

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.

DPP-4 Inhibitors

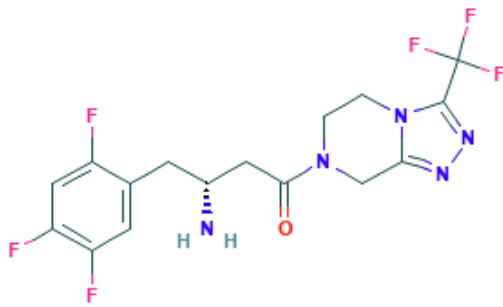
Evidence Summary

There is evidence that DPP-4 inhibitors may reduce the risk of dementia and other age-related diseases, but possibly only for individuals with Type 2 diabetes (T2DM) or poor glucose control.

Neuroprotective Benefit: DPP-4 inhibitors may reduce the risk of Alzheimer's disease in elderly individuals with diabetes, but it is not clear they would be more effective than other anti-diabetics (such as GLP-1 agonists).

Aging and related health concerns: DPP-4 inhibitors are useful for controlling T2DM and related complications and may be beneficial for patients at risk for hypoglycemic episodes.

Safety: DPP-4 inhibitors are generally safe with adverse event profiles similar to placebo.

Availability: Available as a prescription drug	Dose: Varied (see sources/dosing section below)	Chemical formula: C ₁₆ H ₁₅ F ₆ N ₅ O (Sitagliptin) MW: 407.314g/mol  Source: Pubchem
Half life: 2.5-131 hours	BBB: No	
Clinical trials: 1 pilot study in T2DM patients; 1 ongoing for cognitive decline in T2DM patients	Observational studies: Two for dementia	

What is it?

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of diabetes drugs. DPP-4 breaks down incretins (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulintropic polypeptide [GIP]), as well as other peptides such as brain natriuretic peptide (BNP), substance P, neuropeptide Y, and stromal derived factor-1 α (SDF-1 α) ([Angelopoulou and Piperi, 2018](#)). Their primary mechanism of action in relation to diabetes is to increase levels of GLP-1 and GIP, peptides that stimulate glucose-dependent insulin release. It is estimated that incretins are responsible for 50-70% of the postprandial insulin production ([Brunton, 2014](#)). Since GLP-1 insulin release is glucose dependent, there is less of a chance of hypoglycemia compared to older diabetes drugs (such as insulin or sulfonylureas). Although DPP-4 inhibitors increase the levels of GLP-1, they do not do so to the same extent as GLP-1 agonists. GLP-1 has a short half-life (1-2 minutes) due to degradation by DPP-4. Therefore, DPP-4 inhibitors effectively increase the half-life of GLP-1. Although DPP-4 inhibitors are not reported to cross the blood brain barrier, GLP-1 does cross and has receptors in the brain. In contrast to other anti-diabetics, DPP-4 inhibitors are not associated with weight loss.

For Alzheimer's disease, the benefits of DPP-4 inhibitors are related to the increase in GLP-1 and possibly GIP. GLP-1 agonists were reported to reduce amyloid, ptau, and inflammation while improving cognition in Alzheimer's animal models. One small study in Alzheimer's patients found that liraglutide

did not alter cognition or amyloid over 26 weeks, but it did prevent a decrease in the uptake of glucose into the brain ([Geji et al, 2016](#)).

DPP-4 inhibitors approved in the United States include:

- Sitagliptin (Januvia): Available with prescription in US. 100mg/day oral tablet; 12.4-hour half-life
- Saxagliptin (Onglyza): Available with prescription in US. 2.5-5mg/day oral tablet; 2.5-hour half-life
- Linagliptin (Tradjenta): Available with prescription in US. 5mg/day oral tablet; 131-hour half-life
- Alogliptin (Nesina): Available with prescription in US. 25mg/day oral tablet; 21-hour half-life
- Vildagliptin (Galvus): Available with prescription **only in EU**. 50mg/day oral tablet; 90-minute half-life

Neuroprotective Benefit: DPP-4 inhibitors may reduce the risk of Alzheimer's disease in elderly individuals with diabetes, but it is not clear they would be more effective than other anti-diabetics (such as GLP-1 agonists).

Types of evidence:

- 2 observational studies
- 1 open-label pilot study
- Many preclinical animal studies

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

T2DM may increase the risk of Alzheimer's disease, and patients with Alzheimer's disease may suffer from insulin resistance in the brain. Therefore, drugs that increase insulin sensitivity may be beneficial for Alzheimer's.

One observational study compared the effect of DPP-4 inhibitors (vildagliptin, sitagliptin, or saxagliptin)+metformin (D+M) or sulfonylureas+metformin (S+M) over two years in 240 T2DM patients with MCI. They reported statistically significant cognitive benefits (+1 point on MMSE in D+M patients vs. no change in S+M patients, as well as benefits in other cognitive measures such as attention and executive function) and glycemic control in D+M patients. D+M patients also had a greater reduction in HbA1c% and fewer asymptomatic hypoglycemic episodes (they wore a continuous glucose monitor for a two-day period) ([Rizzo et al, 2014](#)). A small pilot study in 10 elderly individuals with T2DM reported no change in cognition or functional outcomes after 10-month treatment of vildagliptin (50mg bid) as an add-on treatment to metformin. However, the patients already had near

maximal cognitive scores at baseline, so the negative results of this study are difficult to interpret ([Tasci et al, 2013](#)).

Human research to suggest benefits to patients with dementia:

In an observational study over 6 months in 205 elderly individuals (~25% had dementia) with T2DM who were taking sitagliptin (100mg/day), metformin, and/or insulin, there was a slight improvement in cognition in dementia patients taking sitagliptin monotherapy vs. patients taking metformin monotherapy (there were too few dementia patients taking insulin for comparison). There were no differences in cognition when considering both those with and without dementia ([Isik et al, 2017](#)).

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

Multiple preclinical studies suggest beneficial effects using different DPP-4 inhibitors.

Sitagliptin: Sitagliptin improved cognitive function in younger, but not older, Alzheimer's transgenic mice, and reduced amyloid, increased spine density, and increased BDNF levels. Increased GLP-1 and BDNF activity was required, as coadministration of GLP-1 or TrkB inhibitors prevented the cognitive benefits ([Dong et al, 2019](#)). [D'Amico et al \(2010\)](#) reported that sitagliptin improved memory, increased levels of GLP-1, and reduced amyloid, nitrosative stress, and inflammation in an Alzheimer's mouse model over 12 weeks. On the other hand, [Kim et al \(2012\)](#) reported that 12-week treatment of sitagliptin in diabetic rats increased ptau, possibly signaling through GSK3 β . They also reported that sitagliptin reduced insulin sensitivity in the brain (though another study reported an increase in insulin sensitivity in the brain with vildagliptin in an obesity model; [Pintana et al, 2015](#)). [Kim et al \(2012\)](#) confirmed sitagliptin increased ptau in a cell culture study.

Vildagliptin: In an Alzheimer's animal model, 30-day treatment with vildagliptin dose-dependently increased brain levels of GLP-1, improved cognition, and reduced amyloid, ptau, markers of inflammation (TNF α and IL-1 β), and neuronal loss ([Kosaraju et al, 2013a](#)). In a rat model of vascular dementia (pancreatectomy-induced diabetes), vildagliptin improved cognition, reduced blood-brain barrier permeability, reduced inflammation, and increased expression of anti-oxidant enzymes ([Jain and Sharma, 2015](#)).

Saxagliptin: In an Alzheimer's animal model, 60-day treatment with saxagliptin dose-dependently increased brain levels of GLP-1, improved cognition, and reduced amyloid, ptau, total tau, and markers of inflammation (TNF α and IL-1 β), and neuronal loss ([Kosaraju et al, 2013b](#)). One study reported that saxagliptin reduced cognitive performance in the sham group in a Parkinson's model, but it has been

effective in other Parkinson's models. The authors speculate that the difference with other Parkinson's studies could be the model used, and that DPP-4 inhibitors may be detrimental because DPP-4 has other substrates beyond GLP-1 and GIP. However, most studies have reported benefits in preclinical models ([Turnes et al, 2018](#)).

Linagliptin: [Kosaraju et al \(2017\)](#) reported that 8-week treatment with linagliptin in an Alzheimer's animal model slightly increased brain levels of GLP-1 and GIP, improved cognition, and, at the highest dose, reduced A β ₄₂ (but not 40), ptau, astrogliosis and amyloid plaques. In diabetic rats, 4-week treatment with linagliptin improved cerebral blood flow and vascular relaxation with no change in cognition ([Hardigan et al, 2016](#)).

APOE₄

None

Aging and related health concerns: DPP-4 inhibitors are useful for controlling T2DM and related complications and may be beneficial for patients at risk for hypoglycemic episodes.

Types of evidence:

- 14 meta-analysis in diabetes and other age-related diseases
- 5 clinical studies of flow-mediated dilation
- 2 preclinical lifespan studies

Mortality: NO EFFECT

In a network meta-analysis of 301 clinical trials, there were no significant differences between diabetes drugs with respect to odds of cardiovascular mortality as monotherapies or add-on therapies to metformin. There were no differences to all-cause mortality as add-on therapies to metformin (there were uncertain results for monotherapy treatment) ([Palmer et al, 2016](#)). Another meta-analysis of RCTs reported that although GLP-1 agonists and SGLT-2 inhibitors reduced mortality compared to control groups, there was not a reduced risk of death using DPP-4 inhibitors ([Zheng et al, 2018](#)).

In mice fed a high fat diet, alogliptin increased lifespan, improved organ pathology (fatty liver and pancreas pathology), and improved mitochondrial function *in vitro*. In the liver, alogliptin increased autophagy, possibly through AMPK/mTOR ([Zhu et al, 2019](#)). Interestingly, in a mouse model of premature aging (Klotho knock-out), 4-week treatment with linagliptin prevented body weight loss, non-significantly increased survival (93% survival in linagliptin, 67% in control group), improved

cognition, increased cerebral blood flow, and increased the number of neurons in the hippocampus ([Hasegawa et al, 2017](#)).

Diabetes/Insulin resistance: NOT AS EFFECTIVE AS OTHER DIABETES DRUGS

A network meta-analysis of 301 clinical trials reported that all diabetes drugs were associated with similar reductions in HbA_{1c}% compared to placebo, though when compared to metformin monotherapy, DPP-4 was not as effective as metformin (though it did reduce the risk of hypoglycemia). As add on therapies to metformin, all were associated with similar HbA_{1c}% reductions ([Palmer et al, 2016](#)).

A meta-analysis of 52 trials showed that DPP-4 inhibitors, as either an add-on therapy or monotherapy, had no effect on insulin resistance in T2DM patients, though they improved beta-cell function. When individual drugs were analyzed, only sitagliptin had a positive effect. The authors speculate this could be due to the fact that DPP-4 inhibitors have no effect on weight loss ([Lyu et al, 2017](#)). On the other hand, a more recent network meta-analysis reported that DPP-4 inhibitors improved insulin sensitivity, although not as much as other diabetes drugs such as GLP-1 agonists or metformin ([We et al, 2018](#)).

Cardiovascular disease/Major Cardiovascular Events (MACE): BENEFIT OVER SULFONYLUREAS, WORSE THAN SGLT₂ INHIBITORS

In a meta-analysis of 69 trials comparing DPP-4 inhibitors to other diabetes drugs or placebo in patients with T2DM, DPP-4 inhibitors were associated with a decreased risk of major adverse cardiovascular events (MACE) compared to sulfonylureas (OR = 0.52; 95%CI 0.36-0.76), a trend toward increased risk compared to sodium-glucose cotransporter 2 (SGLT₂) inhibitors (OR 1.89; 95%CI 0.60-5.93), and no change compared to placebo or other diabetes drugs ([Kaneko and Narukawa, 2016](#)).

In a network meta-analysis of 301 clinical trials, there were no significant differences between diabetes drugs with respect to odds of cardiovascular mortality as monotherapies or add-on therapies to metformin. There were also no differences for myocardial infarction, except for a benefit in those taking DPP-4 inhibitors+metformin vs. sulfonylureas+metformin ([Palmer et al, 2016](#)).

Intima-media thickness (IMT): POTENTIAL BENEFIT (SITAGLIPTIN AND ALOGLIPTIN)

Compared to conventional diabetes therapy, sitagliptin was reported to reduce the internal carotid IMT (but not other measures such as common carotid IMT and plaque area) over 24 months in a group of primary cardiovascular (CVD) prevention patients but not in secondary CVD prevention patients ([Tanaka et al, 2018](#)). Plaque stability was improved after sitagliptin therapy compared to baseline with

no changes in a conventional therapy group; however, there were not significant between-group differences ([Katakami et al, 2018](#)). Similar results were reported with alogliptin therapy, with reductions in carotid IMT compared to conventional therapy and increased plaque stability from baseline with no between group differences compared to conventional therapy ([Mita et al, 2016](#); [Irie et al, 2018](#)).

Lipids: SLIGHT BENEFIT WITH VILDAGLIPTIN AND ALOGLIPTIN

A meta-analysis of 17 randomized-controlled trials (RCTs) reported that DPP-4 inhibitors were associated with slight reductions in total cholesterol and triglycerides compared to controls (placebo and other classes of diabetes drugs). Significant effects were reported specifically for vildagliptin and alogliptin ([Monami et al, 2012](#)).

Flow-mediated dilation (FMD): MIXED RESULTS

Results of DPP-4 inhibitors on FMD have been mixed. Surprisingly, both sitagliptin and alogliptin reduced brachial artery dilation by 30%-50% over a six-week period, while voglibose, and alpha-glucosidase inhibitor, had no effect ([Ayaori et al, 2013](#)). On the other hand, multiple small studies have reported that DPP-4 inhibitors, specifically vildagliptin and sitagliptin, improved FMD over up to 12 months ([van Poppel et al, 2011](#); [Kubota et al, 2012](#); [Dell'Oro et al, 2017](#)). In the largest study to date (n=97), in Japanese patients, vildagliptin did not improve FMD over 12 weeks compared to high dose metformin (both drugs non-significantly attenuated FMD compared to baseline) ([Kitao et al, 2017](#)).

Blood Pressure: BENEFIT (BUT NOT COMPARED TO SGLT2 INHIBITORS)

In a meta-analysis of 15 trials comparing DPP-4 inhibitors to other diabetes drugs or placebo in T2DM patients, DPP-4 inhibitors reduced blood pressure more than placebo (mean difference = -3.04/-1.47) but not compared to SGLT2 inhibitors (mean difference = 4.44/2.15mmHg). There were no differences with other diabetes drugs ([Zhang and Zhao, 2016](#)).

Heart Failure: CONTROVERSIAL (POSSIBLY INCREASED RISK WITH ALOGLIPTIN)

There has been some controversy with regards to the safety of DPP-4 inhibitors and heart failure (two large clinical trials reported an increased risk of hospitalization for heart failure with saxagliptin and alogliptin; [Secrest et al, 2017](#)). A network meta-analysis of 50 RCTs reported that there was no increased risk of heart failure for patients taking vildagliptin, sitagliptin, or saxagliptin. However, an increased risk of heart failure was reported in patients taking alogliptin compared to placebo (RR = 2.13; 95%CI 1.06-6.26). Ranking from best to worst, the study found vildagliptin>saxagliptin>sitagliptin>linagliptin>alogliptin ([Guo et al, 2017](#)).



Patients with T2DM and Chronic kidney disease (CKD): **BENEFIT**

In a systematic review of 12 studies, [Walker et al \(2017\)](#) reported that treatment with DPP-4 inhibitors in patients with T2DM and CKD reduced HbA1c% without increasing the risk of adverse events, cardiovascular events, hypoglycemic episodes, or all-cause mortality. DPP-4 inhibitors may be a useful drug in this group of patients due to the reduced incidence of hypoglycemic episodes.

Fracture risk: **NO EFFECT**

A meta-analysis of 62 trials comparing DPP-4 inhibitors to other diabetes drugs or placebo in T2DM reported no difference in fracture risk ([Fu et al, 2016](#)).

Cancer risk: **MIXED AND INCONCLUSIVE**

Using the FDA Adverse Event Reporting System, studies suggested an increased risk of acute pancreatitis and cancer in those using incretin-based drugs (GLP-1 receptor agonists and DPP-4 inhibitors). Therefore, [Overbeek et al \(2018\)](#) conducted a meta-analysis of RCTs and observational studies for the risk of site-specific cancer. RCTs tended to be ~1-2 years in length while observational studies tended to be 1.5-3 years. The only significant result was a reduced risk of breast cancer from observational studies (HR = 0.76; 95%CI 0.60-0.96). However, there were trends toward *reduced* risk of pancreatic and colorectal cancers from RCTs and trends for *increased* risk of thyroid and colorectal cancer in observational studies. The authors say it is not possible to conclude at this point whether the use of DPP-4 inhibitors alters cancer risk.

Other measures

- **TNF α** : A meta-analysis of 8 studies (using either sitagliptin or vildagliptin) reported DPP-4 use was associated with lower circulating levels of TNF α compared to controls (placebo and other diabetes drugs). There was no difference between sitagliptin or vildagliptin ([Atkin et al, 2017](#)).
- **Adiponectin**: In a meta-analysis of 10 studies (either sitagliptin or vildagliptin), DPP-4 inhibitors increased levels of adiponectin compared to the placebo group by 0.74ug/mL but did not significantly increase levels compared to an active group ([Liu et al, 2016](#)).

Safety: DPP-4 inhibitors are generally safe with adverse event profiles similar to placebo.

Types of evidence:

- 2 meta-analyses of RCTs

DPP-4 inhibitors are generally safe with tolerable side effects. In a meta-analysis of 62 trials, [Park et al \(2012\)](#) reported that DPP-4 inhibitors were associated with an increased risk of hypoglycemia, but only when combined with other hypoglycemic agents. Overall, DPP-4 inhibitors were associated with a similar adverse event profile as placebo, but they were associated with a decreased risk of adverse events compared to other hypoglycemic agents ([Park et al, 2012](#)). Another meta-analysis reported that DPP-4 inhibitors were associated with an increased risk of acute pancreatitis (RR = 1.58; 95%CI = 1.04-2.39; absolute risk difference = 0.1%) ([Zheng et al, 2018](#)).

Other potential side effects that have been reported include joint pain, headache, nausea, nasopharyngitis (swelling of nasal passage), abdominal pain, skin reactions, and heart failure (with certain DPP-4 inhibitors, see section above).

Drug interactions:

DPP-4 inhibitors have a number of moderate drug interactions. Major interactions include:

Bexarotene (can increase risk of pancreatitis)

Gatifloxacin (can affect blood glucose levels)

Interactions with specific DPP-4 inhibitors can be found at [drugs.com](https://www.drugs.com).

Sources and dosing:

Sitagliptin: Available with prescription in US. 100mg/day oral tablet

Saxagliptin: Available with prescription in US. 2.5-5mg/day oral tablet

Linagliptin: Available with prescription in US. 5mg/day oral tablet

Alogliptin: Available with prescription in US. 25mg/day oral tablet

Vildagliptin: Available with prescription only in EU. 50mg/day oral tablet

Metformin is the first line recommendation for T2DM patients, and dosing is based on HbA1c% and other diabetes medications. A recommended dosing chart can be found [here](#). They are also available in combination with other drugs such as metformin.

Research underway:

CAROLINA study: This study will test the cognitive effects of linagliptin vs. glimepiride in patients 40-80 years of age with T2DM over 3 years. Since cognitive decline is relatively slow as an aggregate in patients with T2DM, the novelty of this study is that they will examine whether linagliptin can reduce

the number of individuals with accelerated cognitive decline. Final results are expected in 2019 ([Biessels et al, 2018](#)) ([NCT01243424](#)).

Search terms:

Pubmed:

sitagliptin, vildagliptin, saxagliptin, linagliptin,
alogliptin + alzheimer, dementia, cognition
dpp-4 inhibitor [meta-analysis]
dpp-4 inhibitor + aging, lifespan, longevity,
apolipoprotein, intima-media thickness

Websites visited:

- Clinicaltrials.gov
- Examine.com
- DrugAge (o)
- Geroprotectors (o)
- Drugs.com
- DrugBank.ca
- Labdoor.com (o)

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