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Review

Glucagon-like peptide-1 medicines in neurological and psychiatric disorders

Susanna Fang,[1,4] Fiona Cui,[1,4] and Daniel J. Drucker[1,2,3,*]
[1]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
[2]Department of Medicine, University of Toronto, Toronto, ON, Canada
[3]Lunenfeld-Tanenbaum Research Institute, Mt. Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G1X5, Canada
[4]These authors contributed equally
*Correspondence: drucker@lunenfeld.ca
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SUMMARY

Glucagon-like peptide-1 (GLP-1) medicines are used for the treatment of type 2 diabetes (T2D) and obesity and reduce rates of cardiovascular disease, including stroke, in people with T2D. Substantial evidence from real-world data and clinical trials highlights the therapeutic potential of GLP-1 medicines for the treatment of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. Similarly, there is growing evidence for the potential utility of using GLP-1 medicines to reduce rates of smoking, or use of alcohol, tobacco, cannabis, or cocaine in individuals with substance use disorders. More limited clinical data suggest utility for GLP-1 medicines in patients with migraine or intracranial hypertension. The available data suggest that the use of GLP-1 medicines exhibits an acceptable safety profile in most individuals with neuropsychiatric disorders. Here, we review recent clinical evidence and ongoing trials exploring the efficacy and safety of GLP-1 medicines across a broad range of neurological conditions.

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) medicines, herein defined as drugs that mediate their action wholly or in part through activation of the GLP-1 receptor (GLP-1R), are approved for the treatment of type 2 diabetes (T2D), obesity, associated cardiovascular and kidney disease, and metabolic liver disease.[1] These agents act on GLP-1Rs in the periphery to increase insulin and inhibit glucagon secretion and in the brain to slow gastric emptying and suppress appetite, leading to weight loss.[2] Semaglutide is also approved for reduction of cardiovascular and kidney disease in people with T2D and obesity and for the treatment of metabolic dysfunction-associated steatohepatitis.[3] The GLP-1 medicine tirzepatide activates both the GLP-1R and the glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) and is also approved for T2D, obesity, and obstructive sleep apnea.[3]

DIRECT AND INDIRECT COMMUNICATION WITH THE BRAIN

Considerable preclinical and clinical data support the potential therapeutic benefit of these drugs for a wide range of neurological disorders. Although GLP-1 medicines do not efficiently cross the blood-brain barrier (BBB), both small peptides and larger high-molecular-weight GLP-1 medicines localize to circumventricular organs including the subfornical organ, vascular organ of the lamina terminalis, median eminence, and area postrema.[4–6] Indeed, very low levels of GLP-1 medicines are detected in human cerebrospinal fluid (CSF),[7] with levels of CSF exenatide 100-fold lower than levels detected in the circulation.[8] Despite limited penetration of GLP-1 medicines within the brain, GLP-1 medicines activate neuronal cFos expression in multiple brain regions, even within nuclei that do not express GLP-1R *or* or GIPR.[4,5] Similarly, functional magnetic resonance imaging (fMRI) studies reveal that regions of the brain such as the hypothalamus and parietal cortex are activated by GLP-1 medicines in humans with T2D or obesity. Reduced functional activation of the fusiform gyrus and lateral ventricle has been seen in obese vs. lean individuals with T2D in response to acute administration of GLP-1 medicines such as lixisenatide.[9] Hence, despite limitations in directly accessing structures beyond the BBB, peripherally administered GLP-1 medicines effectively communicate with multiple regions in the central nervous system (CNS), through mechanisms requiring the GLP-1R.[10] Here, we provide some preclinical data on how GLP-1 medicines interact with and ameliorate CNS pathology, while summarizing the clinical data interrogating the actions of GLP-1 medicines in neurodegenerative disorders, substance use disorders (SUDs), psychiatric disorders, headache, stroke, and seizure disorders.

GLP-1 MEDICINES IN NEURODEGENERATIVE DISEASES

Extensive preclinical evidence illustrates the anti-inflammatory and neuroprotective properties of GLP-1 medicines across multiple models of neurodegenerative disease, particularly Alzheimer's disease (AD) and Parkinson's disease (PD).[11,12] These

conditions share some common pathophysiological features such as chronic neuroinflammation, synaptic dysfunction, and progressive neuronal loss. GLP-1 medicines mitigate some overlapping CNS pathways through a set of actions beyond their well-established peripheral metabolic effects. Experimental evidence in rats and mice highlights the neuroprotective potential of GLP-1 medicines, primarily through anti-inflammatory and cytoprotective mechanisms[13] and via metabolic improvements in the CNS (Figure 1).

AD is typically studied using transgenic mouse models that partially recapitulate features of human AD, including amyloid deposition, neuronal degeneration, and cognitive decline.[14] GLP-1 medicines attenuate glial activation, reduce amyloid plaque, and preserve neuronal structure and density, while improving performance in tasks associated with cognitive function.[15,16] Similarly, in animal models of PD, GLP-1 medicines including exenatide, liraglutide, and semaglutide suppress astrocytic and microglial activation, lower pro-inflammatory cytokine levels in the brain, and reduce oxidative stress, while improving motor performance and dopaminergic neuron survival.[17] GLP-1 medicines also reduce α-synuclein aggregation, increase levels of neurotrophic factors such as glial cell line-derived neurotrophic factor, and inhibit apoptotic signaling,[18–20] actions collectively supporting neuronal survival and maintenance of synaptic integrity. Notably, benefits ensuing from GLP-1R activation extend beyond motor improvements and encompass restoration of spatial learning and memory.[21]

Several studies suggest that the neuroprotective actions of GLP-1 medicines may also be mediated by improvements in brain insulin resistance and glucose metabolism, in part through restoration of impairments in insulin receptor substrate 1 phosphorylation,[22] effectively re-establishing functional central insulin signaling, although the data linking GLP-1 action to central insulin signaling are limited. Despite differing pathological progressions in the development of AD and PD, GLP-1 medicines generally reduce central inflammation, improve metabolic function, and support neuronal health in most but not all preclinical studies.[23]

REAL-WORLD DATA

Real-world analyses support an association between the use of GLP-1 medicines and a reduced risk for dementia in people with T2D. A pooled analysis of three major cardiovascular outcome trials (CVOTs) studying 15,820 patients with T2D treated with liraglutide or semaglutide reported a significantly lower hazard ratio ([HR] = 0.47) for subsequent dementia diagnosis compared to placebo, over a median follow-up of 3.61 years.[24] A reduction in the risk of dementia (HR = 0.89) among patients treated with GLP-1 medicines was also observed in a Danish registry of 120,054 patients across a 7.4-year median follow-up period.[24] Similarly, analysis of Sweden's national healthcare data (n = 88,381) revealed a 54% reduction in dementia risk among patients treated with GLP-1 medicines (n = 12,351), with a 31% and 23% lower risk of dementia for treatment with GLP-1 medicines vs. dipeptidylpeptidase-4 (DPP-4) inhibitors or sulfonylureas, respectively.[25] Although rates of dementia are low in cardiovascular outcome trials, a meta-analysis of 26 randomized controlled trials (RCTs) (n = 164,531) found that GLP-1 medicines, but not sodium glucose transport protein 2 (SGLT2) inhibitors, were associated with a lower risk of dementia.[26] A large-scale emulated trial conducted in the United States using a national healthcare database of over 1 million records reported that semaglutide use was associated with a reduction in the risk of first-time AD diagnosis over a 3-year follow-up period compared to the use of other glucose-lowering medications, including other GLP-1 medicines.[27] Consistent with these findings, a large global retrospective cohort study involving over 5 million individuals with obesity across 17 countries supported the neuroprotective potential of semaglutide in people with obesity, revealing reduced rates of AD (relative risk [RR] of 0.627), Lewy body dementia (RR of 0.59), vascular dementia (RR of 0.438), and PD (RR of 0.574).[28]

The impact of GLP-1 medicines on incident PD in real-world data is less consistent A case-control study using data from the Finnish patient register (n = 2,017 cases and 7,934 controls) found no significant association between exposure to GLP-1 medicines and the diagnosis of PD.[29] In contrast, a cohort study of people with T2D from 1999 to 2018 (n = 86,229) showed that GLP-1 medicines reduce the risk of PD when compared to metformin (HR = 0.54).[30] Similarly, analysis of US Medicare claims data from 2016 to 2020 (n = 89,074) found a decreased risk of PD in patients with T2D receiving GLP-1 medicines compared to those on DPP-4 inhibitors (HR = 0.77).[31] The observational nature of these retrospective analyses report intriguing associations that require RCTs to determine whether GLP-1 medicines can prospectively modify the course of neurodegenerative diseases.

CLINICAL TRIALS

Alzheimer's disease

Several clinical trials have been conducted to evaluate the effect of GLP-1 medicines in AD and PD (Figure 2). In 2013, a clinical study (NCT01469351) evaluated 38 individuals without T2D with established mild AD, randomized to placebo or liraglutide (1.8 mg daily [qd]) over a 26-week period. Although this pilot study was underpowered to detect cognitive changes, liraglutide preserved brain glucose metabolism relative to placebo as shown by fluorodeoxyglucose positron emission tomography scans, while amyloid accumulation was not different between groups.[32] The ELAD study (NCT01843075) assessed 204 participants with mild to moderate AD randomized to once-daily liraglutide (up to maximum tolerated doses of 1.2 or 1.8 mg qd) or placebo for 12 months.[33] Although the study did not meet its primary objective of enhancing brain glucose metabolism, liraglutide-treated subjects experienced reduced brain volume loss and slower cognitive decline.[34]

The EVOKE (NCT04777396) and EVOKE+ (NCT04777409) trials evaluate oral semaglutide up to 14 mg qd vs. placebo over 156 weeks in more than 3,600 male and female participants aged 55–85 years with early-stage AD or mild cognitive impairment (MCI). Enrollment criteria include MCI or mild dementia due to AD with confirmed amyloid abnormalities by imaging or CSF biomarker analysis for Aβ1–42 or CSF Aβ1–42/Aβ1–40. EVOKE+ also permitted enrollment of patients with concomitant

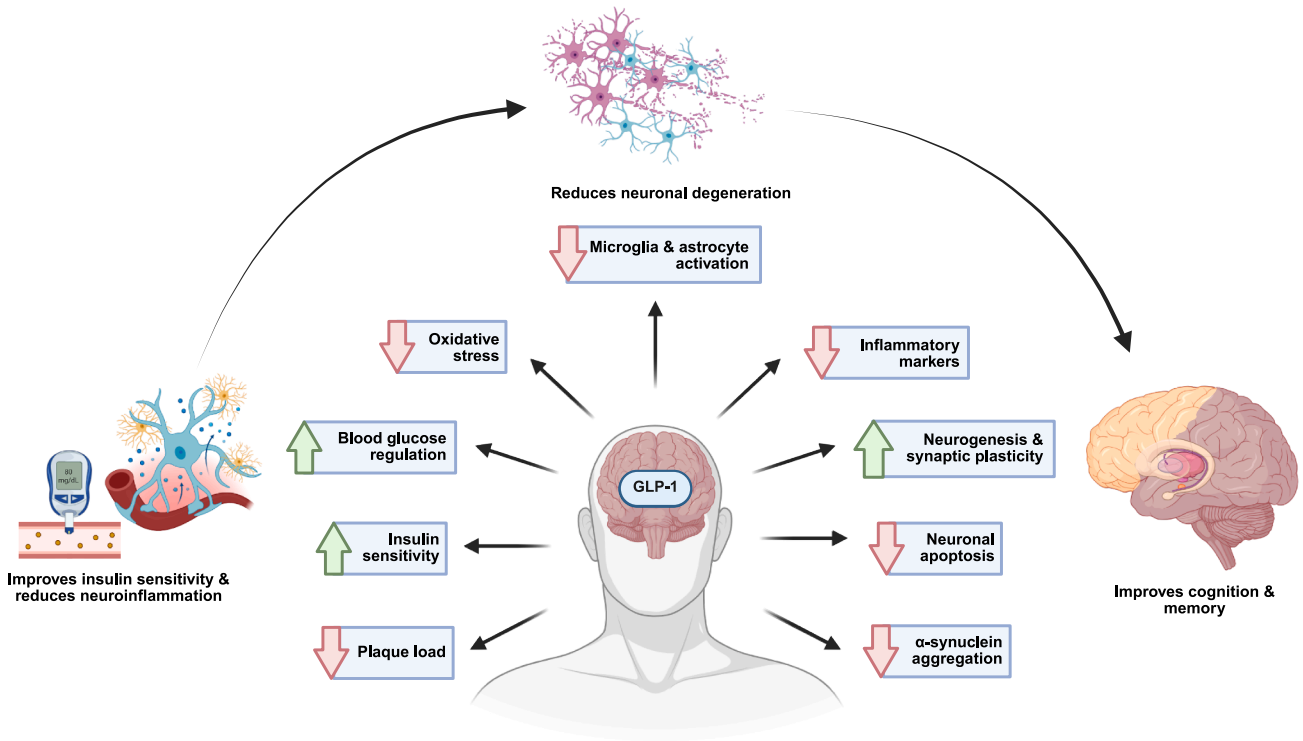

Figure 1. Potential mechanisms underlying the neuroprotective properties of GLP-1R agonists

Preclinical studies demonstrate the ability of GLP-1 medicines to improve central and peripheral glucose metabolism, reduce oxidative stress and neuroinflammation, reduce plaque load, and directly preserve and improve neuronal health. Arrows illustrate the direction of the effect observed with GLP-1 medicines.

small-vessel cerebrovascular disease. These primary endpoint assessed whether semaglutide could delay functional decline, as measured by the Clinical Dementia Rating scale after 104 weeks of treatment.[35] A biomarker sub-study was also included to monitor the impact of semaglutide on neuroinflammation and pathological protein aggregation to explore more mechanistic insights.[35]

Although semaglutide-treated subjects exhibited improvements in AD-related biomarkers, semaglutide was not superior to placebo in reducing rates of progression of AD in either of the EVOKE trials (https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=916462). The LIGHT-MCI study (NCT03113529) is investigating the effects of liraglutide, empagliflozin, and linagliptin ($n = 132$ per arm) on both cognition and olfactory functions in individuals with T2D and MCI over 48 weeks. The ISAP trial (ISRCTN71283871) is assessing whether oral semaglutide (up to 14 mg qd) over a 52-week treatment period can mitigate tau deposition and neuroinflammatory responses in individuals at risk for preclinical AD.[36] Meanwhile, the OxSENSE trial (NCT06363487) is taking a different approach by investigating the immediate impact of a single semaglutide dose 0.5 mg subcutaneously (s.c.) on cognitive performance in healthy adults. Collectively, these studies will extend our understanding of whether GLP-1 medicines represent useful medicines to slow down or prevent cognitive decline and neurodegenerative disease progression at different stages of the disease process.

Parkinson's disease

Clinical exploration into the application of GLP-1 medicines in PD began in 2013 with an open-label pilot study (NCT01174810), which tested exenatide 10 μg twice daily in 45 patients with moderate PD over a 1-year period. Notable improvements in motor function, as assessed by part III of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) were detected in the exenatide-treated group relative to non-treated controls.[37] A subsequent double-blind phase 2 study conducted in 2016 evaluated the effects of exenatide 2 mg weekly (qw) in 60 participants with PD (NCT01971242). Patients receiving exenatide maintained more stable motor function during off-medication periods, in contrast to progressive motor deterioration observed in the placebo group.[38] A preliminary analysis of a trial investigating daily liraglutide administration in 63 PD patients (NCT02953665) reported improvements in motor outcomes over 54 weeks and enhancements in cognitive performance and activities of daily living.[39]

The long-acting exenatide derivative NLY01 was evaluated in a 36-week trial involving 255 individuals with early-stage, untreated PD (NCT04154072). Although no significant clinical differences were observed in the overall cohort treated with NLY01 vs. placebo, post hoc analyses indicated a more favorable response in younger NLY01-treated participants, suggesting that age may influence therapeutic efficacy.[40] Daily lixisenatide was evaluated for a 1-year period in 156 patients with early-stage PD in the LixiPark study (NCT3439943). Motor

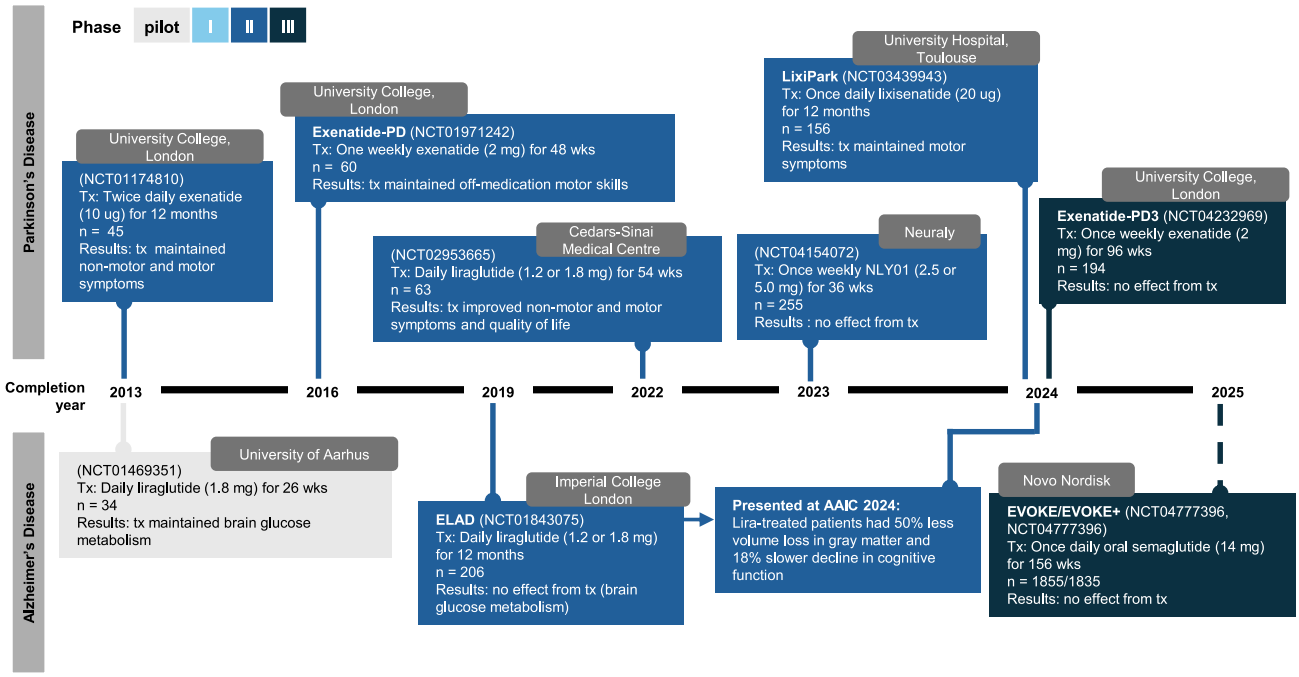

Figure 2. Clinical trials in neurodegenerative disorders

A timeline and results of clinical trials evaluating the effectiveness of GLP-1R agonists in treating Alzheimer's and Parkinson's diseases. tx=treatment;

symptoms remained relatively stable in the treatment group, while the placebo group experienced progressive decline. Notably, these effects appeared to persist beyond the treatment period, raising the possibility of disease-modifying properties of GLP-1 medicines.[41] The exenatide-PD3 trial, the largest and longest trial to date, studied 198 early-stage PD patients over 96 weeks to evaluate once-weekly exenatide (NCT04232969). This trial did not show meaningful improvements in either motor or non-motor outcomes, or evidence of delayed disease progression in patients randomized to exenatide.[8]

Improvements in MDS-UPDRS part III motor scores across multiple PD trials suggest that GLP-1 medicines may alleviate motor symptoms, even during off-medication states. Some studies also reported cognitive benefits, pointing to the potential for broader neuroprotection. However, the lack of consistent findings, especially from two large trials, highlights uncertainties surrounding the magnitude of efficacy, emphasizing the need for better understanding of potentially responsive patient subgroups and how GLP-1 medicines interact with the underlying biological mechanisms.

OTHER NEURODEGENERATIVE DISORDERS

Emerging clinical data suggest the safety and some potential benefits of GLP-1 medicines in patients with multiple sclerosis (MS), although the data are limited. In a retrospective study with an average follow-up of 24.2 months, GLP-1 medicines were well-tolerated in 49 patients with MS, obesity, and features of the metabolic syndrome when used for achievement of weight loss.[42] A retrospective analysis of 60 patients with MS who received GLP-1 medicines reported minimal adverse events and no indication of worsened MS progression with significant weight loss observed in MS patients when compared to placebo.[43] In a prospective study, 12 months of once-weekly dulaglutide treatment preserved endothelial function in 13 MS patients, whereas parameters of endothelial function worsened in control subjects with MS, findings independent of changes in body weight.[44] These small studies support the safety profile and metabolic benefits of GLP-1 medicines in MS. However, larger RCTs are needed to investigate whether GLP-1 medicines alter neurological outcomes in patients with MS.

An open-label trial (n = 50, 1:1) assessing exenatide 2 mg qw (once weekly) vs. placebo in patients with multisystem atrophy found that the Unified Multiple System Atrophy Rating Scale (UMSARS) parts I + II combined score worsened by 6.1 points (95% confidence interval [CI]: 3.0 to 9.3, SD = 6.9) in the exenatide group compared to a reduction of 13.3 points (95% CI: 9.2 to 17.3, SD = 9.4) in the control group over 48 weeks, with an adjusted mean difference of −7.4 points (−11.3 to −3.6, p = 0.0003). Nevertheless, biomarker analyses such as neurofilament light chain and CSF alpha-synuclein oligomer load, as well as imaging and sensor-derived gait measures, were not different between groups; hence the therapeutic activity of exenatide in this trial remains unclear.[45]

GLP-1 MEDICINES IN SUDs

Pharmacological interventions for SUDs encompassing alcohol, cocaine (and other stimulants), opioids, and nicotine are often limited in effectiveness.[46,47] Considerable evidence suggests

that GLP-1 medicines may reduce the rewarding effects of several addictive substances in rodent models of SUD and in humans,[48] reflecting actions of GLP-1 to modulate the mesolimbic system. Notably, GLP-1R is expressed in key areas of the mesolimbic system such as the ventral tegmental area, nucleus accumbens, and laterodorsal tegmental nucleus,[49–51] consistent with their regulation of neurobiological mechanisms that underlie the SUDs.

Alcohol use disorder

Alcohol use disorder (AUD) is a condition characterized by the inability to control alcohol intake. While three medications are Food and Drug Administration (FDA)-approved for treating adults with AUD, incomplete responses are common,[52] warranting the development of new therapeutics. *GLP1R* SNPs are associated with AUD in Caucasian and African American subjects, with an association between rs6923761 and AUD observed in an independent cohort of male subjects.[53] Evidence from observational studies and clinical trials suggests that GLP-1 medicines may be effective in treating AUD. A Danish nationwide cohort study of users of GLP-1 medicines (n = 38,454) and DPP4 inhibitors (n = 49,222), median follow-up of 4.1 years identified 649 subjects with an alcohol-related event such as an AUD diagnosis. Patients treated with GLP-1 medicines had a lower risk of alcohol-related events compared to individuals administered DPP4 inhibitors[54] with greater evidence for benefit during the first 3 months of treatment. An observational study from January 2006 to December 2023 assessed 227,866 individuals with AUD in Sweden. Over a mean follow-up period of 8.8 years, 133,210 persons experienced AUD-related hospitalization.[55] Both semaglutide and liraglutide use were associated with lower rates of SUD- and AUD-related hospitalization. Consistent with these findings, in a secondary analysis of an RCT investigating whether dulaglutide improved abstinence from alcohol during smoking cessation (n = 151), dulaglutide (1.5 mg s.c. once weekly for 12 weeks)-treated subjects drank less alcohol, irrespective of smoking status.[56] An RCT conducted on AUD patients (n = 127) found that exenatide (2 mg s.c. once weekly for 26 weeks) did not reduce the number of heavy drinking days.[57] However, fMRI scans (n = 17) revealed that exenatide reduced alcohol cue reactivity in the ventral striatum, which plays a role in addiction and relapse.[57] In an RCT (n = 48), semaglutide titrated once weekly to a final dose of 1 mg at week 9, reduced the number of drinks per drinking day and weekly alcohol craving compared to placebo-treated subjects.[58]

A nationwide retrospective cohort study using TriNetX data found that patients with obesity and no prior history of AUD treated with semaglutide (n = 26,566) had a lower risk of AUD diagnosis (0.37% vs. 0.73%; HR: 0.50, 95% CI: 0.39–0.63) compared to patients not treated with GLP-1 medications (n = 26,566) over 12 months, findings consistent across gender, age, race, and presence or absence of T2D.[59]

In patients with obesity and history of AUD (n = 1,051 or 715), semaglutide reduced the risk of recurrent AUD diagnosis compared to use of non-GLP-1 anti-obesity medications (n = 1,051; 22.6% vs. 43.0%; HR: 0.44, 95% CI: 0.38–0.52) and naltrexone or topiramate (n = 715; 21.5% vs. 59.9%; HR: 0.25, 95% CI: 0.21–0.30) over 12 months, findings consistent in patients with T2D. Notably, the lower risk of incident and recurrent AUD persisted over 3 years.[59] Several clinical trials are underway to evaluate the use of GLP-1 medicines for reducing alcohol intake in patients with AUD (NCT06015893, NCT05891587, and NCT05892432) and AUD with comorbid obesity (NCT05895643). The available data to date are intriguing, yet the therapeutic efficacy requires confirmation in much larger longer trials. Interestingly, given the therapeutic benefit of GLP-1 medicines in metabolic liver disease,[60,61] semaglutide (NCT06409130), tirzepatide (NCT07046819), and pemvidutide (NCT07009860) are being evaluated in people with alcohol-associated liver disease.

Cocaine use disorder

There are currently no FDA-approved drugs to treat cocaine use disorder (CUD), but preclinical studies suggest that GLP-1 medicines modify neurochemical pathways and addictive behaviors associated with cocaine use.[62] A pilot study in mainly African American men with CUD (n = 13) found that a 3-hour pretreatment with exenatide (5 μg; s.c.) did not affect the number of self-administered cocaine infusions, feelings of euphoria, or cocaine craving compared to placebo.[63] Ongoing studies are investigating the use of repeated doses of longer-acting exenatide (2 mg weekly for 6 weeks; NCT06252623) or semaglutide (up to 2 mg weekly for 16 weeks; NCT06691243) in CUD.

OTHER SUDs

Several studies have interrogated the role of GLP-1 medicines on smoking cessation. In target trial emulations using TriNetX data from T2D patients, semaglutide users (n = 5,967; propensity-score matched 1:1) had a lower risk of medical encounters for tobacco use disorders (TUDs) and reduced prescriptions for both smoking cessation medication and smoking cessation counseling compared to users of other glucose-lowering medications, effects observed in patients with and without obesity.[64] Moreover, the effect of semaglutide on reducing cumulative incidence of medical encounters for TUD was the strongest within the first 30 days, with continued modest divergence over 12 months. Exenatide (2 mg, once weekly) for 6 weeks was studied together with nicotine replacement therapy in prediabetic and/or overweight smoking subjects (n = 84). Exenatide qw reduced end-of-treatment craving and increased rates of smoking abstinence, together with a reduction in post-cessation body weight.[65] Once-weekly dulaglutide (1.5 mg qw over 12 weeks) or placebo was assessed over 12 weeks in 255 adult participants with at least moderate cigarette use who wanted to quit smoking. No difference in abstinence rates was observed after 12 weeks, although post-cessation weight gain was modestly reduced in dulaglutide-treated subjects.[66] An RCT (NCT05610800) is recruiting patients to investigate the effect of exenatide (once weekly 2 mg for 14 weeks) compared to vehicle when combined with daily nicotine patches and smoking cessation counseling on smoking cessation in prediabetic and/or overweight smokers.[67]

A retrospective cohort study evaluated the impact of GLP-1 medicines compared to other anti-obesity medications (such as bupropion, naltrexone, and orlistat) on the incidence and recurrence of cannabis use disorder in subjects with obesity

and/or T2D in the TriNetX database.[68] Semaglutide reduced the risk of incident (0.28% vs. 0.48%; HR: 0.56, 95% CI: 0.42–0.75) and recurrent (13.0% vs. 20.4%; HR: 0.62, 95% CI: 0.46–0.84) cannabis use disorder compared to other anti-obesity medications over 12 months, with the largest effects observed in men, Caucasian subjects, and individuals over 55 years of age.[68] Semaglutide also reduced the risk of incident (0.21% vs. 0.48%; HR: 0.40, 95% CI: 0.29–0.56) and recurrent cocaine use disorder (13.7% vs. 19.1%; HR: 0.66, 95% CI: 0.42–1.03) compared to non-GLP-1 drugs over 12 months, with the strongest effects in men, white subjects, and patients over 55 years old.

GLP-1 MEDICINES IN PSYCHIATRIC DISORDERS

Obesity and diabetes are associated with reduced emotional well-being and greater prevalence of psychiatric disorders such as major depressive behavior and anxiety disorders. In rodents, GLP-1R agonists and DPP4 inhibitors modulate anxiety- and depressive-like behavior, which are assessed by standardized behavioral tests such as the elevated plus maze and forced swim test.[69,70] However, modeling of psychiatric disorders in rodents for prediction of efficacy in humans remains challenging.[71]

It is unclear whether GLP-1 medicines affect psychiatric symptoms independent of the impact of weight loss on psychological well-being in clinical trials. Data from the PIONEER 10 RCT in Japanese patients with T2D (n = 458) taking once-daily oral semaglutide up to 14 mg qd or dulaglutide 0.75 mg qw found reduced anxiety and less dissatisfaction with semaglutide compared to dulaglutide-therapy after 52 weeks.[72] In a non-randomized cohort study, exenatide-treated subjects with T2D (n = 71) reported greater well-being and lower Hospital Anxiety and Depression Scale scores compared to matched insulin-treated patients (n = 67) after 6 months of therapy.[73] Analysis of subjects with T2D treated with liraglutide (1.2 mg, n = 245; 1.8 mg, n = 242) or glimepiride (8 mg, n = 245) for 52 weeks revealed improved scores in health-related quality of life (HRQoL), mental and emotional health, psychological well-being, and psychological distress in the liraglutide (1.8 mg) vs. the glimepiride-treated group, findings associated with improvements in glycemic control and weight loss.[74] A meta-analysis of RCT data in adults (n = 107,860) with overweight/obesity and/or diabetes found that GLP-1 medicines did not affect rates of psychiatric adverse events or depressive symptoms.[75] Rather, patients treated with GLP-1 medicines reported higher mental HRQoL (g = 0.15; 95% CI, 0.07 to 0.22; $p < 0.001$) and improvements in emotional eating behavior (g = 0.32; 95% CI, 0.11 to 0.54; p = 0.003).

Among 354 Danish patients with schizophrenia initiating treatment with glucose-lowering medicines for T2D from 2007 to 2019, rates of schizophrenia-linked hospitalizations or all-cause mortality were not different for subjects treated with GLP-1 medicines vs. DPP4 inhibitors or SGLT2 inhibitors.[76]

In a pilot study of patients (n = 17) with major depressive disorder or bipolar disorder, 4 weeks of liraglutide (up to 1.8 mg/d) in addition to existing pharmacotherapy improved results of cognitive function tests including the Trail Making Test-B, DSST, RAVLT acquisition, Stroop congruent and incongruent, patient-rated PDQ, and composite Z score compared to baseline measurements.[77] A US-based community-based cohort study analyzed 11,683,623 adults with obesity from January 2015 to December 2023, utilizing the TriNetX database and found that the use of liraglutide and semaglutide was associated with increased risk of depression, anxiety, and suicidal behavior in patients with obesity (n = 162,253). The HR for any psychiatric disease was 1.98 (95% CI: 1.94–2.01). For major depressive disorder, the HR was 2.95 (95% CI: 2.82–3.08), for anxiety 2.08 (95% CI: 2.04–2.12), and 2.06 for suicidal ideations or attempts.[78] Notably, female subjects on GLP-1 medicines had a higher risk of major depressive disorder (216% elevated risk [HR: 3.16, 95% CI 2.98–3.34]) and black patients had the highest risk of anxiety (137% elevated risk [HR: 2.37, 95% CI: 2.25–2.50]) compared to non-users.[78] Rates of suicide in clinical trials for T2D or obesity are very low, precluding meaningful assessment of risk with GLP-1 medicines. Several real-world analyses have examined reporting of suicidal ideation or suicide in patients taking GLP-1 medicines for T2D or obesity. Collectively, the majority of these analyses have not revealed evidence for increased risk[79–83] and some studies suggest the possibility of reduced risk of suicidal ideation or behavior.[84,85] Nevertheless, the majority of clinical trials in these areas are small, exploratory, enroll different patients, and use different medicines and endpoints, precluding generalization of limited clinical observations to date.

GLP-1 MEDICINES AND STROKE

Multiple preclinical studies demonstrate that GLP-1 medicines reduce brain injury and the extent of cognitive deficits, benefits largely attributed to protection against BBB deterioration, cytoprotection, and reduction of neuroinflammation and oxidative stress[13,86,87] (Figure 3). Diabetes is an established risk factor for cardiovascular events such as stroke that is evaluated in cardiovascular outcome trials, with non-fatal stroke representing one of the three components of major adverse cardiovascular events (MACE). Data from RCTs largely support the ability of GLP-1 medicines to reduce rates of MACE in people with T2D,[88] and a single trial demonstrates reduced rates of MACE in semaglutide-treated patients with overweight or obesity.[89] Rates of non-fatal stroke are reduced in some but not all GLP-1 CVOTs, with meta-analyses demonstrating ~16% reduction in risk of stroke across multiple CVOTs in people with T2D.[90,91] Mechanistically, some of this benefit may reflect the actions of GLP-1 medicines to reduce blood pressure; however, contributions from reduction of body weight, inflammation, attenuation of atherosclerosis, or inhibition of platelet aggregation cannot be excluded.[92] Consistent with RCT data, analysis of the TriNetX database reveals that GLP-1 medicines are associated with a lower risk of stroke (HR: 0.81, 95% CI: 0.70–0.93; follow-up of 7 years) in patients with T2D and obesity (n = 60,860).[93] The impact of GLP-1 medicines on rates of stroke in people with obesity is less certain, as rates of stroke were not different in people with obesity and established cardiovascular disease treated with semaglutide in the SELECT trial.[89] The available evidence supports a Class 1 recommendation from the 2024 guidelines of the American Heart Association for the use of GLP-1 medicines to reduce the risk of stroke in people with T2D.[94]

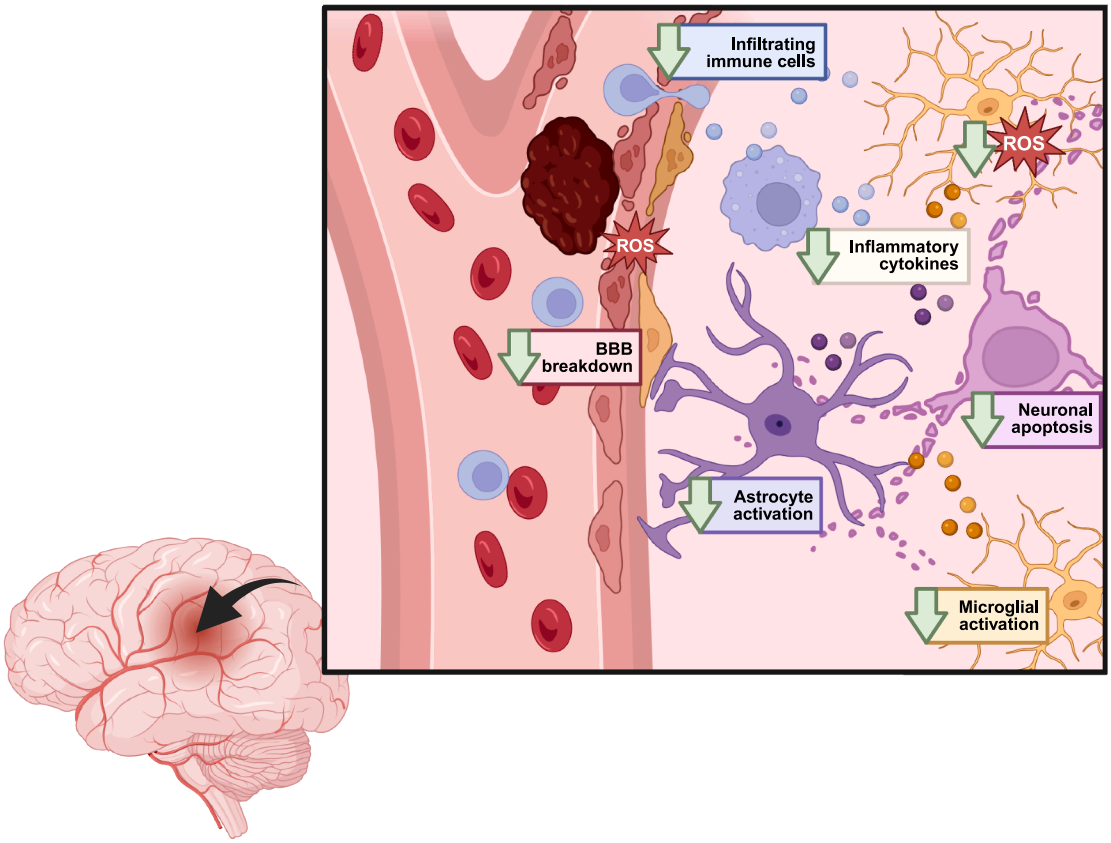

Figure 3. Potential mechanisms of GLP-1-mediated neuroprotection in stroke

Preclinical studies in rodent models of stroke demonstrate that GLP-1R agonists administered before or after cerebral ischemia can reduce BBB breakdown, reduce astrocyte and microglial activation and immune cell infiltration, reduce levels of oxidative stress, and decrease neuronal apoptosis. Arrows illustrate the direction of the effect observed with GLP-1 medicines.

GLP-1 MEDICINES AND SEIZURE DISORDERS

Loss of *Glp1r* in mice increased kainic acid-induced seizure severity and reduced latency to seizure compared to findings in control *Glp1r*$^{+/+}$ mice; these defects were rescued by adeno-associated virus-mediated *Glp1r* expression in the hippocampus, associated with lower cell death, pointing to a role of GLP-1 in neuroprotection.[13] GLP-1R agonism also reduces the severity and increases the latency of seizure in chemically induced or pentylenetetrazole kindling rodent models of epilepsy.[13,95] In comparison, little is known about the effect of GLP-1 medicines on seizures in humans. A study analyzing the data from the US Department of Veterans Affairs database found that male patients with T2D (majority Caucasian males) who initiated GLP-1 medicines (n = 215,970) had a lower risk of seizure (HR: 0.90, 95% CI: 0.85–0.95) compared to patients who continued the use of other glucose-lowering drugs (GLDs) (n = 1,203,097) over a median of 3.68 years.[96] A pooled meta-analysis assessing reports of seizure and epilepsy adverse events in cardiovascular or renal outcome trials investigating newer glucose-lowering agentss including DPP4 inhibitors, GLP-1 medicines, and SGLT2 inhibitors found that patients on a newer medicine had a lower risk of seizure and epilepsy combined (RR: 0.76, 95% CI: 0.62–0.95, p = 0.01) with an average follow-up of 29.2 months (SD: 12.6).[97] When assessing seizure and epilepsy separately, newer agents significantly lowered the risk of seizure (RR = 0.78, 95% CI: 0.60–1.00; p: 0.05) but not epilepsy (RR = 0.75, 95% CI: 0.51–1.11; p = 0.15). Similarly, subgroup analysis revealed that GLP-1 medicines lowered the risk of seizure and epilepsy (RR = 0.67, 95% CI: 0.46–0.98; p: 0.034) and seizure (RR = 0.60, 95% CI: 0.38–0.94; p: 0.03). Notably, only 182 (0.19%) patients treated with placebo and 154 (0.015%) patients treated with newer glucose-lowering agents had a seizure or epilepsy event, limiting the statistical power of the analysis.[97]

Headache and benign intracranial hypertension

Clinical trial and real-world data suggest that users of GLP-1 medicines report a reduction in migraine frequency and severity. A prospective study of 31 patients with obesity and treatment-resistant migraine administered liraglutide 1.2 mg daily for 6 months revealed reduced monthly days with headache, findings not correlated with reduction in body mass index.[98] Analysis of TriNetX data reveals that users of GLP-1 medicines with intracranial hypertension report significantly lower medication use (RR, 0.53; 95% CI, 0.46–0.61; p < 0.001), fewer headaches (RR, 0.45; 95% CI, 0.35–0.58; p < 0.001), visual disturbances

or blindness (RR, 0.60; 95% CI, 0.41–0.88; $p = 0.007$), and papilledema (RR, 0.19; 95% CI, 0.10–0.34; $p < 0.001$), observations that did not correlate with the extent of weight loss.[99] These findings largely mirror results from a separate independent analysis of the same patients in the TriNetX database,[100] with both studies suggesting a reduction in rates of mortality with use of GLP-1 medicines. A 12-week randomized trial evaluated the efficacy of exenatide in 16 adult women with intracranial hypertension, including telemetric intracranial pressure monitoring, demonstrating significant and clinically meaningful (−5.6 ± 3.0 cm CSF at 12 weeks) reductions in intracranial pressure with exenatide.[101] An investigator-initiated trial is studying the impact of semaglutide over 10 months in patients with new-onset intracranial hypertension (NCT06027567).

Conclusions and future directions

While extensive preclinical and real-world evidence supports exploration of GLP-1 medicines across a broad range of neuropsychiatric disorders, there are currently no large definitive P3 trials enabling approval of GLP-1 medicines for any neurological disorder. GLP-1 medicines might improve brain health through direct or indirect propagation of signals to relevant CNS circuits or by improvement of accompanying metabolic comorbidities (T2D, obesity, hypertension, dyslipidemia, central and peripheral insulin resistance, and dysregulated inflammation). The EVOKE trials provide a sobering reminder of the importance of large randomized trials in people with AD, and multiple smaller trials are underway in a wide range of SUDs. Hence, the evolving role of GLP-1 medicines in the neurology clinic will continue to be rapidly shaped by emerging clinical trial data that will provide more definitive evidence for potential use and limitations of GLP-1 medicines in neuropsychiatric disorders. While enthusiasm for the therapeutic potential of GLP-1 medicines in CNS disorders is widespread, as yet there are no large-phase trials demonstrating conclusive efficacy and acceptable safety in the evaluation of GLP-1 medicines for any of the neuropsychiatric disorders discussed herein.

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REFERENCES

1. Drucker, D.J. (2025). GLP-1-based therapies for diabetes, obesity and beyond. Nat. Rev. Drug Discov. *24*, 631–650. https://doi.org/10.1038/s41573-025-01183-8.
2. Drucker, D.J., and Holst, J.J. (2023). The expanding incretin universe: from basic biology to clinical translation. Diabetologia *66*, 1765–1779. https://doi.org/10.1007/s00125-023-05906-7.
3. Gonzalez-Rellan, M.J., and Drucker, D.J. (2025). The expanding benefits of GLP-1 medicines. Cell Rep. Med. *6*, 102214. https://doi.org/10.1016/j.xcrm.2025.102214.
4. Liu, C.M., Killion, E.A., Hammoud, R., Lu, S.C., Komorowski, R., Liu, T., Kanke, M., Thomas, V.A., Cook, K., Sivits, G.N., Jr., et al. (2025). GIPR-Ab/GLP-1 peptide-antibody conjugate requires brain GIPR and GLP-1R for additive weight loss in obese mice. Nat. Metab. *7*, 1266–1281. https://doi.org/10.1038/s42255-025-01295-w.
5. Gabery, S., Salinas, C.G., Paulsen, S.J., Ahnfelt-Rønne, J., Alanentalo, T., Baquero, A.F., Buckley, S.T., Farkas, E., Fekete, C., Frederiksen, K.S., et al. (2020). Semaglutide lowers body weight in rodents via distributed neural pathways. JCI Insight *5*, e133429. https://doi.org/10.1172/jci.insight.133429.
6. de Bray, A., Roberts, A.G., Armour, S., Tong, J., Huhn, C., Gatin-Fraudet, B., Roßmann, K., Shilleh, A.H., Jiang, W., Figueredo Burgos, N.S., et al. (2025). Fluorescent GLP1R/GIPR dual agonist probes reveal cell targets in the pancreas and brain. Nat. Metab. *7*, 1536–1549. https://doi.org/10.1038/s42255-025-01342-6.
7. Christensen, M., Sparre-Ulrich, A.H., Hartmann, B., Grevstad, U., Rosenkilde, M.M., Holst, J.J., Vilsbøll, T., and Knop, F.K. (2015). Transfer of liraglutide from blood to cerebrospinal fluid is minimal in patients with type 2 diabetes. Int. J. Obes. *39*, 1651–1654. https://doi.org/10.1038/ijo.2015.136.
8. Vijiaratnam, N., Girges, C., Auld, G., McComish, R., King, A., Skene, S.S., Hibbert, S., Wong, A., Melander, S., Gibson, R., et al. (2025). Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial. Lancet *405*, 627–636. https://doi.org/10.1016/S0140-6736(24)02808-3.
9. Bae, J.H., Choi, H.J., Cho, K.I.K., Kim, L.K., Kwon, J.S., and Cho, Y.M. (2020). Glucagon-Like Peptide-1 Receptor Agonist Differentially Affects Brain Activation in Response to Visual Food Cues in Lean and Obese Individuals with Type 2 Diabetes Mellitus. Diabetes Metab. J. *44*, 248–259. https://doi.org/10.4093/dmj.2019.0018.
10. Secher, A., Jelsing, J., Baquero, A.F., Hecksher-Sørensen, J., Cowley, M.A., Dalbøge, L.S., Hansen, G., Grove, K.L., Pyke, C., Raun, K., et al. (2014). The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J. Clin. Investig. *124*, 4473–4488. https://doi.org/10.1172/JCI75276.
11. Kopp, K.O., Glotfelty, E.J., Li, Y., and Greig, N.H. (2022). Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment. Pharmacol. Res. *186*, 106550. https://doi.org/10.1016/j.phrs.2022.106550.
12. Nowell, J., Blunt, E., and Edison, P. (2023). Incretin and insulin signaling as novel therapeutic targets for Alzheimer's and Parkinson's disease. Mol. Psychiatry *28*, 217–229. https://doi.org/10.1038/s41380-022-01792-4.
13. During, M.J., Cao, L., Zuzga, D.S., Francis, J.S., Fitzsimons, H.L., Jiao, X., Bland, R.J., Klugmann, M., Banks, W.A., Drucker, D.J., and Haile, C.N. (2003). Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat. Med. *9*, 1173–1179.
14. Granzotto, A., Vissel, B., and Sensi, S.L. (2024). Lost in translation: Inconvenient truths on the utility of mouse models in Alzheimer's disease research. eLife *13*, e90633. https://doi.org/10.7554/eLife.90633.
15. McClean, P.L., Parthsarathy, V., Faivre, E., and Hölscher, C. (2011). The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J. Neurosci. *31*, 6587–6594. https://doi.org/10.1523/JNEUROSCI.0529-11.2011.
16. Bomfim, T.R., Forny-Germano, L., Sathler, L.B., Brito-Moreira, J., Houzel, J.C., Decker, H., Silverman, M.A., Kazi, H., Melo, H.M., McClean, P.L., et al. (2012). An anti-diabetes agent protects the mouse brain

from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers. J. Clin. Investig. *122*, 1339–1353. https://doi.org/10.1172/JCI57256.

17. Lv, D., Feng, P., Guan, X., Liu, Z., Li, D., Xue, C., Bai, B., and Hölscher, C. (2024). Neuroprotective effects of GLP-1 class drugs in Parkinson's disease. Front. Neurol. *15*, 1462240. https://doi.org/10.3389/fneur.2024.1462240.
18. Liu, W., Jalewa, J., Sharma, M., Li, G., Li, L., and Hölscher, C. (2015). Neuroprotective effects of lixisenatide and liraglutide in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. Neuroscience *303*, 42–50. https://doi.org/10.1016/j.neuroscience.2015.06.054.
19. Wang, V., Kuo, T.T., Huang, E.Y.K., Ma, K.H., Chou, Y.C., Fu, Z.Y., Lai, L.W., Jung, J., Choi, H.I., Choi, D.S., et al. (2021). Sustained Release GLP-1 Agonist PT320 Delays Disease Progression in a Mouse Model of Parkinson's Disease. ACS Pharmacol. Transl. Sci. *4*, 858–869. https://doi.org/10.1021/acsptsci.1c00013.
20. Feng, P., Liu, Z., Lv, D., Hao, W., Li, D., Xue, G., Bai, B., and Hölscher, C. (2025). The novel GLP-1/GIP dual agonist DA3-CH is more effective than liraglutide in the MPTP mouse model of Parkinson's disease. Eur. J. Pharmacol. *1003*, 177972. https://doi.org/10.1016/j.ejphar.2025.177972.
21. Harkavyi, A., Abuirmeileh, A., Lever, R., Kingsbury, A.E., Biggs, C.S., and Whitton, P.S. (2008). Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. J. Neuroinflammation *5*, 19. https://doi.org/10.1186/1742-2094-5-19.
22. Long-Smith, C.M., Manning, S., McClean, P.L., Coakley, M.F., O'Halloran, D.J., Holscher, C., and O'Neill, C. (2013). The diabetes drug liraglutide ameliorates aberrant insulin receptor localisation and signalling in parallel with decreasing both amyloid-beta plaque and glial pathology in a mouse model of Alzheimer's disease. NeuroMolecular Med. *15*, 102–114. https://doi.org/10.1007/s12017-012-8199-5.
23. Forny Germano, L., Koehler, J.A., Baggio, L.L., Cui, F., Wong, C.K., Rittig, N., Cao, X., Matthews, D., and Drucker, D.J. (2024). The GLP-1 medicines semaglutide and tirzepatide do not alter disease-related pathology, behaviour or cognitive function in 5XFAD and APP/PS1 mice. Mol. Metab. *89*, 102019. https://doi.org/10.1016/j.molmet.2024.102019.
24. Norgaard, C.H., Friedrich, S., Hansen, C.T., Gerds, T., Ballard, C., Moller, D.V., Knudsen, L.B., Kvist, K., Zinman, B., Holm, E., et al. (2022). Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: Data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. Alzheimer's Dement. *8*, e12268. https://doi.org/10.1002/trc2.12268.
25. Tang, B., Sjölander, A., Wastesson, J.W., Maura, G., Blotiere, P.O., Szilcz, M., Mak, J.K.L., Qin, C., Alvarsson, M., Religa, D., et al. (2024). Comparative effectiveness of glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, and sulfonylureas on the risk of dementia in older individuals with type 2 diabetes in Sweden: an emulated trial study. eClinicalMedicine *73*, 102689. https://doi.org/10.1016/j.eclinm.2024.102689.
26. Seminer, A., Mulihano, A., O'Brien, C., Krewer, F., Costello, M., Judge, C., O'Donnell, M., and Reddin, C. (2025). Cardioprotective Glucose-Lowering Agents and Dementia Risk: A Systematic Review and Meta-Analysis. JAMA Neurol. *82*, 450–460. https://doi.org/10.1001/jamaneurol.2025.0360.
27. Wang, W., Wang, Q., Qi, X., Gurney, M., Perry, G., Volkow, N.D., Davis, P.B., Kaelber, D.C., and Xu, R. (2024). Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US. Alzheimer's Dement. *20*, 8661–8672. https://doi.org/10.1002/alz.14313.
28. Siddeeque, N., Hussein, M.H., Abdelmaksoud, A., Bishop, J., Attia, A.S., Elshazli, R.M., Fawzy, M.S., and Toraih, E.A. (2024). Neuroprotective effects of GLP-1 receptor agonists in neurodegenerative Disorders: A Large-Scale Propensity-Matched cohort study. Int. Immunopharmacol. *143*, 113537. https://doi.org/10.1016/j.intimp.2024.113537.
29. Sunnarborg, K., Tiihonen, M., Huovinen, M., Koponen, M., Hartikainen, S., and Tolppanen, A.M. (2022). Association between different diabetes medication classes and risk of Parkinson's disease in people with diabetes. Pharmacoepidemiol. Drug Saf. *31*, 875–882. https://doi.org/10.1002/pds.5448.
30. Rozani, V., Bezimianski, M.G., Azuri, J., Bitan, M., and Peretz, C. (2024). Anti-diabetic drug use and reduced risk of Parkinson's disease: A community-based cohort study. Parkinsonism Relat. Disord. *128*, 107132. https://doi.org/10.1016/j.parkreldis.2024.107132.
31. Tang, H., Lu, Y., Okun, M.S., Donahoo, W.T., Ramirez-Zamora, A., Wang, F., Huang, Y., Armstrong, M., Svensson, M., Virnig, B.A., et al. (2024). Glucagon-Like Peptide-1 Receptor Agonists and Risk of Parkinson's Disease in Patients with Type 2 Diabetes: A Population-Based Cohort Study. Mov. Disord. *39*, 1960–1970. https://doi.org/10.1002/mds.29992.
32. Gejl, M., Gjedde, A., Egefjord, L., Møller, A., Hansen, S.B., Vang, K., Rodell, A., Brændgaard, H., Gottrup, H., Schacht, A., et al. (2016). In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial. Front. Aging Neurosci. *8*, 108. https://doi.org/10.3389/fnagi.2016.00108.
33. Femminella, G.D., Frangou, E., Love, S.B., Busza, G., Holmes, C., Ritchie, C., Lawrence, R., McFarlane, B., Tadros, G., Ridha, B.H., et al. (2019). Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study). Trials *20*, 191. https://doi.org/10.1186/s13063-019-3259-x.
34. Edison, P., Femminella, G.D., Ritchie, C.W., Holmes, C., Walker, Z., Ridha, B.H., Raza, S., Livingston, N.R., Nowell, J., Busza, G., et al. (2021). Evaluation of liraglutide in the treatment of Alzheimer's disease. Alzheimer's Dement. *17*, e057848. https://doi.org/10.1002/alz.057848.
35. Cummings, J.L., Atri, A., Feldman, H.H., Hansson, O., Sano, M., Knop, F.K., Johannsen, P., León, T., and Scheltens, P. (2025). evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease. Alzheimers Res. Ther. *17*, 14. https://doi.org/10.1186/s13195-024-01666-7.
36. Koychev, I., Adler, A.I., Edison, P., Tom, B., Milton, J.E., Butchart, J., Hampshire, A., Marshall, C., Coulthard, E., Zetterberg, H., et al. (2024). Protocol for a double-blind placebo-controlled randomised controlled trial assessing the impact of oral semaglutide in amyloid positivity (ISAP) in community dwelling UK adults. BMJ Open *14*, e081401. https://doi.org/10.1136/bmjopen-2023-081401.
37. Aviles-Olmos, I., Dickson, J., Kefalopoulou, Z., Djamshidian, A., Ell, P., Soderlund, T., Whitton, P., Wyse, R., Isaacs, T., Lees, A., et al. (2013). Exenatide and the treatment of patients with Parkinson's disease. J. Clin. Investig. *123*, 2730–2736. https://doi.org/10.1172/JCI68295.
38. Athauda, D., Maclagan, K., Skene, S.S., Bajwa-Joseph, M., Letchford, D., Chowdhury, K., Hibbert, S., Budnik, N., Zampedri, L., Dickson, J., et al. (2017). Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet *390*, 1664–1675. https://doi.org/10.1016/S0140-6736(17)31585-4.
39. Hogg, E., Wu, T., Bresee, C., Wertheimer, J., Malatt, C., Tan, E., Pomeroy, H., Nuno, M., Wyse, R., and Tagliati, M. (2022). A Phase II, Randomized, Double-Blinded, Placebo-Controlled Trial of Liraglutide in Parkinson's Disease. Lancet. https://doi.org/10.2139/ssrn.4212371.
40. McGarry, A., Rosanbalm, S., Leinonen, M., Olanow, C.W., To, D., Bell, A., Lee, D., Chang, J., Dubow, J., Dhall, R., et al. (2024). Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. *23*, 37–45. https://doi.org/10.1016/S1474-4422(23)00378-2.
41. Meissner, W.G., Remy, P., Giordana, C., Maltête, D., Derkinderen, P., Houéto, J.L., Anheim, M., Benatru, I., Boraud, T., Brefel-Courbon, C.,

et al. (2024). Trial of Lixisenatide in Early Parkinson's Disease. N. Engl. J. Med. *390*, 1176–1185.

42. Udawatta, M., Fidalgo, N., and Mateen, F.J. (2025). Multiple sclerosis patients taking glucagon-like peptide-1 receptor (GLP-1) agonists: a single-institution retrospective cohort study of tolerability and weight loss. Neurol. Sci. *46*, 343–349. https://doi.org/10.1007/s10072-024-07701-7.

43. Balshi, A., Leuenberger, G., Dempsey, J., Baber, U., and Sloane, J.A. (2025). Glucagon-like peptide-1 agonist safety and efficacy in a multiple sclerosis cohort. Mult. Scler. Relat. Disord. *93*, 106229. https://doi.org/10.1016/j.msard.2024.106229.

44. Hardonova, M., Siarnik, P., Sivakova, M., Sucha, B., Penesova, A., Radikova, Z., Havranova, A., Imrich, R., Vlcek, M., Zitnanova, I., et al. (2023). Endothelial Function in Patients with Multiple Sclerosis: The Role of GLP-1 Agonists, Lipoprotein Subfractions, and Redox Balance. Int. J. Mol. Sci. *24*, 11162. https://doi.org/10.3390/ijms241311162.

45. Vijiaratnam, N., Girges, C., Wiegand, M., Ismail, C., Lameirinhas, A., Yarnall, A., Kirk, C., Del-Din, S., Rochester, L., Kobylecki, C., et al. (2025). Exenatide Once Weekly in the Treatment of Patients with Multiple System Atrophy. Ann. Neurol. *98*, 991–1003. https://doi.org/10.1002/ana.70004.

46. Montoya, I.D., and Volkow, N.D. (2024). IUPHAR Review: New strategies for medications to treat substance use disorders. Pharmacol. Res. *200*, 107078. https://doi.org/10.1016/j.phrs.2024.107078.

47. Yaruss, J.S., and Conture, E.G. (1993). F2 transitions during sound/syllable repetitions of children who stutter and predictions of stuttering chronicity. J. Speech Hear. Res. *36*, 883–896. https://doi.org/10.1044/jshr.3605.883.

48. Srinivasan, N.M., Farokhnia, M., Farinelli, L.A., Ferrulli, A., and Leggio, L. (2025). GLP-1 Therapeutics and Their Emerging Role in Alcohol and Substance Use Disorders: An Endocrinology Primer. J. Endocr. Soc. *9*, bvaf141. https://doi.org/10.1210/jendso/bvaf141.

49. Hernandez, N.S., Weir, V.R., Ragnini, K., Merkel, R., Zhang, Y., Mace, K., Rich, M.T., Christopher Pierce, R., and Schmidt, H.D. (2021). GLP-1 receptor signaling in the laterodorsal tegmental nucleus attenuates cocaine seeking by activating GABAergic circuits that project to the VTA. Mol. Psychiatry *26*, 4394–4408. https://doi.org/10.1038/s41380-020-00957-3.

50. Hernandez, N.S., Ige, K.Y., Mietlicki-Baase, E.G., Molina-Castro, G.C., Turner, C.A., Hayes, M.R., and Schmidt, H.D. (2018). Glucagon-like peptide-1 receptor activation in the ventral tegmental area attenuates cocaine seeking in rats. Neuropsychopharmacology *43*, 2000–2008. https://doi.org/10.1038/s41386-018-0010-3.

51. Hernandez, N.S., O'Donovan, B., Ortinski, P.I., and Schmidt, H.D. (2019). Activation of glucagon-like peptide-1 receptors in the nucleus accumbens attenuates cocaine seeking in rats. Addict. Biol. *24*, 170–181. https://doi.org/10.1111/adb.12583.

52. McPheeters, M., O'Connor, E.A., Riley, S., Kennedy, S.M., Voisin, C., Kuznacic, K., Coffey, C.P., Edlund, M.D., Bobashev, G., and Jonas, D.E. (2023). Pharmacotherapy for Alcohol Use Disorder: A Systematic Review and Meta-Analysis. JAMA *330*, 1653–1665. https://doi.org/10.1001/jama.2023.19761.

53. Suchankova, P., Yan, J., Schwandt, M.L., Stangl, B.L., Caparelli, E.C., Momenan, R., Jerlhag, E., Engel, J.A., Hodgkinson, C.A., Egli, M., et al. (2015). The glucagon-like peptide-1 receptor as a potential treatment target in alcohol use disorder: evidence from human genetic association studies and a mouse model of alcohol dependence. Transl. Psychiatry *5*, e583. https://doi.org/10.1038/tp.2015.68.

54. Wium-Andersen, I.K., Wium-Andersen, M.K., Fink-Jensen, A., Rungby, J., Jørgensen, M.B., and Osler, M. (2022). Use of GLP-1 receptor agonists and subsequent risk of alcohol-related events. A nationwide register-based cohort and self-controlled case series study. Basic Clin. Pharmacol. Toxicol. *131*, 372–379. https://doi.org/10.1111/bcpt.13776.

55. Lahteenvuo, M., Tiihonen, J., Solismaa, A., Tanskanen, A., Mittendorfer-Rutz, E., and Taipale, H. (2025). Repurposing Semaglutide and Liraglutide for Alcohol Use Disorder. JAMA Psychiatry *82*, 94–98. https://doi.org/10.1001/jamapsychiatry.2024.3599.

56. Probst, L., Monnerat, S., Vogt, D.R., Lengsfeld, S., Burkard, T., Meienberg, A., Bathelt, C., Christ-Crain, M., and Winzeler, B. (2023). Effects of dulaglutide on alcohol consumption during smoking cessation. JCI Insight *8*, e170419. https://doi.org/10.1172/jci.insight.170419.

57. Klausen, M.K., Jensen, M.E., Moller, M., Le Dous, N., Jensen, A.O., Zeeman, V.A., Johannsen, C.F., Lee, A., Thomsen, G.K., Macoveanu, J., et al. (2022). Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. JCI Insight *7*, e159863. https://doi.org/10.1172/jci.insight.159863.

58. Hendershot, C.S., Bremmer, M.P., Paladino, M.B., Kostantinis, G., Gilmore, T.A., Sullivan, N.R., Tow, A.C., Dermody, S.S., Prince, M.A., Jordan, R., et al. (2025). Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry *82*, 395–405. https://doi.org/10.1001/jamapsychiatry.2024.4789.

59. Wang, W., Volkow, N.D., Berger, N.A., Davis, P.B., Kaelber, D.C., and Xu, R. (2024). Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population. Nat. Commun. *15*, 4548. https://doi.org/10.1038/s41467-024-48780-6.

60. Sanyal, A.J., Newsome, P.N., Kliers, I., Østergaard, L.H., Long, M.T., Kjær, M.S., Cali, A.M.G., Bugianesi, E., Rinella, M.E., Roden, M., et al. (2025). Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N. Engl. J. Med. *392*, 2089–2099. https://doi.org/10.1056/NEJMoa2413258.

61. Loomba, R., Hartman, M.L., Lawitz, E.J., Vuppalanchi, R., Boursier, J., Bugianesi, E., Yoneda, M., Behling, C., Cummings, O.W., Tang, Y., et al. (2024). Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. N. Engl. J. Med. *391*, 299–310. https://doi.org/10.1056/NEJMoa2401943.

62. Merkel, R., Hernandez, N.S., Weir, V., Zhang, Y., Caffrey, A., Rich, M.T., Crist, R.C., Reiner, B.C., and Schmidt, H.D. (2025). An endogenous GLP-1 circuit engages VTA GABA neurons to regulate mesolimbic dopamine neurons and attenuate cocaine seeking. Sci. Adv. *11*, eadr5051. https://doi.org/10.1126/sciadv.adr5051.

63. Angarita, G.A., Matuskey, D., Pittman, B., Costeines, J.L., Potenza, M.N., Jastreboff, A.M., Schmidt, H.D., and Malison, R.T. (2021). Testing the effects of the GLP-1 receptor agonist exenatide on cocaine self-administration and subjective responses in humans with cocaine use disorder. Drug Alcohol Depend. *221*, 108614. https://doi.org/10.1016/j.drugalcdep.2021.108614.

64. Wang, W., Volkow, N.D., Berger, N.A., Davis, P.B., Kaelber, D.C., and Xu, R. (2024). Association of Semaglutide With Tobacco Use Disorder in Patients With Type 2 Diabetes : Target Trial Emulation Using Real-World Data. Ann. Intern. Med. *177*, 1016–1027. https://doi.org/10.7326/M23-2718.

65. Yammine, L., Green, C.E., Kosten, T.R., de Dios, C., Suchting, R., Lane, S.D., Verrico, C.D., and Schmitz, J.M. (2021). Exenatide Adjunct to Nicotine Patch Facilitates Smoking Cessation and May Reduce Post-Cessation Weight Gain: A Pilot Randomized Controlled Trial. Nicotine Tob. Res. *23*, 1682–1690. https://doi.org/10.1093/ntr/ntab066.

66. Lengsfeld, S., Burkard, T., Meienberg, A., Jeanloz, N., Vukajlovic, T., Bologna, K., Steinmetz, M., Bathelt, C., Sailer, C.O., Vogt, D.R., et al. (2023). Effect of dulaglutide in promoting abstinence during smoking cessation: a single-centre, randomized, double-blind, placebo-controlled, parallel group trial. eClinicalMedicine *57*, 101865. https://doi.org/10.1016/j.eclinm.2023.101865.

67. Yammine, L., Kosten, T.R., Cinciripini, P.M., Green, C.E., Meininger, J.C., Minnix, J.A., and Newton, T.F. (2018). Exenatide once weekly for smoking cessation: study protocol for a randomized clinical trial. Medicine (Baltim.) *97*, e9567. https://doi.org/10.1097/MD.0000000000009567.

68. Wang, W., Volkow, N.D., Berger, N.A., Davis, P.B., Kaelber, D.C., and Xu, R. (2024). Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a

retrospective cohort study. Mol. Psychiatry *29*, 2587–2598. https://doi.org/10.1038/s41380-024-02498-5.

69. Kamble, M., Gupta, R., Rehan, H.S., and Gupta, L.K. (2016). Neurobehavioral effects of liraglutide and sitagliptin in experimental models. Eur. J. Pharmacol. *774*, 64–70. https://doi.org/10.1016/j.ejphar.2016.02.003.
70. Anderberg, R.H., Richard, J.E., Hansson, C., Nissbrandt, H., Bergquist, F., and Skibicka, K.P. (2016). GLP-1 is both anxiogenic and antidepressant; divergent effects of acute and chronic GLP-1 on emotionality. Psychoneuroendocrinology *65*, 54–66. https://doi.org/10.1016/j.psyneuen.2015.11.021.
71. Planchez, B., Surget, A., and Belzung, C. (2019). Animal models of major depression: drawbacks and challenges. J. Neural Transm. *126*, 1383–1408. https://doi.org/10.1007/s00702-019-02084-y.
72. Ishii, H., Hansen, B.B., Langer, J., and Horio, H. (2021). Effect of Orally Administered Semaglutide Versus Dulaglutide on Diabetes-Related Quality of Life in Japanese Patients with Type 2 Diabetes: The PIONEER 10 Randomized, Active-Controlled Trial. Diabetes Ther. *12*, 613–623. https://doi.org/10.1007/s13300-020-00985-w.
73. Grant, P., Lipscomb, D., and Quin, J. (2011). Psychological and quality of life changes in patients using GLP-1 analogues. J. Diabetes Complications *25*, 244–246. https://doi.org/10.1016/j.jdiacomp.2011.03.002.
74. Bode, B.W., Testa, M.A., Magwire, M., Hale, P.M., Hammer, M., Blonde, L., and Garber, A.; LEAD-3 Study Group (2010). Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. Diabetes Obes. Metab. *12*, 604–612. https://doi.org/10.1111/j.1463-1326.2010.01196.x.
75. Pierret, A.C.S., Mizuno, Y., Saunders, P., Lim, E., De Giorgi, R., Howes, O.D., McCutcheon, R.A., McGowan, B., Sen Gupta, P., Smith, D., et al. (2025). Glucagon-Like Peptide 1 Receptor Agonists and Mental Health: A Systematic Review and Meta-Analysis. JAMA Psychiatry *82*, 643–653. https://doi.org/10.1001/jamapsychiatry.2025.0679.
76. Jacobsen, S.L., Köhler-Forsberg, O., Danielsen, A.A., and Rohde, C. (2025). Efficacy and safety of GLP1-ras compared to SGLT2is and DPP-4is in individuals with schizophrenia and diabetes: A Danish nationwide target-trial emulation study. Psychiatry Res. *351*, 116592. https://doi.org/10.1016/j.psychres.2025.116592.
77. Mansur, R.B., Ahmed, J., Cha, D.S., Woldeyohannes, H.O., Subramaniapillai, M., Lovshin, J., Lee, J.G., Lee, J.H., Brietzke, E., Reininghaus, E.Z., et al. (2017). Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: A pilot, open-label study. J. Affect. Disord. *207*, 114–120. https://doi.org/10.1016/j.jad.2016.09.056.
78. Kornelius, E., Huang, J.Y., Lo, S.C., Huang, C.N., and Yang, Y.S. (2024). The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon like peptide-1 receptor agonist therapy. Sci. Rep. *14*, 24433. https://doi.org/10.1038/s41598-024-75965-2.
79. Her, Q.L., Wang, T., Sturmer, T., Buse, J.B., Jonsson Funk, M., Pate, V., and Webster-Clark, M. (2025). Risk of suicidal ideation and suicidality among adults prescribed semaglutide for weight management: A population-based cohort study. Diabetes Obes Metab *27*, 6178–6187. https://doi.org/10.1111/dom.70002.
80. Peng, Z.Y., Yan, V.K.C., Wong, V.K.C., Wong, I.C.K., Chan, E.W.Y., Wan, E.Y.F., and Ou, H.T. (2025). Use of GLP-1 receptor agonists and risks of suicide attempts or self-harm in patients with type 2 diabetes: a multicountry self-control case series study. BMJ Ment. Health *28*, e301635. https://doi.org/10.1136/bmjment-2025-301635.
81. Shapiro, S.B., Yin, H., Yu, O.H.Y., Rej, S., Suissa, S., and Azoulay, L. (2025). Glucagon-like peptide-1 receptor agonists and risk of suicidality among patients with type 2 diabetes: active comparator, new user cohort study. BMJ *388*, e080679. https://doi.org/10.1136/bmj-2024-080679.
82. Bezin, J., Bénard-Laribière, A., Hucteau, E., Tournier, M., Montastruc, F., Pariente, A., and Faillie, J.L. (2025). Suicide and suicide attempt in users of GLP-1 receptor agonists: a nationwide case-time-control study. eClinicalMedicine *80*, 103029. https://doi.org/10.1016/j.eclinm.2024.103029.
83. Hurtado, I., Robles, C., Peiró, S., García-Sempere, A., and Sanfélix-Gimeno, G. (2024). Association of glucagon-like peptide-1 receptor agonists with suicidal ideation and self-injury in individuals with diabetes and obesity: a propensity-weighted, population-based cohort study. Diabetologia *67*, 2471–2480. https://doi.org/10.1007/s00125-024-06243-z.
84. Kerem, L., and Stokar, J. (2024). Risk of Suicidal Ideation or Attempts in Adolescents With Obesity Treated With GLP1 Receptor Agonists. JAMA Pediatr. *178*, 1307–1315. https://doi.org/10.1001/jamapediatrics.2024.3812.
85. Wang, W., Volkow, N.D., Berger, N.A., Davis, P.B., Kaelber, D.C., and Xu, R. (2024). Association of semaglutide with risk of suicidal ideation in a real-world cohort. Nat. Med. *30*, 168–176. https://doi.org/10.1038/s41591-023-02672-2.
86. Shan, Y., Tan, S., Lin, Y., Liao, S., Zhang, B., Chen, X., Wang, J., Deng, Z., Zeng, Q., Zhang, L., et al. (2019). The glucagon-like peptide-1 receptor agonist reduces inflammation and blood-brain barrier breakdown in an astrocyte-dependent manner in experimental stroke. J. Neuroinflammation *16*, 242. https://doi.org/10.1186/s12974-019-1638-6.
87. Kuroki, T., Tanaka, R., Shimada, Y., Yamashiro, K., Ueno, Y., Shimura, H., Urabe, T., and Hattori, N. (2016). Exendin-4 Inhibits Matrix Metalloproteinase-9 Activation and Reduces Infarct Growth After Focal Cerebral Ischemia in Hyperglycemic Mice. Stroke *47*, 1328–1335. https://doi.org/10.1161/STROKEAHA.116.012934.
88. Lee, M.M.Y., Sattar, N., Pop-Busui, R., Deanfield, J., Emerson, S.S., Inzucchi, S.E., Mann, J.F.E., Marx, N., Mulvagh, S.L., Poulter, N.R., et al. (2025). Cardiovascular and Kidney Outcomes and Mortality With Long-Acting Injectable and Oral Glucagon-Like Peptide 1 Receptor Agonists in Individuals With Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Trials. Diabetes Care *48*, 846–859. https://doi.org/10.2337/dc25-0241.
89. Lincoff, A.M., Brown-Frandsen, K., Colhoun, H.M., Deanfield, J., Emerson, S.S., Esbjerg, S., Hardt-Lindberg, S., Hovingh, G.K., Kahn, S.E., Kushner, R.F., et al. (2023). Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N. Engl. J. Med. *389*, 2221–2232. https://doi.org/10.1056/NEJMoa2307563.
90. Adamou, A., Barkas, F., Milionis, H., and Ntaios, G. (2024). Glucagon-like peptide-1 receptor agonists and stroke: A systematic review and meta-analysis of cardiovascular outcome trials. Int. J. Stroke *19*, 876–887. https://doi.org/10.1177/17474930241253988.
91. Kristensen, S.L., Rørth, R., Jhund, P.S., Docherty, K.F., Sattar, N., Preiss, D., Køber, L., Petrie, M.C., and McMurray, J.J.V. (2019). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. *7*, 776–785. https://doi.org/10.1016/S2213-8587(19)30249-9.
92. Ussher, J.R., and Drucker, D.J. (2023). Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. Nat. Rev. Cardiol. *20*, 463–474. https://doi.org/10.1038/s41569-023-00849-3.
93. Lin, H.T., Tsai, Y.F., Liao, P.L., and Wei, J.C.C. (2025). Neurodegeneration and Stroke After Semaglutide and Tirzepatide in Patients With Diabetes and Obesity. JAMA Netw. Open *8*, e2521016. https://doi.org/10.1001/jamanetworkopen.2025.21016.
94. Bushnell, C., Kernan, W.N., Sharrief, A.Z., Chaturvedi, S., Cole, J.W., Cornwell, W.K., 3rd, Cosby-Gaither, C., Doyle, S., Goldstein, L.B., Lennon, O., et al. (2024). 2024 Guideline for the Primary Prevention of Stroke: A Guideline From the American Heart Association/American Stroke Association. Stroke *55*, e344–e424. https://doi.org/10.1161/STR.0000000000000475.
95. Koshal, P., and Kumar, P. (2016). Neurochemical modulation involved in the beneficial effect of liraglutide, GLP-1 agonist on PTZ kindling

epilepsy-induced comorbidities in mice. Mol. Cell. Biochem. *415*, 77–87. https://doi.org/10.1007/s11010-016-2678-1.

96. Xie, Y., Choi, T., and Al-Aly, Z. (2025). Mapping the effectiveness and risks of GLP-1 receptor agonists. Nat. Med. *31*, 951–962. https://doi.org/10.1038/s41591-024-03412-w.

97. Sindhu, U., Sharma, A., Zawar, I., and Punia, V. (2024). Newer glucose-lowering drugs reduce the risk of late-onset seizure and epilepsy: A meta-analysis. Epilepsia Open *9*, 2528–2536. https://doi.org/10.1002/epi4.13091.

98. Braca, S., Russo, C.V., Stornaiuolo, A., Cretella, G., Miele, A., Giannini, C., and De Simone, R. (2025). Effectiveness and tolerability of liraglutide as add-on treatment in patients with obesity and high-frequency or chronic migraine: A prospective pilot study. Headache *65*, 1831–1838. https://doi.org/10.1111/head.14991.

99. Sioutas, G.S., Mualem, W., Reavey-Cantwell, J., and Rivet, D.J., 2nd. (2025). GLP-1 Receptor Agonists in Idiopathic Intracranial Hypertension. JAMA Neurol. *82*, 887–894. https://doi.org/10.1001/jamaneurol.2025.2020.

100. O'Leary, S., Price, A., Camarillo-Rodriguez, L., Costa, M., Karas, P., Young, C.C., Srinivasan, V.M., and Kan, P. (2025). Impact of GLP-1 receptor agonists on idiopathic intracranial hypertension clinical and neurosurgical outcomes: a propensity-matched multi-institutional cohort study. J. Neurosurg. *143*, 1034–1047. https://doi.org/10.3171/2025.1.JNS242357.

101. Mitchell, J.L., Lyons, H.S., Walker, J.K., Yiangou, A., Grech, O., Alimajstorovic, Z., Greig, N.H., Li, Y., Tsermoulas, G., Brock, K., et al. (2023). The effect of GLP-1RA exenatide on idiopathic intracranial hypertension: a randomized clinical trial. Brain *146*, 1821–1830. https://doi.org/10.1093/brain/awad003.