nature mental health

Supplementary information

https://doi.org/10.1038/s44220-025-00390-x

An analysis on the role of glucagon-like peptide-1 receptor agonists in cognitive and mental health disorders

In the format provided by the authors and unedited

S1. Search methods

Database:
Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present

#	**Query**	**Results from 20 Nov 2023**
1	Glucagon-Like Peptide 1/ag, aa, de, pd, tu [Agonists, Analogs & Derivatives, Drug Effects, Pharmacology, Therapeutic Use]	3,091
2	Glucagon-Like Peptide-1 Receptor/ag, de, tu [Agonists, Drug Effects, Therapeutic Use]	2,145
3	glp-1 agonist.mp.	382
4	glp-1 analogue.mp.	648
5	glp-1 receptor agonist.mp.	1,583
6	glucagon-like peptide-1 receptor agonist.mp.	1,575
7	Liraglutide/aa, pd, tu [Analogs & Derivatives, Pharmacology, Therapeutic Use]	1,451
8	Exenatide/ag, aa, pd, tu [Agonists, Analogs & Derivatives, Pharmacology, Therapeutic Use]	485
9	Semaglutide.mp.	1,382
10	Dulaglutide.mp.	757
11	Tirzepatide.mp.	339
12	Albiglutide.mp.	244
13	Lixisenatide.mp.	595
14	Taspoglutide.mp.	63
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	9,602

Database:
Embase 1974 to present

#	Query	Results from 20 Nov 2023
1	glucagon like peptide 1/ct, cb, cm, dv, dt, pd [Clinical Trial, Drug Combination, Drug Comparison, Drug Development, Drug Therapy, Pharmacology]	2,175
2	glucagon like peptide 1 receptor/ct, cb, cm, dt, ec, pd [Clinical Trial, Drug Combination, Drug Comparison, Drug Therapy, Endogenous Compound, Pharmacology]	2,841
3	glucagon like peptide 1 receptor agonist/ct, cb, cm, dt, ec, pd [Clinical Trial, Drug Combination, Drug Comparison, Drug Therapy, Endogenous Compound, Pharmacology]	6,257
4	1 or 2 or 3	10,618

Database:
Cochrane CENTRAL
Date Run: 21/11/2023 08:49:14

ID	Search	Hits
#1	MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees	2196
#2	MeSH descriptor: [Glucagon-Like Peptide-1 Receptor] explode all trees	326
#3	#1 OR #2	2375

2367 Trials matching "#3 - #1 OR #2"

Database:
PsycINFO 1806 to present

#	Query	Results from 20 Nov 2023
1	glp-1.mp.	626
2	glp-1 agonist.mp.	30
3	glp-1 receptor.mp.	208

4	Dulaglutide.mp.	9
5	Albiglutide.mp.	1
6	Liraglutide.mp.	127
7	Semaglutide.mp.	14
8	Exenatide.mp.	77
9	Taspoglutide.mp.	0
10	Lixisenatide.mp.	9
11	Tirzepatide.mp.	1
12	glucagon-like peptide 1.mp.	728
13	glp-1 analogue.mp.	34
14	glucagon-like peptide.mp.	755
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	884

S2. Miscellaneous clinical studies

Supplementary Table S2. Summary of included studies regarding the adverse psychiatric outcomes associated with GLP1-RAs

Study ID	Study design	Population	Exposure	Comparison	Follow-up	Outcomes	Major Findings
Chen 2023	Pharmacovigilance study	507,514 AE reports	Albiglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Semaglutide	Any drug in database	18 years	Incidence of suicidal and self-injurious behaviour	534 reports, including suicidal ideation (n = 275, 51.50%) Disproportionality analysis: No over-reporting of suicide/ self-injury with GLP1-RA (ROR = 0.16, 95%CI = 0.15, 0.18 p<0.001) No over-reporting of suicide/ self-injury with GLP1-RA before or after the COVID-19 pandemic outbreak.
Chen 2024b	Pharmacovigilance study	181,238 AE reports	Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Semaglutide or Tirzepatide)	-	19 years	Incidence of any psychiatric AEs	8,240 reports, including insomnia (n = 1,198, 11.7%), anxiety (n = 1,131, 11.04%), nervousness (n = 941, 9.19%), depression (n = 770, 7.52%).
						Median time to onset of psychiatric AEs	31 days (IQR 7-145.4 days)
De Giorgi 2024	Historical cohort	130,352 patients	Semaglutide	Sitagliptin, Empagliflozin, Glipizide	1 year	Incidence of any neuropsychiatric diagnosis	"Semaglutide is not associated with higher 12-month risk of adverse neuropsychiatric outcomes compared to other antidiabetic medications"
Silverii 2024	Meta-analysis of 31 RCTs	84,713 patients	Any GLP1-RA	Placebo	>1 year	Incidence of any psychiatric AEs	OR = 0.97 95% CI = 0.83, 1.15 (p=0.76)
Tobaiqy 2024	Pharmacovigilance study	31,444 AE reports	Liraglutide, Semaglutide or Tirzepatide	-	1.5 years	Incidence of any psychiatric AEs	372 reports (1.18%), including depression (n = 187, 50.3%), anxiety (n = 144, 38.7%), suicidal ideation (n = 73, 19.6%)
Zhou 2024	Pharmacovigilance study	8,857,300 cases	Albiglutide, Dulaglutide, Exenatide, Liraglutide, Semaglutide	-	5 years	Incidence of suicidal and self-injurious behaviour	204 reports Disproportionality analysis did not indicate an association between GLP-1RAs and suicide / self-injury

Legend: Values are mean±SD unless otherwise specified. Study ID reports the first author and year only.
AE: Adverse Events; GLP1-RA: Glucagon-Like Peptide 1 Receptor Agonist; OR: Odds Ratio; RCT: Randomised Controlled Trial, ROR: Reporting Odds Ratio.

S3. Ongoing/planned trials

Supplementary Table S3. Summary of ongoing/planned clinical studies of GLP1-RAs in psychiatric populations or related to mental health outcomes.

Study ID	Study design	Population	Exposure/Intervention	Comparison	Follow-up	Outcomes	Stage
Cognitive disorders							
GLP1-RAs effect on dementia risk / cognitive outcomes in patients with diabetes							
Davidy 2023	RCT (protocol)	80 older adults metabolic syndrome and MCI	Dulaglutide + Intranasal insulin	Placebo	1 year	Feasibility study study (adherence, safety)	Ongoing
NCT05313529	RCT	324 patients T2DM and MCI	Liraglutide	Other oral antidiabetics: Empagliflozin, Linagliptin	1 year	Change in cognitive function (MoCA)	To be completed 2027
NCT05360147	RCT	30 patients T2DM	Liraglutide	Other oral antidiabetics, insulin	3 months	Change in cognitive function (MMSE)	Completed 2021, unpublished
NCT02847403	RCT	40 patients dysglycaemia /prediabetes and MCI	Exenatide	Placebo	8 months	ADAS-cog score	Completed 2019, unpublished
GLP1-RAs in patients with cognitive impairment (without physical comorbidities)							
Femminella 2019	RCT (protocol)	204 patients MCI or probable AD, not on any antidiabetics	Liraglutide	Placebo	1 year	Change in cerebral glucose metabolic rate	Completed 2019, only preliminary results published (Edison, 2021)
NCT04777396	RCT	1840 patients MCI or mild AD	Semaglutide	Placebo	>3 years	CDR-SB score	To be completed 2026
NCT04777409	RCT	1840 patients MCI or mild AD	Semaglutide	Placebo	>3 years	CDR-SB score	To be completed 2026
GLP1-RAs effects on cognition in healthy subjects							
NCT01550653	RCT	40 healthy volunteers	Liraglutide	Placebo	5 weeks	Change in performance in cognitive battery	Completed 2013, No published results found
Substance use disorders							
Alcohol							
NCT06015893	RCT (Phase 2)	52 patients AUD	Semaglutide	Placebo	6 months	Alcohol consumption (number of drinks consumed per week)	Estimated completion 2030
NCT05891587	RCT (Phase 2)	80 patients AUD	Semaglutide	Placebo	3 months	Alcohol consumption (number of drinks consumed per week)	Estimated completion 2025
NCT05520775	RCT (Phase 2)	48 patients AUD	Semaglutide	Placebo	2 months	Volume of alcohol consumption (in self-administration procedure), Breath alcohol concentration	Estimated completion April 2024

NCT05892432	RCT (Phase 2)	135 patients AUD	Semaglutide	Placebo	2 months	Cue craving visual analog score	Estimated completion 2025
NCT05895643	RCT (Phase 2)	108 patients AUD	Semaglutide	Placebo	6 months	Number of heavy drinking days	Estimated completion 2027
NCT03645408	RCT Crossover (Phase 1)	3 patients classified as "heavy drinkers"	Exenatide	Placebo	2 hours - after acute dose	Alcohol consumption (standard drink units)	Full report not published, preliminary results on clinicaltrials.gov: Exenatide: 0.93±0.87, Placebo: 2.78±2.66
Opiates							
NCT04199728	RCT	27 treatment-seeking adults opiate use disorder	Liraglutide	Placebo	1 month	Change in ambient drug craving and in self-reported cue-elicited drug craving as measured by VAS	Completed 2023 - results not yet published
Nicotine							
NCT03712098	RCT	40 adult smokers overweight BMI	Liraglutide	Placebo	8 months	7-day point prevalence abstinence rate (at 12 weeks)	Study completed 2022 – full results not yet published
NCT02690987	RCT crossover (Phase 1)	95 adults previous alcohol or tobacco dependence, overweight BMI	Exenatide	Placebo	4 years	fMRI measures during cigarette, alcohol and food picture evaluation task	Estimated completion 2020 - full results not yet published
Psychotic disorders							
NCT05333003	RCT	92 patients psychotic illness, on antipsychotic, BMI ≥30	Semaglutide	Placebo	8 months	Body weight	Estimated completion 2025
NCT05897398	Cohort	1000 patients severe eating disorder or iatrogenic obesity induced by psychotropics	Semaglutide	Baseline	1 year	Body weight	Estimated completion 2026
Sailer, 2019	RCT (protocol)	154 adults on a second-generation antipsychotic (Clozapine, Olanzapine)	Dulaglutide	Placebo	6 months (+1 year follow-up)	Body weight	Ongoing study
Sass, 2023	RCT (protocol)	104 patients schizophrenia and prediabetes or T2DM, on Clozapine / Olanzapine	Semaglutide	Placebo	6 months	HbA1c	Estimated completion 2024
Siskind, 2023	RCT (protocol)	80 patients schizophrenia and BMI ≥26 on Clozapine	Semaglutide	Placebo	9 months	Body weight	Ongoing study
Mood and anxiety disorders							

NCT04466345	RCT	60 patients MDD and pre-treatment cognitive dysfunction	Semaglutide	Placebo	4 months	Executive function	Estimated completion 2024
NCT05492305	Prospective cohort	20 patients on any GLP1-RA for obesity or diabetes	Any GLP1-RA	Baseline	3-4 months	Subjective effect on mental health (qualitative analysis, semi-structured interview)	Estimated completion 2023, full results not published

Legend: Values are mean±SD unless otherwise specified. Study ID reports the first author and year only.
AD: Alzheimer's Disease; ADAS: Alzheimer's Disease Assessment Scale; AUD: Alcohol Use Disorder; BED: Binge Eating Disorder; CDR-SB: Clinical Dementia Rating – Sum of Boxes; DSST: Digit Symbol Substitution Test; fMRI: functional Magnetic Resonance Imaging; GLP1-RA: Glucagon-Like Peptide 1 Receptor Agonist; HbA1c: Haemoglobin A1c; MCI: Mild Cognitive Impairment; MDD: Major Depressive Disorder; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; RCT: Randomised Controlled Trial; T2DM: Type 2 Diabetes Mellitus; VAS: Visual Analog Score.

S4. List of pre-clinical/mechanistic studies on cognitive disorders

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S5. Pre-clinical/mechanistic studies on cognitive disorders, substance use disorders, psychotic disorders, mood and anxiety disorders, and eating disorders

Supplementary Table S5. Summary of included pre-clinical/mechanistic studies regarding the effects of GLP1-RAs on mental health outcomes.

Study ID	Sample	Model	Intervention	Main Finding(s)	
Cognitive disorders					
Erbil 2019	Review of pre-clinical studies		Any GLP1-RA	GLP-1RAs may reverse neurovascular complications of diabetes and neuropathological changes related to AD, PD or vascular occlusion. Neuroprotective mechanisms include: enhancing the viability of neurons and restoring neurite outgrowth by increased neurotrophic factors, increasing subventricular zone progenitor cells, decreasing apoptosis, decreasing the level of pro-inflammatory factors, and strengthening the blood-brain barrier.	NA
Kong 2023	Review of pre-clinical studies		Any GLP1-RA	GLP-1 RAs improve the learning and memory abilities of AD rodents and reduce Aβ deposition and phosphorylated tau levels in the brains of AD rodents.	NA
Nowell 2023	Review of pre-clinical studies		Any GLP1-RA	GLP-1 RAs reduce neuroinflammation, reduce tau phosphorylation, reduce Aβ deposition, increase synaptic function, and improve memory formation.	NA
Reich 2022	Review of pre-clinical studies		Any GLP1-RA	Neuroprotective pathways induced following GLP-1R activation in neurons, microglia and astrocytes include: synaptic protection, Aβ pathology amelioration, suppression of Ca^{2+} deregulation and ER stress, potent anti-inflammatory effects, the blockage of oxidative stress, mitochondrial dysfunction and apoptosis pathways, enhancements in the neuronal insulin sensitivity and energy metabolism, functional improvements in autophagy and mitophagy, elevated BDNF and GDNF synthesis, as well as neurogenesis.	NA
Substance use disorders					
Alcohol					
Abtahi 2018	Animal	Rats	Exendin-4	Exendin-4 administration in the NAc decreases alcohol consumption in alcohol-habituated rats.	+
Allingbjerg 2023	Animal	Mice	Exendin-4	Exendin-4 infusion into the NAc, ventral hippocampus and lateral septum reduced alcohol self-administration.	+
Aranas 2023a	Animal	Rats	Semaglutide	Semaglutide reduces alcohol intake and prevents relapse-like drinking via dopaminergic mechanisms in the NAc.	+
Aranas 2023b	Animal	Rats	Semaglutide + Bupropion / Varenicline	No additive effects on alcohol intake reduction by adding antismoking agents (bupropion or varenicline) to semaglutide.	=
Bornebusch 2019	Animal	Mice	Exendin-4	Exendin-4 dose-dependently decreases oral alcohol self-administration.	+
Chuong 2023	Animal	Mice and rats	Semaglutide	Semaglutide reduces binge-like alcohol drinking in mouse and rat models of alcohol use disorder models.	+
Colvin 2020	Animal	Rats	Exendin-4	VTA, NAc and lateral hypothalamus are involved in the inhibition of alcohol intake by Exendin-4.	+
Colvin 2022	Animal	Rats	Exendin-4	VTA exendin-4 inhibits alcohol intake and reverses the stimulatory effect of cocaine and d-amphetamine on alcohol consumption.	+

Davis 2012	Animal	Rats	Exendin-4	GLP-1 agonism attenuates alcohol intake in rats selectively bred to consume alcohol. Roux-en-Y gastric bypass surgery in rats decreases alcohol intake by increasing GLP-1 levels.	+
Diaz-Megido 2023	Animal	Mice	Exendin-4	Suppression of alcohol reinforcement and reinstatement by Exendin-4 in male mice.	+
Dixon 2020	Animal	Rats	Exendin-4	VTA administration of exendin-4 inhibits alcohol self-administration in male rats.	+
Farokhnia 2022	Human	Post-mortem brain samples of patients with severe AUD	-	Increased hippocampal expression of GLP-1R gene in post-mortem tissue from individuals with AUD versus controls.	+
Egecioglu 2013	Animal	Mice	Exendin-4	Exendin-4 reduces alcohol-induced locomotor stimulation, DA release in the NAc shell, and attenuates the reinforcing properties of alcohol.	+
Marty 2020	Animal	Rats	Liraglutide Semaglutide	Transient reduction in voluntary alcohol intake by liraglutide or semaglutide.	+
Sharma 2015a	Animal	Rats	Liraglutide	Liraglutide inhibits withdrawal-induced anxiety and prevents tolerance to the anxiolytic effect of alcohol.	+
Shirazi 2013	Animal	Rats	Exendin-4	Peripheral or VTA injection of exendin-4 reduces alcohol intake.	+
Sorensen 2016	Animal	Mice	Exendin-4	Pre-treatment with exendin-4 attenuates voluntary alcohol self-administration.	+
Suchankova 2015	Animal	Mice	AC3174 ([Leu14]-exendin-4)	GLP-1R agonism significantly reduces alcohol consumption in a mouse model of alcohol dependence.	+
Thomsen 2017	Animal	Mice	Exendin-4	Treatment with exendin-4 during alcohol deprivation decreases relapse-like drinking in socially housed mice.	+
Thomsen 2019	Animal	African vervet monkeys	Exenatide Liraglutide	Liraglutide and, to a lesser extent, exenatide reduce voluntary alcohol consumption in non-human primates.	+
Vallof 2016	Animal	Rats	Liraglutide	Liraglutide suppresses alcohol-induced effects on the mesolimbic DA system and attenuates the reinforcing properties of alcohol.	+
Vallof 2019a	Animal	Mice and rats	Exendin-4	Exendin-4 prevents alcohol-induced locomotion, suppresses memory of alcohol reward or reduces alcohol intake depending on the brain region it is infused into.	+
Vallof 2019b	Animal	Mice and rats	Exendin-4	Exendin-4 infusion into the NST inhibits alcohol-induced locomotion, accumbal DA release, CPP-dependent alcohol memory in mice, and alcohol intake in rats.	+
Vallof 2020	Animal	Rats	Dulaglutide	Long-term dulaglutide reduces alcohol intake and preference, which was sustained after discontinuation in males, but not females.	+
Cocaine/Amphetamines					
Bouhlal 2017	Human	8 experienced cocaine users	IV cocaine	IV cocaine decreases plasma GLP-1 concentration. Endogenous GLP-1 is associated with subjective responses to cocaine.	+
Egecioglu 2013b	Animal	Mice	Exendin-4	Exendin-4 reduces amphetamine- and cocaine-induced locomotor stimulation, accumbal DA release and CPP.	+
Erreger 2012	Animal	Rats	Exendin-4	Single acute dose of exendin-4 decreases amphetamine-induced locomotor activity.	+
Fortin 2017	Animal	Rats	Exendin-4	Central exendin-4 suppresses cocaine-induced phasic DA signalling in the NAc core which may decrease the reinforcing properties of cocaine.	+
Graham 2013	Animal	Mice	Exendin-4	Exendin-4 attenuates cocaine-induced CPP (but even at the highest doses did not eliminate CPP).	+

Harasta 2015	Animal	Mice	AAV-mediated Glp-1r gene delivery to the dorsal lateral septum	Septal Glp-1r gene expression in Glp-1r−/− animals reduces cocaine-induced locomotion and CPP to wild-type levels.	+
Hernandez 2018	Animal	Rats	Exendin-4	Exendin-4 reduces cocaine seeking through effects on the VTA.	+
Hernandez 2019	Animal	Rats	Exendin-4	Increased activation of GLP-1R in the NA during cocaine abstinence is sufficient to reduce cocaine-seeking behaviour.	+
Hernandez 2021	Animal	Rats	Exendin-4	Exendin-4 attenuates cocaine seeking via GABAergic GLP-1R-expressing circuits in the midbrain.	+
Reddy 2016	In Vitro	Rat lateral septum slices	Exendin-4	Exendin-4 abolishes cocaine-induced elevation of DA in lateral septum slices by decreasing arachidonic acid levels.	+
Schmidt 2016	Animal	Rats	Exendin-4	VTA administration of exendin-4 reduces cocaine self-administration.	+
Sirohi 2016	Animal	Mice	Exendin-4	Amphetamine-induced CPP was completely blocked in FLOX, but not in GLP-1R KD mice by exendin-4.	+
Sorensen 2015	Animal	Mice	Exendin-4	GLP-1R stimulation reduces acute and chronic cocaine self-administration and attenuates cocaine-induced hyperlocomotion.	+
Zhu 2021a	Animal	Mice	Exendin-4	Exendin-4 facilitates the extinction of cocaine-induced CPP.	+
Zhu 2021b	Animal	Mice	Exendin-4	Exendin-4 ameliorates cocaine-induced behaviours through inhibition of TLR4, TNF-α, and IL-1β.	+
Zhu 2021c	Animal	Mice	Exendin-4	Exendin-4 attenuates cocaine- and stress-primed reinstatement of cocaine-induced CPP.	+
Opiates					
Bornebusch 2019	Animal	Mice	Exendin-4	Exendin-4 did not attenuate morphine-induced CPP, withdrawal or hyperlocomotion, and did not decrease remifentanil self-administration.	=
Douton 2022a	Animal	Rats with heroin self-administration experience	Liraglutide	Acute dose of liraglutide prevents cue-, stress-, and drug-induced heroin-seeking in rats.	+
Douton 2022b	Animal	Rats	Liraglutide	Daily treatment with liraglutide reduces heroin self-administration and drug-induced reinstatement of heroin-seeking behaviour in rats.	+
Douton 2021	Animal	Rats with reward devaluation model	Exendin-4	Exendin-4 decreases cue- and drug-induced heroin seeking.	+
Evans 2022	Animal	Rats with history of high drug-taking	Liraglutide	Liraglutide titration decreases cue- and drug-induced heroin seeking	+
Urbanik 2022	Animal	Rats	Liraglutide	Acute dose of liraglutide attenuates cue-induced fentanyl-seeking and drug-induced reinstatement of fentanyl-seeking with the same efficacy as buprenorphine.	+
Zhang 2020	Animal	Rats	Exendin-4	Administration of exendin-4 systematically or into the NAc shell reduces oxycodone self-administration and the reinstatement of oxycodone-seeking behaviour.	+
Zhang 2021	Animal	Rats fentanyl-experienced	GEP44 (dual agonist of GLP-1Rs and neuropeptide Y2 receptors)	GEP44 attenuates opioid taking and seeking at a dose that does not suppress food intake or produce adverse malaise-like effects.	+
Nicotine					
Egecioglu 2013c	Animal	Mice	Exendin-4	Exendin-4 attenuates the nicotine-induced effects on the mesolimbic DA system (locomotor stimulation, accumbal DA release, CPP, expression of locomotor sensitisation).	+

Falk 2023	Animal	Mice obese	Liraglutide	Co-administration of nicotine and liraglutide reduces body weight and increases DA neuron excitability in the VTA. Liraglutide inhibits nicotine-induced DA release in the Nac.	+
Herman 2023	Animal	Rats	Liraglutide	Liraglutide attenuates nicotine self-administration and reinstatement, as well as withdrawal-induced hyperphagia.	+
Tuesta 2017	Animal	Mice	Optogenetic stimulation of GLP-1R	Optogenetic activation of GLP-1Rs in habenular circuits abolished nicotine reward and decreased nicotine intake.	+
Psychotic disorders					
Cardiometabolic side effects of antipsychotics					
Babic 2018	Animal	Rats treated with olanzapine or clozapine	Liraglutide	Liraglutide co-treatment improves aspects of cognition (recognition and working memory), prevents obesity side-effects of olanzapine, and hyperglycaemia caused by clozapine.	+
Babic 2021	Animal	Rats treated with olanzapine or clozapine	Liraglutide	Chronic APD and liraglutide co-treatment did not alter neural and peripheral markers of metabolic function. Acute liraglutide co-treatment did not prevent clozapine-induced hyperglycaemia.	=
Klemettila 2021	Human	190 patients with schizophrenia on clozapine treatment	-	Serum GLP-1 levels are associated with metabolic risk markers (BMI, leptin, insulin) among men with schizophrenia on clozapine treatment.	NA
Li 2021b	Animal	Rats treated with brexpiprazole	Liraglutide	Liraglutide ameliorates brexpiprazole-caused glycolipid metabolic abnormalities.	+
Lykkegaard 2008	Animal	Rats treated with olanzapine	Liraglutide	Olanzapine-induced weight gain and metabolic changes were reversed by liraglutide treatment.	+
Mansur 2019	Human	Post-mortem brain tissue of patients with mood and psychotic disorders	-	Significant differences in dlPFC and hippocampal GLP-1R gene expression between healthy controls and MD post-mortem subjects, moderated by BMI.	NA
Medak 2020	Animal	Mice treated with olanzapine	Liraglutide, Exendin-4	GLP1-R agonism protects against acute olanzapine-induced hyperglycaemia.	+
Sharma 2015b	Animal	Rats treated with olanzapine	Liraglutide	Liraglutide partially reversed metabolic abnormalities and depression-like behaviour associated with long-term olanzapine treatment.	+
Smith 2009	Animal	Obese rats treated with olanzapine or quetiapine	Exendin-4	Exendin-4 normalised both glucagon levels and glucose metabolism in clozapine or quetiapine-treated obese rats.	+
Smith 2014	Animal	Mice treated with clozapine	Boc5 (non-peptidic GLP1-RA)	Boc5 can overcome the inhibitory effects of clozapine on glucose metabolism.	+
Effects on psychosis					
Bocchio-Chiavetto 2018	Human	260 patients with FEP	-	Significantly lower levels of serum GLP-1 in FEP patients compared to healthy controls.	NA
Dixit 2013	Animal	Mouse model of psychosis induced by apomorphine	Liraglutide	Antipsychotic-like effect of liraglutide significantly attenuated apomorphine-induced cage climbing.	+
Kutlu 2023	Animal	Mouse schizophrenia model induced by MK-801	Liraglutide	Liraglutide prevents MK-801-induced schizophrenia-like behaviours and BDNF, CREB, p-CREB, Trk-B expressions in the hippocampus and prefrontal cortex.	+
Ramsey 2014	Human	Patients on antipsychotics from the CATIE trial	Various APDs	GLP-1R haplotypes significantly correlate with reduction in response to multiple antipsychotics as measured by dPANSS.	NA
Sedky 2021	Animal	Diabetic and non-diabetic rats with ketamine-induced psychotic-like behaviours	Liraglutide	Beneficial effects of liraglutide on ketamine-induced hyperlocomotion and cognitive dysfunction associated with reduction in TNF-α and oxidative stress, in both diabetic and non-diabetic rats.	+

Mood and anxiety disorders					
GLP -1RA effects on mood symptoms					
Anderberg 2016	Animal	Rats	Exendin-4	Chronic central administration of Exendin-4 does not alter anxiety-like behaviour but significantly reduces depression-like behaviour in the forced swim test.	+ (depression) = (anxiety)
Aygun 2021	Animal	WAG/Rij rat - genetic model of absence epilepsy and depression-like comorbidity	Exendin-4	Exendin-4 increases incidence of absence-like seizures, as well as anxiety- and depression-like behaviours.	-
Cicekli 2022	Animal	Ouabain-induced bipolar disease model in rats	Liraglutide + Sodium valproate	Ouabain-induced mania and depressive-like behaviours are ameliorated by liraglutide, which exerts antioxidant action, possibly improving GSK-3β phosphorylation.	+
Chaves Filho 2020	Animal	Mice with D-amphetamine-induced mania	Liraglutide +/- Lithium	Liraglutide reverses mania-like alterations and memory deficits induced by D-amphetamine and augments lithium effects in mice.	+
Darwish 2023	Animal	Social defeat stress model in C57BL/6 male mice	Dulaglutide	Dulaglutide reduces depressive behaviours by activating the GLP-1R/cAMP/PKA pathway. Social interaction ratio, sucrose consumption, and exploration time in open arms (in the EPM test) significantly increased after the administration of Dulaglutide.	+
DeSouza 2019	Animal	Mice subjected to PTZ-induced kindling (model for epileptogenesis)	Liraglutide +/- Levetiracetam	Liraglutide prevents the depressive-like behaviour induced by PTZ kindling or by PTZ + levetiracetam.	+
Krass 2015	Animal	Mice / Flinders sensitive line (FSL) rats	Exenatide / Liraglutide	Exenatide or liraglutide do not induce anxiolytic or antidepressant-like effects in mice in the FST. Chronic liraglutide treatment does not affect depression-related behaviour in FSL rats.	=
López-Ferreras 2020	Animal	Male and female rats	Exendin-4	Microinjecting exendin-4 into the SuM has anxiogenic effects which persist after exposure to high-fat diet. Knocking down GLP-1R expression in the SuM is anxiolytic in females only.	-
Ren 2021	Animal	CUMS mouse model of depression	Lixisenatide	Intranasal lixisenatide improves depressive and anxiety symptoms, possibly by increasing phosphorylation of CREB protein in hippocampal tissue.	+
Saglam 2022	Animal	Rats with ovariectomy-induced behavioural despair and anxiety-like behaviours	Liraglutide	Liraglutide reduces behavioural despair and anxiety-like behaviour, possibly through preservation of BDNF/Nrf2 levels and decrease in oxidative stress in the hippocampus.	+
Seo 2023	Animal	CUMS mouse model of depression	Liraglutide	Liraglutide exerts antidepressant effects and could improve cognitive function.	
Turan 2021	Animal	Mice subjected to REM sleep deprivation	Exenatide	Treatment with exenatide did not affect depression-like behaviour in the FST.	=
Verovnik 2023	Human	18 women with obesity or PCOS	Semaglutide	No significant change compared to placebo in fMRI resting state functional connectivity in regions of interest related to suicidal ideation and MD behaviours at 16 weeks	=
Weina 2018	Animal	CORT mouse model of depression	Liraglutide	Liraglutide administration attenuates depressive- and anxiety-like behaviours in behavioural tasks.	+
Yang 2022	Animal	Mice diabetic	Exendin-4	Exendin-4 exhibits antidepressant effects in depression associated with diabetes i, which may be mediated by inhibiting microglial pyroptosis via promoting mitophagy.	+
Other related agonists and their effects on depression models / other comorbid conditions					
Sun 2021	Animal	Diabetes-associated depression mouse model	Geniposide	Geniposide treatment improves cognitive dysfunctions and depressive/anxiety symptoms.	+

Hu 2021	Animal	Mice subjected to HFD which induces T2DM and depressive-like symptoms	Puerarin	Puerarin ameliorates depressive symptoms, possibly through activating the GLP-1R/Wnt/mTOR signalling pathway and improving hippocampal neuroplasticity.	+
Iwai 2009	Animal	Mice	GLP-2	GLP-2 exerts antidepressant-like effects in the FST.	+
Iwai 2013	Animal	ACTH-treated mice as a model of TCA-resistant depression	GLP-2	GLP-2 induces antidepressant-like effects in the FST, decreases serum corticosterone levels after the FST, and increases 5-HT levels in the frontal cortex.	+
Liu 2023	Animal	Diabetic mice	Puerarin	Taken together, puerarin exerts anti-depressant-like effects on HFD diabetic mice by improving hippocampal neuroplasticity via GLP-1R/BDNF/TrkB signalling.	+
Zhao 2018	Animal	RRS-induced depression model in mice	Geniposide	Geniposide ameliorates depression-like behaviours, such as decreased sucrose preference, reduced locomotor activity, and extended immobility time on the FST.	+
Eating disorders					
Cao 2014	Animal	Ovarectomised female mice	GLP-1	GLP-1 alone and GLP-1-estrogen suppress binge eating in ovariectomised female mice.	+
Mukherjee 2020	Animal	Rats	-	Binge-like palatable food intake reduces expression of GLP-1R in the NST of rats.	NA
Pierce-Messick 2020	Animal	Rats	Exendin-4	Exendin-4 reduces binge-like feeding induced by NAc □-opioid receptor stimulation.	+
Yamaguchi 2017	Animal	Mouse model of binge eating	GLP-1	Systemic GLP-1 reduces binge-like sucrose overconsumption.	+

Legend: + : positive effect; = : no effect; - : negative effect. Study ID reports the first author and year only.
Aβ: Amyloid Beta; ACTH: Adrenocorticotropic hormone; AD: Alzheimer's Disease; APD: Anti-Psychotic Drugs; AUD: Alcohol Use Disorder; BDNF: Brain-Derived Neurotrophic Factor; cAMP: Cyclic Adenosine Monophosphate; CORT: Chronic Corticosterone; CPP: Conditioned Place Preference; CREB: cAMP Response Element-Binding Protein; CUMS: Chronic unpredictable mild stress; DA: Dopamine; dlPFC: dorsolateral prefrontal cortex; EPM: Elevated Plus Maze; ER: Endoplasmic Reticulum; FEP: First Episode Psychosis; FST: Forced Swim Test; GDNF: Glial cell line-Derived Neurotrophic Factor; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; GSK-3β: Glycogen synthase kinase-3 beta; HFD: High-Fat Diet; IL-1β: Interleukin-1 beta; KD: Knock Down; MD: Major Depression; NA: Not Applicable; NAc: Nucleus Accumbens; NST: nucleus of the solitary tract; dPANSS: Positive and Negative Syndrome Scale (Total); PKA: Protein Kinase A; PTZ: Pentylenetetrazole; RRS: Repeated Restraint Stress; SuM: supramammillary nucleus; TCA: Tricyclic Antidepressant; T2DM: Type 2 Diabetes Mellitus; TLR4: Toll-Like Receptor 4; TrkB: Tyrosine Receptor Kinase B; TNF-α: Tumour Necrosis Factor alpha; VTA: Ventral Tegmental Area.