score with the induction of BDNF [4]. Whether pentoxifylline offers significant benefits in the absence of an SSRI has not been established.

Stroke: Potential minor benefit

Stroke is the major risk factor for vascular dementia. A meta-analysis of 4 RCTs (n=90, 110, 264, 297) testing pentoxifylline for acute ischemic stroke found a **non-significant reduction in mortality** by 35% (95% Confidence Interval (CI) 59% reduction to 4% increase) within 4 weeks of the stroke odds ratio (OR): 0.64, (95% CI 0.41 to 1.02) [6]. There was an inadequate level of evidence to determine whether there was an impact on neurological disability. One of the RCTs found that neurological deficit scores improved over 4 weeks in both the pentoxifylline and placebo groups, suggesting that patients with mild stroke are likely to improve irrespective of treatment. Patients with the most deficit at baseline appeared to benefit most, although it was still only a trend toward improved neurological deficit scores relative to placebo (Change in total neurological deficit scores compared to baseline 9.73 ± 2.68 , n = 75 vs. 5.29 ± 3.17 , n = 70; P = 0.118) [7]. The low level of observed benefit may be related to the timing of the intervention, as this latter trial was the only one in the meta-analysis to administer pentoxifylline within 12 hours of stroke onset [6]. In preclinical rodent stroke models, modestly protective effects in terms of reducing infarct size, blood brain barrier (BBB) permeability, edema, and neurological dysfunction were achieved when pentoxifylline was given before or up to 3 hours after cerebrovascular injury [8; 9; 10]. While this suggests that pentoxifylline may not be able to be administered early enough to mitigate damage in most stroke patients in a clinical setting, it may be able to help prevent future strokes. In a one-year follow-up study of stroke patients, pentoxifylline (400 mg TID) was able to **lower the incidence of new transient ischemic attacks** (10% vs 28% with aspirin-dipyridamole, P<0.05) [11].

Human research to suggest benefits to patients with dementia:

Vascular dementia: Potential benefit

Multi-infarct dementia involves memory loss due to a disruption of blood flow to the brain following multiple strokes. Pentoxifylline is expected to be beneficial for vascular dementia based on its abilities to promote blood flow. A systematic review of 4 double-blind, placebo-controlled RCTs for vascular dementia, primarily multi-infarct dementia, found only one study where pentoxifylline treatment was associated with significantly improved cognitive outcomes for the entire study population [12]. However, significant improvements in primary outcome measures of cognitive function relative to placebo were found in all the studies within the subpopulation that met a stricter criterion for vascular dementia. A meta-analysis could not be performed due to the heterogeneity in the analytic techniques and diagnostic criteria used across the trials. Pentoxifylline is thought to be beneficial for vascular dementia based on its ability to promote cerebrovascular blood flow. In patients with cerebrovascular

disease, pentoxifylline treatment (400 mg TID) for 4 or 8 weeks was shown to **enhance cerebral blood flow** by approximately 16%, based on $^{133}\text{Xenon}$ clearance. Notably, the greatest increases in regional blood flow occurred in areas that were hypoxemic (20-40%) [13; 14].

Mental deterioration: Potential benefit (in combination with piracetam)

In a placebo-controlled RCT, patients within 6 months of the onset of clinical mental deterioration ($n=80$, age 72 ± 1) were tested for the ability of pentoxifylline (400 mg TID), piracetam (1600 TID), or the combination, to affect neuropsychological and hematological parameters [15]. Pentoxifylline increased whole blood filterability (+24% at 28 weeks, $P<0.01$), while piracetam improved long-term memory by 31%, relative to placebo, based on the 15W test. With combination treatment, the hematological effects were driven solely by pentoxifylline, but there was a synergistic effect on cognitive function, as patients improved long-term memory by 70% and short-term memory by 21% relative to placebo, both of which were significantly greater than with piracetam alone. The effect does not appear to be driven by a practice effect since there was no significant improvement in the placebo group with repeated testing.

Parkinson's Disease: Harm

Adenosine 2 receptor antagonists have been shown to have antiparkinsonian activity, and dopamine signaling is modulated by cAMP/PKA activity. Since pentoxifylline has been shown to act as an adenosine 2 receptor antagonist [16] and PDE inhibitor in cell culture, it was expected to increase levels of dopamine and exert antiparkinsonian activity. Pentoxifylline (400 mg TID) was tested in combination with levodopa in a small RCT ($n=11$) in patients with Parkinson's disease (PD) [17]. None of the patients showed improvement, and **8 developed involuntary movements or had disease worsening**. Case studies have also revealed 4 patients without PD taking pentoxifylline who showed clinical signs of drug-induced parkinsonism or PD [18]. This effect is thought to stem from pentoxifylline's actions as a D1 dopamine receptor agonist and shifting the balance between D1 and D2 activity in favor of D1. Notably, the only patient in the RCT treated with pentoxifylline who did not worsen was also taking a D2 agonist [17]. Although it was not understood at the time of the study, it is now known that antiparkinsonian activity is mediated by D2 agonists. It is not known whether pentoxifylline induces PD or it unmasks pre-existing subclinical PD.

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

Alzheimer's Disease: Potential benefit (based on mechanism)

Pentoxifylline has not been tested for efficacy in improving cognitive function or Alzheimer's disease (AD)-related pathology in AD patients or preclinical AD models. However, it is hypothesized to offer benefits toward ameliorating vascular dysfunction that is thought to contribute to disease pathogenesis. Blood cell analysis comparing healthy older adults (n=14) and those with Alzheimer's type dementia (n=12) found that the AD patients had higher blood viscosity, erythrocyte aggregation, fibrinogen levels, and induction of inflammatory mediators (TNF α) [19]. Furthermore, there were **inverse correlations between these hematological parameters and level of cognitive decline**, as assessed by Mini-Mental State Exam (MMSE) ($r = -0.77$, $p < 0.01$ for plasma fibrinogen; $r = -0.79$, $p < 0.01$ for erythrocyte aggregability). Following treatment with pentoxifylline (400 mg BID) for 4 weeks, the patients significantly reduced these elevated hematological parameters, but post-treatment cognition was not assessed. Elevated fibrinogen levels have been hypothesized to contribute to BBB dysfunction and interact with A β to promote blood clots in the brain [20]. Injection of fibrinogen into the brain of healthy animals activated the immune system and triggered the destruction of synapses, which could be prevented through use of a fibrinogen-blocking antibody [21]. Blocking fibrinogen was also found to be protective in an AD mouse model. This suggests that pentoxifylline may be beneficial in preventing the induction of hematological dysfunction that may contribute to AD, though it is unclear whether it could offer meaningful benefits after the onset of significant neurological damage.

Amyotrophic lateral sclerosis: Harm (in combination with riluzole)

Pentoxifylline was tested in an RCT for ALS (n=400) based on its activity as an antioxidant and a PDE inhibitor, as overexpression of PDE4B has been implicated in motor neuron degeneration [22]. Pentoxifylline treatment (400 mg TID) plus riluzole for 18 months resulted in significantly **worse survival** than riluzole plus placebo (51.7% vs 59.7%, adjusted risk 1.43, $p=0.02$). It is unknown why the pentoxifylline led to worse outcomes, or whether a negative drug interaction was involved.

APOE4 interactions: Unknown

Aging and related health concerns: May protect against minor inflammation or oxidative stress damage in the vasculature, kidney, and liver. May help mitigate cancer treatment-associated fibrosis. Benefits observed typically as combination rather than monotherapy.

Types of evidence:

- 15 meta-analyses and/or systematic reviews [1 Intermittent claudication (n=24 RCT, n=3,377 patients); 1 Venous leg ulcers (n=12 RCT, n=864 patients, 4 Chronic kidney disease (n=11 trials, n=705 patients; n=12 trials, n=613 patients; n=17 trials, n=991 patients; n=26 trials, n=1518); 2



Heart failure (n=4 RCT, n=144 patients; n=5 RCT, n=221 patients); 1 Blood pressure (n=15 studies); 2 Alcohol hepatitis (n=4 RCT, n=336 patients; n=25 RCT (8 with pentoxifylline), n=2639 patients); 2 Non-alcoholic fatty liver disease (n=5 RCT, n=147 patients); 1 osteonecrosis (n=7 studies, n=211 patients); 1 radiation-induced fibrosis (n=5 studies, n=252 patients)]

- 6 clinical trials (Cervical cancer, Phase 2 n= 47; Non-small cell lung cancer, Phase 3 n=64; Metastatic brain cancer, Phase 2 n= 17; Metastatic renal cancer n=5, 2 Heart-injury prevention, n=85, n=178)
- Numerous laboratory studies

Many of the clinical trials testing pentoxifylline have had methodological flaws, such as high-risk bias, which has made it difficult to draw clinically relevant conclusions from meta-analyses. The results from these clinical trials suggest that **pentoxifylline has low potency**, thus significant effects are typically only detected in cases where endogenous repair mechanisms are severely compromised. The predominant mechanisms of action ascribed to pentoxifylline suggest that it is **more likely to offer benefits as a preventative to mitigate damage, rather than as treatment** to repair pre-existing damage. But, due to its low potency, it has limited capacity on its own to meaningfully mitigate severe damage. Larger, better designed studies would be needed to determine the patient populations most likely to benefit from pentoxifylline.

Cardiovascular: Potential benefit

Vascular disease: Although no adequately designed studies have been conducted to test the ability of pentoxifylline to protect the vasculature by preventing vascular inflammation-associated atherosclerosis, a beneficial role is supported by its protective vasodilatory effects in vascular-related diseases, such as intermittent claudication and venous leg ulcers. Pentoxifylline is FDA approved for intermittent claudication, which is muscle pain associated with peripheral arterial occlusion. However, a meta-analysis of (n=24) RCTs revealed a high level of heterogeneity, indicating that its efficacy may be dependent upon patient characteristics [23]. A separate meta-analysis of (n=12) RCTs found that pentoxifylline is more effective than placebo for the healing of venous leg ulcers with (Risk ratio (RR):1.56, 95% CI 1.14 to 2.13) or without (RR 1.70, 95% CI 1.30 to 2.24) concomitant compression therapy [24]. Those in the **hard-to-heal population appeared to receive the most benefit** [37% (26-48%) vs 21% (8-34%) overall population]. Although it is a vasodilator, a meta-analysis found that pentoxifylline had **no significant effects on systolic or diastolic blood pressure**, based on 9 and 8 RCTs, respectively [25].

Heart failure: Pentoxifylline has been tested for its ability to improve outcomes in patients with heart failure both as a prophylactic measure to reduce heart surgery-associated tissue damage, and as a treatment to improve heart function after the onset of damage. A systematic review of 4 RCT including patients with idiopathic or ischemic cardiomyopathy found that pentoxifylline was more likely to lead to improvements in function, as measured by left ventricular ejection volume, in patients with late stage (IV) heart failure (stage II-III OR: 10.15, 95% CI: 1.96 to 52.69, $p = 0.006$; stage IV Weighted mean difference (WMD): 8.40, 95% CI: 8.32 to 8.48) [26]. A meta-analysis could not be performed due to high heterogeneity in the patient populations across trials. The different patient populations were combined to assess mortality. This meta-analysis included one additional RCT, and found that pentoxifylline was associated with a decrease in mortality relative to placebo (5.4% vs. 18.3%; OR 0.29; CI 0.12 to 0.74; $P < 0.01$), although none of the individual studies was powered to assess a significant effect on mortality [27]. Two studies ($n=178$, $n=85$) assessed whether pentoxifylline can mitigate organ damage during heart surgery, and the results suggest that pentoxifylline is **unlikely to prevent myocardial injury** [28; 29]. However, one study ($n=178$) showed a decrease in ventilation time (10.4 vs 14.7 hours, $P=0.01$) and time in intensive care (2.6 vs 4.4 days, $P<0.001$), suggesting it may promote recovery [29]. All of these studies included patients that had pre-existing heart damage, and it has not been determined whether prophylactic pentoxifylline can help prevent the induction of heart disease in healthy people.

Mechanism: Pentoxifylline improves blood flow through capillaries by increasing the deformability of erythrocytes and reducing the adhesiveness of neutrophils [30]. It also reduces vascular smooth cell proliferation and regulates the activity level of vascular wall cells by decreasing the level of inflammatory cytokines. A meta-analysis found that pentoxifylline treatment was associated with a significant reduction in plasma levels of the inflammatory mediator $\text{TNF}\alpha$ (WMD: -1.03 pg/ml, 95% CI: -1.54 to -0.51; $P < 0.001$, 11 trials) [25]. The **anti-inflammatory effect** is thought to stem from a reduction in the activation of neutrophils and macrophages/monocytes [2]. The decrease in neutrophil activation also drives pentoxifylline's antioxidant properties. Notably, the work characterizing pentoxifylline's effects on neutrophil activation was done at physiologically relevant concentrations (nanomolar range), and indicates that the effects are mediated by its active metabolites, rather than pentoxifylline itself [31].

Cancer: Non-benefit as monotherapy, but has potential benefit in reducing radiation-induced damage in combination therapy.

Preclinical studies have indicated that pentoxifylline may have anti-cancer properties such as inhibiting tumor cell proliferation and interfering with DNA repair processes [1]. The cytotoxic effects appear to be cancer-type dependent, as pentoxifylline has been shown to inhibit metastatic potential in some

cancer cell lines, while promoting it in others. Preclinical studies have also suggested that pentoxifylline could potentiate the anti-cancer effects and mitigate the side-effects of other anti-cancer agents, such as radiation or chemotherapeutics. Based on these preclinical studies, pentoxifylline has been tested in conjunction with radiation therapy or chemotherapy in a variety of clinical trials, but was **largely found to be ineffective for improving outcomes**. In some cases, the addition of pentoxifylline led to worse outcomes. The discrepancies may relate to the use of non-physiologically relevant concentrations of pentoxifylline in the preclinical experiments. Cell culture studies often use micromolar or millimolar concentrations, when the maximum plasma level in patients is only around 1 μ M. For example, pentoxifylline's anti-cancer effects on melanoma cells were seen at concentrations of 3 mM and above [32]. However, studies in pediatric patients with acute lymphocytic leukemia have shown that pentoxifylline can potentiate the apoptotic effects of glucocorticoid treatment [33; 34], suggesting that, as supported by the preclinical studies, the potential anti-cancer efficacy may be dependent upon the patient, tumor-type, and treatment-method characteristics.

Pentoxifylline and Chemotherapy: In contrast to preclinical studies, pentoxifylline has **not been shown to significantly improve sensitivity** to chemoresistant tumors in clinical trials. While a small Phase 1 study (n=13) showed a 46% objective response rate for patients with recurrent cervical cancer receiving pentoxifylline in addition to cisplatin, these results could not be replicated in Phase 2 trial (n=40) [35]. In the larger study, the objective response rate was 10%, and the one patient with a complete response was one of the only ones in the trial to not have chemoresistance. High dose pentoxifylline (400 mg 5x/day) was unable to increase the efficacy or reduce the toxicity of IL-2 therapy in metastatic renal cell carcinoma [36].

Pentoxifylline and Radiotherapy: Pentoxifylline (400 mg TID) **did not significantly improve median survival** in patients with brain cancer or non-small cell lung cancer treated with radiation [37; 38]. Some case reports suggest that pentoxifylline could help prevent/treat radiation-induced retinopathy by improving capillary blood flow [39], however, it has not been formally tested in this capacity.

Pentoxifylline in combination and Radiotherapy: Although pentoxifylline alone has not been shown to significantly reduce the side effect profile of radiation, it has shown **benefits in clinical trials when used in combination with another antioxidant**. Pentoxifylline (400 mg TID) in combination with the anticoagulant enoxaparin and antioxidant ursodeoxycholic acid (UDCA) reduced radiation-induced liver injury (occurred in 45.5% treated vs 90.9% control), while increasing the minimum dose of radiation that could be used without incurring damage (19.1 Gy vs 14.6 Gy, P=0.011) [40]. Pentoxifylline (400 mg TID) has been most commonly tested in combination with tocopherol (Vitamin E). A systematic review of studies (n=5) using this combination in breast cancer patients for the treatment

(n=2) or prevention (n=3) of radiation-induced fibrosis found that the treatment significantly reduced fibrosis in a 22-person study, but not in a 68-person study [41]. Significant benefits were also found in terms of improving tissue compliance and mobility, indicative of less fibrosis, when used as preventative. Importantly, the use of the combination did not negatively impact the anti-cancer efficacy of the radiation therapy. A meta-analysis of clinical trials (n=7) testing the combination to improve osteoradionecrosis of the jaw supports a beneficial effect [42]. The estimated proportion of full recovery was 62.7% (95%CI 55.8-69.1%). These studies suggest that the combination of pentoxifylline and tocopherol may be radioprotective.

Kidney disease: Potential benefit (in combination with ACEi/ARBs)

Chronic kidney disease (CKD) is characterized by excessive inflammation, which results in the development of fibrotic tissue and the impairment of kidney function. Pentoxifylline has been tested in RCTs for both diabetic and non-diabetic CKD based on its **anti-inflammatory activity**. Meta-analyses have indicated that pentoxifylline treatment (400 mg TID) is **associated with significant decreases in proteinuria**, however pentoxifylline alone was not better than an angiotensin converting enzyme (ACE) inhibitor [43; 44; 45]. Pentoxifylline appears to offer the most benefit when used in conjunction with an ACE inhibitor or angiotensin II receptor blocker (ARB). The combination was found to decrease proteinuria (Standardized mean difference (SMD): -0.52; 95% CI -0.90 to 0.15) and attenuate the decline in enhanced glomerular filtration rate eGFR in patients with stage 3-5 CKD after 6 months (SMD: 0.30; 95% CI 0.06 to 0.54) [46]. However, since none of these trials used hard renal outcomes, such as the need for dialysis, it is not clear if the improvements on these measures are clinically meaningful. The renal protective effect of pentoxifylline may stem from its ability to reduce levels of the pro-inflammatory mediator TNF α , and preserve levels of klotho. In patients with diabetic stage 3-4 CKD treated with pentoxifylline as part of the PREDIAN trial, the decrease in urinary TNF α was associated with the decreased albuminuria (adjusted R² = 0.60; P < 0.0001) [47]. Meanwhile, urinary klotho increased by 9.3% (4.6 to 13.9%; P < 0.001) with pentoxifylline, but decreased by 3.9% (-5.1 to -2.7%; P < 0.01) in the control group (mean difference between groups P < 0.001). In cell culture, pentoxifylline also prevented a decline in klotho levels in cultured renal cells in response to an inflammatory challenge.

Liver disease: Potential benefit (Non-alcoholic fatty liver disease)

Preclinical rodent studies have indicated that pentoxifylline could induce antioxidants in the liver, primarily glutathione [48], and protect against non-alcoholic fatty-liver disease by increasing fatty acid beta-oxidation [49]. Pentoxifylline has been tested in RCTs for both alcoholic hepatitis (n=5) and non-

alcoholic fatty liver disease (n=5). A meta-analysis found that pentoxifylline significantly reduced overall mortality and hepatic-related mortality in the context of alcoholic hepatitis, however, most of the trials suffered from high risk bias, and a trial sequential analysis indicated that these risk reductions could not be supported by the amount of available evidence [50]. A separate finding that the combination of pentoxifylline with corticosteroids does not significantly improve mortality over the use of corticosteroids alone [51] suggests that pentoxifylline does not provide clinically meaningful benefit in this population. Meanwhile, meta-analyses suggest that pentoxifylline **may offer benefits for non-alcoholic fatty liver disease**, including reductions in body weight, body mass index, , fasting glucose, liver enzyme activity, inflammation, and fibrosis [52; 53]. However, these trials had small sample sizes, thus the quality of evidence going into these analyses was low. These studies suggest that pentoxifylline may exert beneficial effects on liver metabolism.

Safety: Generally well-tolerated with mild nausea as the primary side effect. Associated with an increased risk for bleeding.

Types of evidence:

- 16 meta-analyses or systematic reviews
- 11 clinical trials that are not in the meta-analyses/syst rev
- Numerous laboratory studies

The results of numerous RCTs indicate that pentoxifylline is generally well-tolerated in a variety of patient populations. Most trials found similar levels of adverse events between pentoxifylline and placebo-treated groups. **Mild, dose-related gastrointestinal events**, primarily nausea and diarrhea, were the most common side effects across trials. Other reported side effects include headache, dysphagia, anxiety, vomiting, and flushing [4; 22; 43; 45; 46]. Due to its anticoagulant properties, pentoxifylline is also associated with **an increased risk for bleeding**. Pentoxifylline is primarily metabolized by erythrocytes and in the liver, but does not affect cytochrome P450 activity ([LiverTox](#)). According to [Drugs.com](#), there are 371 known drug interactions. Pentoxifylline may potentiate the activity of antihypertensives, hypoglycemics, and anticoagulants. The 3 major drug interactions are with dexamethasone, inotersen, and ketorolac due to risk for severe bleeding. Pentoxifylline is contraindicated in patients with a recent cerebral or retinal hemorrhage.

Pentoxifylline has a rating of 4.1 out of 5 on [Treato.com](#). There are twice as many positive comments as negative ones (100 vs 51). Nausea is the most common listed concern that pertains to use of the drug.

Sources and dosing:

Pentoxifylline is sold under the brand Trental®, which is marketed by Sanofi-Aventis ([FDA product insert](#)). The standard dose is one 400 mg tablet 3 times per day. It is recommended that the dose be reduced to one 400 mg tablet 2 times per day if adverse events occur. In patients with impaired renal or liver function, the recommended adjusted dose is one 400 mg tablet per day. Taking with food reduces the plasma concentration of pentoxifylline and its active metabolites.

Research underway:

According to [Clinicaltrials.gov](#), there are 19 active clinical trials for pentoxifylline. It will be tested for diabetic kidney disease, biliary atresia in infants, pediatric patients with leukemia with chemotherapy, lumbar disc disease, vertigo, in combination with radiotherapy for prostate cancer and lung cancer, osteonecrosis of the jaw (with Vitamin E), infertility (with Vitamin E), Crohn's disease (with Vedolizumab), alcohol hepatitis (with G-CSF and NAC) and mucosal leishmaniasis (with Miltefosine).

Pentoxifylline has relatively low oral bioavailability (~20%) [30], and some groups have been working to develop formulations with higher bioavailability. One group in the Middle East is working on the development of an elastic transferosome formulation that can be used for transdermal delivery. In a pharmacokinetic study in 6 healthy men, the transferosome formulation had a longer elimination half-life (8.15 ± 0.09 vs 3.85 ± 0.13 hours), and a greater amount of the drug was absorbed into the circulation, based on the area under the curve (AUC) (2324 ± 300 vs 1412 ± 154 ng h/ml, $P < 0.05$), than for the Trental® slow-release tablets [54]. It is not known whether this type of formulation will be developed for commercialization.

Search terms:

Pubmed, Google: Pentoxifylline or oxpentifylline +

Alzheimer's disease, vascular dementia, neurodegeneration, cognition, stroke, cardiovascular, cancer, diabetes, safety, clinical trials, meta-analysis, systematic review, pharmacokinetics

Websites visited for Pentoxifylline:

- [Clinicaltrials.gov](#)
- [Treato.com](#)
- [Drugs.com](#)
- [WebMD.com](#)

- [PubChem](#)
- [DrugBank.ca](#)
- [Patientslikeme.com](#)
- [Cafepharma](#)

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