

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.

GLP-1 Receptor Agonists

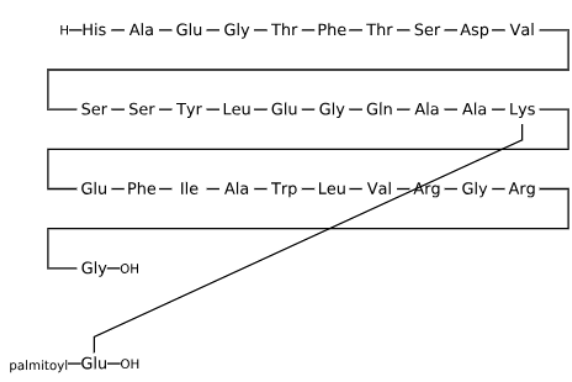
Evidence Summary

GLP-1 agonists are beneficial for patients with type 2 diabetes and obesity. Some evidence suggests benefits for Alzheimer's disease. It is unclear whether it is beneficial for individuals without underlying metabolic disease. Semaglutide seems to be most effective for metabolic dysfunction, though liraglutide has more preclinical data for Alzheimer's disease.

Neuroprotective Benefit: Evidence from many preclinical studies and a pilot biomarker study suggest some neuroprotective benefits with GLP-1 agonists. However, whether they may be beneficial for everyone or only a subset of individuals (e.g. diabetics) is unclear.

Aging and related health concerns: GLP-1 agonists are beneficial for treating diabetes and cardiovascular complications relating to diabetes. It is not clear whether they have beneficial effects in otherwise healthy individuals.

Safety: GLP-1 agonists are generally safe for most people with minor side effects. However, long-term side effects are not known.

Availability: Available as a prescription medicine.	Dose: Varies - see chart at the end of the report	Chemical formula: $C_{172}H_{265}N_{43}O_{51}$ (Liraglutide) MW: 3751.262 g/mol  Source: Pubchem
Half life: Varies – see 'What is it'	BBB: penetrant in animals	
Clinical trials: One ongoing for Alzheimer's disease, one completed for Alzheimer's.	Observational studies: None for Alzheimer's	

What is it?

GLP-1 is an incretin peptide hormone found in the gut that stimulates insulin release by binding to GLP-1 receptors (GLP-1R) on pancreatic β cells. It is increased after eating to help regulate blood glucose levels and induce satiety. GLP-1 is degraded within minutes by dipeptidyl peptidase-4 (DPP4). GLP-1 analogues resist degradation by DPP4, and thus have a longer half-life. Of these, exenatide, lixisenatide and liraglutide were reported to cross the blood brain barrier, though it is likely the entire class does.

GLP-1 agonists vary in their half-lives and dosing schedule:

- Liraglutide (Victoza): 12-13 hours, once-daily
- Exenatide (Byetta): 2.4 hours, twice-daily
- Exenatide once weekly (Bydureon): same half-life as Exenatide but released more slowly, once-weekly
- Lixisenatide (Lyxumia): 1.5-3 hours, once-daily
- Albiglutide (Tanzeum): 5 days, once-weekly
- Dulaglutide (Trulicity): 5 days, once-weekly
- Semaglutide (Ozempic): 7 days, once-weekly

All GLP-1 agonists are sub-cutaneous injectables. However, a once-daily oral formulation of semaglutide is under development and appears nearly as effective as the once-weekly injectable formulation (see diabetes section below).

Type 2 diabetes increases the risk of Alzheimer's disease and vascular dementia. Each are associated with insulin resistance and vascular complications. Alzheimer's disease is associated with impaired insulin signaling in the brain. Increased phosphorylation of serine residues on the insulin receptor IRS-1 (IRS-1 p-Ser) is indicative of reduced insulin signaling while phosphorylation on tyrosine residues (IRS-1 p-Tyr) is indicative of increased insulin signaling ([Bomfim et al, 2012](#)). In addition to pancreatic cells, GLP-1Rs are found on myocardial cells, vascular endothelium and CNS cells. GLP-1 agonists, therefore, may be beneficial in these cell types by providing neuroprotective and anti-inflammatory effects ([Calsolaro and Edison, 2015](#)).

Neuroprotective Benefit: Evidence from many preclinical studies and a pilot biomarker study suggest some neuroprotective benefits with GLP-1 agonists. However, whether they may be beneficial for everyone or only a subset of individuals (e.g. diabetics) is unclear.

Types of evidence:

- One small randomized controlled trial (RCT)
- One RCT in Parkinson's
- Multiple preclinical animal and in vitro studies

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

None.

Human research to suggest benefits to patients with dementia:

One randomized controlled trial in patients with Alzheimer's disease reported that 26 weeks of liraglutide (1.2mg daily) did not change cognition or brain amyloid accumulation. It did prevent a decrease in the uptake of glucose in the brain (between groups was only significant in cingulate cortex and cerebellum, likely due to low numbers). Blood pressure also decreased in the liraglutide group ([Geji et al, 2016](#)).

[Bomfim et al \(2012\)](#) reported an increase in IRS-1 p-Ser (suggesting impaired insulin signaling) in postmortem Alzheimer's brain tissue and in monkeys injected with amyloid-beta oligomers.

Parkinson's disease

In a 60-week clinical study (the drug was given for 48 weeks) in Parkinson's patients, 2mg exenatide once per week improved motor symptoms on the MDS-UPDRS (a Parkinson's scale) when patients were off-medication (i.e. having not taken a dopaminergic drug for 8-36 hours). The MDS-UPDRS is a scale to measure symptoms of Parkinson's disease and consists of four parts: 1) Cognition, behavior, mood; 2) Activities of daily living; 3) Motor evaluation; 4) Complications of medication. There were no effects on parts 1, 2, or 4. Additionally, there were no changes on the MDS-UPDRS when patients were on-medication (i.e. taking dopaminergic drugs). Exenatide patients did have more severe Parkinson's at baseline ([Athauda et al, 2017](#)). [Athauda et al \(2019\)](#) found that the patients treated with exenatide had improved insulin signaling in the brain measured by IRS-1 tyrosine phosphorylation and phosphorylation of downstream effectors such as mTOR and AKT in neuronally-derived extracellular vesicles.

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

GLP-1 agonists have been tested in many animal models of Alzheimer's disease, generally showing beneficial effects (table below). Alzheimer's mouse models also often show signs of impaired insulin signaling in the brain (increased expression of IRS-1 p-Ser) as do primate models of Alzheimer's disease (amyloid-beta oligomer ventricle injections) ([Long-Smith et al, 2013](#); [Batista et al, 2018](#)).

Liraglutide and lixisenatide injections slightly increased brain levels of GLP-1 (suggesting that it crossed the blood brain barrier) with lixisenatide having a greater effect ([Hunter and Holscher, 2012](#)). Exenatide presumably crosses the blood brain barrier, as it improved insulin signaling in the brain of patients with Parkinson's disease (Parkinson's trial above). There is no data on whether albiglutide, dulaglutide, or semaglutide cross the blood brain barrier and increase GLP-1, though given the structural similarities of GLP-1 agonists, it is likely.



A summary of preclinical studies follows: Green = benefit; red = detriment

↑ = Increase; ↓ = Decrease; -- = No Change

Reference	Model	Paradigm	Length of treatment	Cognition	AD Pathology	Other AD-related pathology	Other markers
<i>Exenatide</i>							
Bomba et al, 2013	PS1-KI (no amyloid pathology but cog impairments) (3 month)	Prevention	9 months	No change			Shift toward anaerobic glucose catabolism (↑ lactate, BHB)
	3xTg (3 month)	Early Disease	9 months	No change	-- Amyloid, tau		No change in glucose metabolism
Bomfim et al, 2012	APP/PS1 (13 month)	Late disease	3 weeks	Improved	↓ Amyloid plaques, soluble AB		↓ IRS-1 p-Ser
Chen et al, 2012	ICV-STZ (brain insulin resistance)	Treatment	2 weeks	Improved	↓ ptau	↓ Neuronal death	↑ pAKT, pGSK3B (suggesting reduced signaling thus tau phosph through GSK)
Xu et al, 2015	T2DM (peripheral STZ inj)	Treatment	4 weeks		↓ ptau		↑ insulin signaling in brain ↓ Insulin in periphery
<i>Liraglutide</i>							
McClellan et al, 2015	APP/PS1 (2 months)	Prevention	8 months	Improved	↓ Amyloid plaques	↑ Hippocampal LTP, neurogenesis, synapses ↓ Microglia	



McClellan et al, 2011	APP/PS1 (7 months)	Early disease	8 weeks	Improved	↓ Amyloid plaques, soluble AB	↑ Hippocampal LTP, neurogenesis, synapses ↓ Microgliosis	↑ GLP-1 in the brain
Long-Smith et al, 2013	APP/PS1 (7 months)	Early disease	8 weeks		↓ Amyloid plaques	↓ Microgliosis, astrogliosis	↓ IRS-1 p-Ser
McClellan and Holscher, 2014	APP/PS1 (14 months)	Late disease	8 weeks	Slightly improved	↓ Amyloid plaques, amyloid-beta oligomers	↓ Slightly reduced microgliosis ↑ LTP, new neurons, synaptic density	
Kelly et al, 2015	APP/PS1 (14 months)	Late disease	8 weeks			↓ cerebral microaneurysms and leakage	
Chen et al, 2017	APP/PS1/Tau 3xTg (7 months)	Mid disease	8 weeks	Improved	↓ Slight ptau decrease	↓ Slight NFL, neuronal death	-- Plasma glucose, body weight
Hansen et al, 2016	APP/PS1 (2 versions) (5 and 7 months)	Early disease	3 months (for 5-month mice) 5 months (for 7-month mice)	No change	--Amyloid plaques		-- Body weight
Hansen et al, 2016	hTauP301L (tau model) (3 months)	Prevention	6 months		↓ ptau	↑ Survival	
Qi et al, 2016	AB injections	Treatment	8 weeks	Improved	↓ ptau	↑ p-AKT, p-GSK3B, synaptic integrity	-- Body weight, plasma glucose, plasma insulin, hippocampal insulin



							↑ GLP-1 receptor in brain
Han et al, 2013	AB injections	Treatment	Single hippocampal injection; cognition measured 2 weeks later	Improved		↑ LTP	
Hansen et al, 2015	SAMP8 (6 months)	Prevention	4 months	Improved (memory retention but not acquisition or recognition)			
Xiong et al, 2013	ICV-STZ (brain insulin resistance)	Treatment	1 month	Improved	↓ tau	↓ Neurofilament, cell death	
Zhang et al, 2019	Hyperhomocysteine	Treatment	2 weeks	Improved	↓ ptau, AB42 (only at low and medium doses)		↓ IRS-1 p-Ser
<i>Lixisenatide</i>							
Cai et al, 2018	APP/PS1/tau (3xTg) (12 months)	Early disease	2 months		↓ Amyloid plaques, ptau	↓ Microglial staining, ↑ PKA-pCREB signaling	
McClean and Holscher, 2014*	APP/PS1	Early disease	10 weeks	Improved	↓ Amyloid plaques	↓ Microglial staining, ↑ LTP	
Cai et al, 2014	AB injections	Treatment	2 weeks (single injection of lix)	Improved		↑ LTP, p-GSK3B	



<i>Dulaglutide</i>							
Zhou et al, 2019	STZ-ICV (brain insulin resistance)	Treatment	4 weeks	Improved	↓ ptau	↑ GLP-1 receptor, pAKT, pPI3K, pGSK3B	
<i>Albiglutide</i>							
None							
<i>Semaglutide</i>							
None							

APOE4 interactions:

None.

Aging and related health concerns: GLP-1 agonists are beneficial for treating diabetes and cardiovascular complications relating to diabetes. It is not clear whether they have beneficial effects in otherwise healthy individuals.

Types of evidence:

- Multiple clinical trials and meta-analyses in patients with type 2 diabetes or obesity
- Two open-label studies for cIMT in patients with type 2 diabetes
- A biomarker study in type 2 diabetics undergoing carotid endarterectomy
- Preclinical studies for cardiovascular disease

Longevity

No studies have looked specifically at lifespan.

Diabetes

In a meta-analysis of RCTs, [Andreadis et al \(2018\)](#) reported that semaglutide was more effective than placebo and other anti-diabetics for glycemic control. Other drugs studied included sitagliptin, exenatide, liraglutide, dulaglutide, and insulin glargine.

A once-daily oral formulation of semaglutide is under development by Novo Nordisk and, at higher doses, appears to be as effective as controlling diabetes as a once-weekly semaglutide injectable ([Davies et al, 2017](#)).

Cardiovascular outcomes: Potential Benefit

In a meta-analysis of four GLP-1 receptor agonist trials, [Bethel et al \(2018\)](#) reported that GLP-1 receptor agonists were associated with a 10% reduced risk of a major adverse cardiovascular events (CVD mortality, non-fatal MI, and non-fatal stroke), 13% reduced risk of cardiovascular (CVD) mortality, and 12% reduced risk in all-cause mortality compared to placebo. There were no significant effects on fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, or hospital admission for unstable angina or heart failure. Trials included ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN 6 (semaglutide), and EXSCCEL (extended-release exenatide). Another meta-analysis reported that GLP-1 agonists were associated with a 12% reduced risk of mortality, 15% reduced risk of CVD mortality, but no significant effects on heart failure, MI, unstable angina, or stroke ([Zheng et al, 2018](#)).

LEADER (liraglutide): In a randomized controlled trial over 3.5 years in 9,340 type 2 diabetic patients over the age of 50 with either established CVD or CVD risk factors, liraglutide reduced the risk of major cardiovascular events (HR 0.87; 95%CI 0.78-0.97), cardiovascular deaths (HR 0.78; 95%CI 0.66-0.93), and all-cause mortality (0.85; 95%CI 0.74-0.97) ([Marso et al, 2016](#)). A sensitivity analysis, however, showed that these benefits were in patients with established CVD and not in patients with CVD risk factors ([Singh and Singh, 2017](#)).

SUSTAIN-6 (semaglutide): In an RCT over 104 weeks in 3297 patients with T2DM, semaglutide (0.5 or 1mg weekly) significantly reduced the risk of the primary composite outcome (CVD death, nonfatal MI, and nonfatal stroke) (HR 0.74; 95%CI 0.58-0.95). For individual outcomes, semaglutide significantly reduced the risk of nonfatal stroke, revascularization, and new or worsening nephropathy. However, it significantly *increased* the risk of retinopathy complications (HR 1.76; 95%CI 1.11-2.78) ([Marso et al, 2016](#)). In an analysis of all RCTs using semaglutide, [Vilsboll et al \(2018\)](#) suggested that this increased risk of retinopathy complications was due to the magnitude and rapidity of HbA1c% reductions and primarily in patients with retinopathy at baseline. In a meta-analysis of RCTs, [Dicembrini et al \(2017\)](#) reported that semaglutide, and GLP-1 agonists as a class, was associated with a reduced risk of nephropathy compared to placebo (OR = 0.74; 95%CI 0.60-0.92).

Blood Pressure: Potential Benefit

Compared to placebo, insulin, sulfonylureas, and GLP-1 agonists significantly reduced systolic blood pressure, ranging from -1.84 mmHg to -4.60 mmHg. They slightly increased heart rate (2-3 beats per minute) ([Sun et al, 2015](#)).

Artery health: Potential Benefit

An open label study in 121 type 2 diabetic patients taking metformin showed that adding liraglutide decreased waist circumference, total cholesterol, triglycerides, LDL, and HbA1c. It also decreased carotid intima-media thickness (cIMT) by 0.19mm – back to “healthy” measurements ([Rizzo et al, 2016](#)). Another open label study showed even greater reduction in cIMT in patients with larger cIMT at baseline (by 0.26mm) ([Rizzo et al, 2014](#)).

In patients undergoing carotid endarterectomy, plaques removed from individuals taking a drug that affects the incretin system (either GLP-1 agonists or DPP4 antagonists) had decreased macrophage-rich areas, decreased number of T-cells, increased collagen content, decreased TNF α levels, and increased SIRT6 expression compared to those not taking an incretin-based therapy ([Balestrieri et al, 2015](#)).

A small RCT in patients with T2DM reported that exenatide (twice per day) over 3 months had no effect on exercise capacity or endothelial function (measured with flow-mediated dilation) but did slightly improve arterial stiffness compared to placebo ([Scalzo et al, 2017](#)).

Lipid Profiles: Modest Benefit

In a network meta-analysis of RCTs using diabetes drugs, GLP-1 agonists were associated with modest reductions in LDL-c and triglycerides, but the reductions are not likely to be clinically meaningful (e.g. GLP-1 agonists reduced LDL-c < 10mg/dL) ([Sun et al, 2015](#)).

Preclinical Studies

Preclinical animal studies suggest that liraglutide can slow the formation and progression of atherosclerotic plaques and improve plaque stability. However, it had no effect late in the disease process. *In vivo* and *in vitro* studies suggest that liraglutide inhibits the induction of inflammatory markers such as NF-kB, ICAM1, endothelin 1 and VCAM1. It also increased the expression of eNOS and ABCA1 (involved in cholesterol efflux) in endothelial cells and macrophages, respectively ([Gaspari et al, 2011](#); [Schisano et al, 2012](#); [Dai et al, 2013](#); [Tashiro et al, 2014](#); [Gaspari et al, 2013](#)).

Safety: GLP-1 agonists are generally safe for most people with minor side effects. However, long-term side effects are not known.

Types of evidence:

- Multiple clinical trials and meta-analyses



The most common side effects of GLP-1 agonists are gastrointestinal in nature (e.g. nausea and diarrhea). These generally fade over time but are the most common reason for drop outs. Preclinical studies and postmarketing pharmacovigilance studies suggest some concerns over chronic use and pancreatitis (due to overstimulation of GLP-1 receptors on the pancreas), pancreatic cancer, or thyroid carcinoma. However, these effects are not increased in clinical trials (but long-term side effects are uncertain) ([Gallo, 2013](#); [Monami et al, 2017](#)). Some studies have reported an increased risk for hypoglycemia when taking sulphonylureas in combination with GLP-1 agonists. ([Shyangdan et al, 2011](#)). A meta-analysis of RCTs reported an increased risk of gallstones with GLP1 agonists (OR 1.30; 95%CI 1.01-1.68; incidence 141/14,872 for GLP-1 agonists, 99/17,232 for comparators) ([Monami et al, 2017](#)).

Drug Interactions

GLP-1 agonists should not be taken with other drugs that can cause hypoglycemia (such as insulin and gatifloxacin). In addition, they should not be taken with bexarotene (due to increased risk of pancreatitis). They can also increase resting heart rate, so it should be used with caution in patients with a history of CVD (although cardiovascular outcome trials suggest a benefit). For more drug interactions see drugs.com.

Sources and dosing:

None of the drugs are yet available as a generic. Dosing information for specific drugs can be found on [The Johns Hopkins Patient Guide to Diabetes](#).

Research underway:

ADDF is [currently funding a phase 2 trial](#) testing liraglutide in Alzheimer's patients that is expected to be completed in 2019. [Liraglutide](#), [Exenatide](#), [Lixisenatide](#), and [Semaglutide](#) are all in clinical trials for Parkinson's. There are almost 200 clinical trials ongoing using different GLP-1 agonist (mostly liraglutide and exenatide) for different indications, mostly metabolic in nature. Neuraly is in phase 1 [clinical trials](#) using a PEGylated form of exenatide for Parkinson's and Alzheimer's disease.

Search terms:

Pubmed:

liraglutide + alzheimer, cognition, dementia, aging, longevity,
lifespan, cardiovascular [MA/SR], mortality [MA/SR],

peripheral neuropathy, orthostatic hypotension,
atherosclerosis, cancer, apoe, apolipoprotein
semaglutide [meta-analysis]
semaglutide + cognition, alzheimer, dementia, blood brain
barrier
lixisenatide + alzheimer, cognition
albiglutide + alzheimer, blood brain barrier, cognition
dulaglutide + alzheimer, blood brain barrier, cognition
glp-1 agonist + insulin resistance

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