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.

Pioglitazone

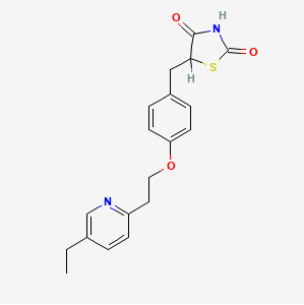
Evidence Summary

Pioglitazone improves insulin sensitivity and lipid profiles and modulates inflammation. Pioglitazone can also cause heart failure, weight gain, and potentially bladder cancer.

Neuroprotective Benefit: Pioglitazone can improve insulin sensitivity, regulate inflammation, and decrease accumulation of amyloid-beta, and some observational studies have found decreased risk of dementia in diabetes patients taking pioglitazone.

Aging and related health concerns: Pioglitazone improves glucose and lipid profiles and may be protective against stroke and certain cardiovascular risks. However, it also increases risk of heart failure and weight gain.

Safety: Pioglitazone can significantly increase the risk of heart failure, anemia, weight gain, edema, and fractures. Pioglitazone may be associated with increased risk of bladder cancer in some populations.

Availability: Rx	**Dose**: 15 – 45 mg per day for type 2 diabetes patients	**Chemical formula:** $C_{19}H_{20}N_2O_2S$ **MW**: 356.4  Source: PubChem
Half life: 3-7 hours for pioglitazone; 16-24 hours for its metabolites	**BBB**: Penetrant	
Clinical trials: Largest meta-analysis included 19,779 patients enrolled in RCTs.	**Observational studies**: Meta-analysis of multiple observational studies included almost 4.5 million patients, though some patient records may have been duplicated between studies.	

What is it?

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors that influence expression of large networks of genes involved in a variety of cellular functions, such as metabolism and differentiation. PPARγ is best known for its regulation of networks of genes involved in lipid and glucose metabolism as well as inflammatory responses. Pioglitazone is an agonist primarily for PPARγ and is typically prescribed to help control blood glucose levels in type 2 diabetes, in part by increasing sensitivity to insulin (Liu & Wang, 2019).

Through activating PPARγ and the many genes that PPARγ regulates, pioglitazone has a variety of documented effects beyond improving insulin sensitivity and concomitant glucose homeostasis. Pioglitazone has anti-inflammatory and anti-oxidant effects, such as promoting phagocytosis in macrophages and microglia, inhibiting the *NF-κB* pro-inflammatory pathway and reducing production of cytokines such as IL-1, IL-6, and TNFα, and enhancing anti-oxidant pathways such as *Nrf2*-regulated networks and expression of antioxidants like SOD and catalase. Pioglitazone also increases cerebral blood flow (Saunders et al., 2021, Cai et al., 2017). Pioglitazone also has effects on lipid metabolism and can improve blood lipid profile, but this can involve redistributing those lipids to adipocyte fat stores, leading to weight gain (Janani & Kumari, 2015).

Neuroprotective Benefit: Pioglitazone can improve insulin sensitivity, regulate inflammation, and decrease accumulation of amyloid-beta, and some observational studies have found decreased risk of dementia in diabetes patients taking pioglitazone.

Types of evidence:

- 2 meta-analyses
- 4 clinical trials
- 1 observational study
- Numerous laboratory studies

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

A 2016 observational study using electronic medical records in Germany examined the association of dementia incidence with use of pioglitazone in 145,928 patients 60 years and older. The authors found that diabetics who were prescribed pioglitazone for 2 years or more had a 47% reduced risk of dementia (RR = 0.531, p = 0.029) compared to non-diabetics, and diabetics who had been prescribed pioglitazone at least once had a similar dementia rate to non-diabetics (RR=1.161, p = 0.317). In this population, diabetics who were not prescribed pioglitazone had a 23% increased risk of dementia compared to non-diabetics (RR = 1.234, p < 0.001). The risk was also described in dementia cases per 1,000 patient years. Non-diabetics had 18 new dementia cases; diabetics without pioglitazone prescription had 28 new cases. Patients prescribed pioglitazone for less than 2 years had 20 new cases. Patients with pioglitazone prescriptions for more than 2 years had 7 new cases (Heneka et al., 2015).

A meta-analysis from 2018 examined 19 randomized controlled trials (RCTs) of different anti-diabetic medications with a total of 4,855 patients. The authors found that use of an anti-diabetic was associated with improved cognitive performance (p<0.001). Of the six anti-diabetics, 15 and 30 mg of pioglitazone were the most effective at improving cognitive performance as compared to placebo (p<0.001). The authors did not control for factors such as age, sex, or APOE genotype. They also did not find an association with improved cognitive performance and the highest dose of pioglitazone, indicating that there may be an ideal dosing range for cognitive efficacy (Cao et al., 2018).

The TOMORROW study was a larger RCT that enrolled 3494 patients and tested a low dose (0.8 mg a day) of pioglitazone versus placebo in a population of cognitively intact 65-83 year old people. They

divided their subjects into low-risk or high-risk of conversion to mild cognitive impairment (MCI) or AD based on APOE and TOMM40 genotype. The low-risk group all received placebo; the high-risk group received placebo or pioglitazone, with approximately 1500-1600 patients in each arm of the high-risk group. The study ended early after a pre-specified futility analysis found no benefit for pioglitazone. Forty-six (3.3%) of 1406 participants at high risk given placebo had mild cognitive impairment due to Alzheimer's disease, versus 39 (2.7%) of 1430 participants at high risk given pioglitazone had mild cognitive impairment (HR= 0.80, 95% CI 0.45–1.40; p=0.307). In the safety analysis set, seven (0.5%) of 1531 participants at high risk given pioglitazone died versus 21 (1.4%) of 1507 participants at high risk given placebo. In a subgroup analysis, the authors found a potential decrease in risk of MCI or AD in male participants but this did not reach significance (HR=0.56; 95% CI 0.30–1.06, p=0.074) (Burns et al., 2019). This study leaves several open questions, including whether the dose was sufficient, whether the follow-up period was long enough before the futility analysis, and whether their population of relatively well-educated participants with relatively fewer cardiovascular risk factors would have had enough conversions to MCI or AD to show an effect.

A recent meta-analysis and systematic review of observational and case-control studies found that long-term use of pioglitazone is associated with a decreased risk of Parkinson's disease (PD) in diabetic patients (RR=0.87; 95% CI 0.62–0.99, p=0.039). The study included 3 studies that enrolled a total of 131,410 patients (Chen et al., 2022).

Human research to suggest benefits to patients with dementia:

Three studies of pioglitazone in patients with mild cognitive impairment (MCI) or dementia were found.

In an open-label trial of 42 patients with diabetes and mild AD, patients were randomized to either a control group with no treatment or pioglitazone treatment of 15-30 mg daily. After 6 months, the patients who received pioglitazone had improved cerebral blood flow in certain brain regions, whereas the control group did not show increased cerebral blood flow in any region. Patients taking pioglitazone had increased insulin sensitivity and also improvements in cognition as measured by the MMSE, ADAS-J-cog, and WMS-R logical memory-I scales, whereas the control group had decreased ADAS-J-cog scores (Sato et al., 2011).

Another study of 78 patients with MCI and insulin resistance examined the cognitive effects of exercise, pioglitazone, or no treatment over the course of 18 months. The authors found no differences in cognition between groups (Hildreth et al., 2015).

A 29 person study assessed the safety and tolerability of 15-45 mg daily of pioglitazone versus placebo over the course of 18 months in AD patients. The authors found that pioglitazone was well-tolerated, with peripheral edema, a known side effect of pioglitazone, being the only significantly different adverse event between the two groups (28.6% of pioglitazone patients vs 0% of placebo patients). The study was not powered to detect cognitive effects, and the authors did not observe any differences in cognitive performance over time between the two groups (Geldmacher et al., 2011).

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

There are a variety of proposed mechanisms through which pioglitazone exerts a neuroprotective effect (reviewed in Saunders et al., 2021, and Alhowail et al., 2022). Pioglitazone is thought to affect amyloid-beta processing and clearance, tau phosphorylation, oligomerization, and localization, modulation of microglia, cerebral glucose uptake, mitochondrial biogenesis, lipid homeostasis, and oxidative stress, among other effects.

PPARγ and PPARγ targets such as CDK5 downregulate expression and activation of BACE1, an enzyme involved in the processing of amyloid beta. Targets of PPARγ also increase the clearance of amyloid beta peptides. Cell and animal models have shown that as a PPARγ agonist, pioglitazone decreases amyloid-beta formation and plaque deposition. Pioglitazone also decreases tau hyperphosphorylation, oligomerization, and mislocalization in both cell and animal models.

Activation of the immune system is a hallmark of Alzheimer's disease and other neurodegenerative diseases. Pioglitazone has a variety of anti-inflammatory and anti-oxidant effects through promoting anti-inflammatory and suppressing pro-inflammatory pathways. The pro-inflammatory NF-κB pathway is a PPARγ target, with PPARγ inhibiting the transcription factor NF-κB. Pioglitazone blocks production of inflammatory cytokines such as IL-1, TNFα, IL-6, iNOS, COX2, MMP9, and Caspase 3, and promotes activation of Nrf2 anti-oxidant pathways and synthesis of anti-inflammatory and/or anti-oxidant molecules including catalase, SOD, IL-4, IL-10, and TGFβ. Pioglitazone also helps to shift microglia to an immunosuppressive phenotype and promotes a phagocytic phenotype conducive to removing toxic proteins.

Beyond its antioxidant effects, PPARγ can maintain mitochondrial homeostasis or improve mitochondrial bioenergetics through stimulating mitochondrial biogenesis and improving mitochondrial membrane potential. PPARγ can also increase expression of its co-activator, PGC-1α, which is involved in a variety of aspects of mitochondrial and energy metabolism and homeostasis. These functions in maintaining mitochondrial respiration have also drawn attention to pioglitazone as a potential neuroprotective agent in traumatic brain injury and stroke contexts.

Glucose uptake and metabolism is often perturbed in AD, with many AD patients displaying cerebral hypometabolism. Pioglitazone can increase both cerebral blood flow and brain glucose uptake in patients. The medication has also been shown to restore glucose homeostasis through both improving mitochondrial function and also through increasing expression of insulin-sensitive glucose transporters in the hippocampus in animal models. Pioglitazone can also improve insulin sensitivity by increasing expression of insulin pathway genes and through its anti-inflammatory actions.

APOE4 interactions:

The interactions of pioglitazone and APOE4 are not yet fully elucidated. *APOE* is a target of the PPARγ gene but there are mixed reports of whether PPARγ increases or decreases APOE expression. These discrepancies may be due to dosing differences, as bi-phasic dose effects of PPARγ have been described (reviewed in Saunders et al., 2021).

Hildreth and colleagues did see a trend towards increased cognitive performance in APOE4 negative patients treated with pioglitazone (Hildreth et al., 2015), and a randomized controlled trial in 511 patients of a related drug, rosiglitazone, did find potential cognitive improvement in APOE4 negative, mild-to-moderate AD patients in the rosiglitazone group but not those who were APOE4 positive (p=0.024, not adjusted for multiplicity) (Risner et al., 2006). These results are very preliminary but suggest that there may be differential effects based on APOE status that are important to explore in future trials.

Aging and related health concerns: Pioglitazone improves glucose and lipid profiles and may be protective against stroke and certain cardiovascular risks. However, it also increases risk of heart failure and weight gain.

Types of evidence:

- 1 professional society guideline from American Diabetes Association
- 2 Cochrane meta-analyses
- 1 meta-analyses with systematic reviews
- 2 meta-analyses
- 1 clinical trial
- Numerous observational studies

***Diabetes*:** BENEFIT; SECOND-LINE TREATMENT OPTION FOR TYPE 2 DIABETES

Pioglitazone is considered a second-line treatment option for glycemic control in diabetes patients as per the American Diabetes Association (Doyle-Delgado et al., 2020). Pioglitazone use led to a median decrease of 0.8% in HbA1C, whereas placebo group experienced a median decline of 0.3% (p=0.0001) in a 2005 RCT of 5238 patients taking either pioglitazone or placebo (Dormandy et al., 2005).

A 2020 Cochrane meta-analysis of randomized controlled trials that included 4,186 patients at risk of diabetes found that pioglitazone, as compared to placebo, reduced or delayed the development of type 2 diabetes with moderate certainty (RR=0.40; 95% CI 0.17 - 0.95; p=0.04) (Ipsen et al., 2020).

***Mortality*:** NEITHER BENEFIT NOR HARM

A 2017 systematic review and meta-analysis of 12,026 patients enrolled in RCTs found no effect of pioglitazone treatment on mortality (RR=0.93; 95% CI 0.80 -1.09; p for heterogeneity=0.88, I2=0%) (Liao et al., 2017).

Stroke: PROBABLE BENEFIT

A 2019 Cochrane meta-analysis of randomized controlled trials with a total of 5,039 patients with stroke or transient ischemic attack (TIA) found that treatment with pioglitazone or a related PPAR agonist glitazone, rosiglitazone, reduced the risk of recurrent stroke (RR=0.66; 95% CI 0.44 - 0.99). The authors

also found that PPAR agonists appeared to reduce serious vascular events, defined as a composite outcome of total events of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (RR=0.73; 95% CI 0.54 - 0.99) (Liu et al., 2019).

A 2020 meta-analysis of 10,890 patients with type 2 diabetes compared outcomes between patients who took pioglitazone and those who took other anti-glycemic agents and no pioglitazone. They found a significant 23% reduction in stroke in the pioglitazone group (Mantel-Haenszel odds ratio [MH-OR)=0.77; 95% CI 0.60–0.99), though this difference did not reach significance on subgroup analysis comparing pioglitazone to placebo only rather than combining studies examining pioglitazone vs. placebo or active control (Sinha & Ghosal, 2020).

Cardiovascular disease: DECREASED CARDIOVASCULAR EVENTS; INCREASED HEART FAILURE

Pioglitazone has been associated with heart failure in a number of studies; see 'Safety' section for further discussion.

A meta-analysis was performed as part of updating the Italian guidelines for treatment of type 2 diabetes and published in 2022. The meta-analysis examined the cardiovascular effects of glucose-lowering medications in type 2 diabetic populations in randomized controlled trials. In their analysis of 12,336 patients on pioglitazone, the authors found that pioglitazone was associated with a significantly lower risk of major cardiovascular events (MH-OR=0.85; 95% CI 0.74 - 0.97). In this study, major cardiovascular events were defined as: non-fatal myocardial infarction, non-fatal stroke or cardiovascular death (Mannucci et al., 2022).

A 2020 meta-analysis of risks and benefits of pioglitazone in 10,890 RCT patients with type 2 diabetes included some but not all studies that Mannucci and colleagues examined and found similar lower risks of major cardiovascular events (MH-OR=0.86; 95% CI 0.75–0.98) (Sinha & Ghosal, 2020).

A 2017 systematic review and meta-analysis of RCTs including 12,026 patients showed a reduction in risk of major cardiovascular events in patients with insulin resistance or pre-diabetes who were administered pioglitazone (RR=0.77; 95% CI 0.64 - 0.93) (Liao et al., 2017).

Pioglitazone use is associated with improved lipid profile. In the PROactive randomized controlled study of 5238 patients, the authors observed a greater decrease in triglycerides (-11.4% vs +1.8%) and a

greater increase in HDL cholesterol (19% vs 10.1%) in patients treated with pioglitazone as compared to patients taking placebo. The authors did note a greater increase in LDL cholesterol in pioglitazone vs placebo (7.2% vs 4.9%), but the LDL/HDL ratio declined more in the treated group (-9.5% vs -4.9%) and the authors speculated that the increase in LDL might not be clinically significant (Dormandy et al., 2005).

Safety: Pioglitazone can significantly increase the risk of heart failure, anemia, weight gain, edema, and fractures. Pioglitazone may be associated with increased risk of bladder cancer.

Types of evidence:

- 2 meta-analysis and systematic review
- 2 meta-analyses
- Numerous clinical trials
- Numerous observational studies

Several studies have found increased risk of heart failure in patients taking pioglitazone. A 2022 meta-analysis of glucose-lowering drugs found that in a population of 11,595 type 2 diabetics receiving pioglitazone, risk of hospitalization for heart failure was significantly higher as compared to active comparators (MH-OH=1.30; 95% CI 1.04-1.62) (Mannucci et al., 2022). Sinha & Ghosal included many of the same studies in their 2020 meta-analysis of 10,890 and similarly found increased odds of heart failure with pioglitazone use as compared to no pioglitazone use (MH-OR=1.47; 95% CI 1.26–1.71) and hospitalization for heart failure (MH-OR=1.48; 95% CI 1.21–1.81) (Sinha & Ghosal, 2020). A meta-analysis that included patients with insulin resistance, pre-diabetes, or type 2 diabetes also found an increased risk of heart failure in those who took pioglitazone compared to those who did not take pioglitazone (RR=1.32; 95% CI 1.14 - 1.54) (Liao et al., 2017).

The 2020 meta-analysis from Sinha & Ghosal also found a significant increase in anemia (MH-OR=2.56; 95% CI 1.55–4.21) and fractures in women who took pioglitazone compared to those who did not (MH-OR=2.05; 95% CI 1.28–3.27) (Sinha & Ghosal, 2020).

Liao and colleagues also showed an increased risk of bone fracture (RR=1.52; 95% CI 1.17 - 1.99), edema (RR=1.63; 95% CI 1.52 - 1.75) and weight gain (RR=1.60; 95% CI 1.50 -1.72) with pioglitazone use as compared to no pioglitazone use (Liao et al., 2017).

There are mixed reports on whether pioglitazone use increases risk of bladder cancer. Some have found no increase in risk (Liao et al., 2017, Sinha & Ghosal 2020). However, a 2018 systematic review and meta-analysis of 2 RCTs with a total of 9,114 patients and 20 observational studies with a population of 4,846,088 patients found an increased risk in the RCTs (OR=1.84; 95% CI, 0.99 - 3.42) and the observational studies (OR=1.13; 95% CI, 1.03 - 1.25) when comparing pioglitazone to either placebo or never-use, respectively. This 2018 study noted that the risk seemed to increase with both time-on-pioglitazone as well as dose. The authors also found regional differences, with studies conducted in Europe finding significant risk increases, while studies conducted in the US or Asia did not. Further studies are needed, but regular bladder cancer screenings are warranted for any long-term use of pioglitazone, especially in Caucasian populations, and potentially in men (Tang et al., 2018).

Drug interactions:

Pioglitazone has interactions with 316 medications; 9 of these are major, 271 are moderate, and 36 are minor interactions. Major interactions with pioglitazone include insulin or other drugs that affect blood sugar levels, and CYP2C8 inhibitors, which can increase the amount of pioglitazone in the blood. Beta blockers should be used with caution with pioglitazone, as beta-blockers can mask symptoms of low blood sugar. Those with congestive heart failure, liver disease, or type 1 diabetes, or have had issues with edema or weight gain, should use particular caution with pioglitazone. (Drugs.com)

Research underway:

There are 89 ongoing clinical trials in the US and EU using pioglitazone and 48 active studies through NIH Reporter. Many of the trials are in type 2 diabetic populations, and others are in populations as diverse as cancer, nonalcoholic fatty liver disease, stroke, MS, COVID-19, and PCOS. No trials or studies are examining pioglitazone in aging or dementia.

Search terms:

Pubmed, Google:

- +Dementia, +meta-analysis, +Alzheimer's, +bladder cancer, +diabetes, +APOE4, +cognition

Websites visited for pioglitazone:

- Clinicaltrials.gov
- Clinicaltrialsregister.eu
- Geroprotectors
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca