Table 1.

Articles on Liraglutide

Author	Study design	Age (range), y	Diagnosis	Duration	Group, n	Dose range	Scales to measure the clinical outcome	Clinical outcome	Common side effects
Gejl et al[19]	RCT	Liraglutide group = 63.1 (55–70), placebo group = 66.6 (50–80)	Alzheimer disease	26 wk	Liraglutide = 14, placebo = 20	Liraglutide 0.6 mg subcutaneously for 1 wk; thereafter, 1.2 mg daily for 1 wk before finally increasing to 1.8 mg daily	Cognition with the WMS-IV scale, tracer [carbon 11] PIB to measure Aβ load in the brain, [18F] FDG to assess glucose metabolic rate	No significant differences from baseline in total cognitive scores after treatment within or between the 2 groups. Average scores at baseline were 27.1 in the liraglutide group and 27.2 in the placebo group ($P = .99$), and no significant differences were found from baseline in total cognitive score after treatment within or between the 2 groups (liraglutide 0.43, placebo 1.7, $P = .50$)	Transient nausea, weight loss, and reduction in systolic blood pressure were noted after 6 mo of GLP-1 analog treatment
Mansur et al[20]	Open-label study	22–54	Mood disorder	4 wk	19	Liraglutide 0.6 mg for 1st wk, 1.2 mg for the next wk, and 1.8 mg for the final 2 wk	TMTB	Adjunctive liraglutide results in clinically significant weight loss, with corresponding improvement in cognitive function; changes in cognitive function were partially moderated by changes in brain morphometry, underscoring the interrelationship between weight and brain structure/function	Two participants discontinued the study due to severe nausea
O'Neil et al[21]	Post hoc analysis of 5 RCTs	No specific age range	Obesity	One phase 2 trial duration was 2 y, but only 1 y of data were included; 4 phase 3 trials, which were of 3 y, 56 wk, 56 wk, and 32 wk duration, respectively	Liraglutide = 3,384, placebo = 1,941	Liraglutide = 3.0 mg subcutaneous	PHQ-9, C-SSRS	Results of this exploratory pooled analysis provide no cause for concern regarding the neuropsychiatric safety of treatment with liraglutide 3.0 mg in patients similar to those included in the examined trials. Although there was a small numerical imbalance in suicidal ideation with liraglutide through adverse event reporting, no between-treatment imbalances in suicidal ideation/behavior or depression were noted through prospective questionnaire assessments. However, in phase 3a trials, mean baseline PHQ-9 scores of 2.8 ± 3.0 vs 2.9 ± 3.1 for liraglutide vs placebo improved to 1.8 ± 2.7 vs 1.9 ± 2.7, respectively, at treatment end	No side effects were reported

(continued)

Table 1 (continued).

Author	Study design	Age (range), y	Diagnosis	Duration	Group, n	Dose range	Scales to measure the clinical outcome	Clinical outcome	Common side effects
Li et al[22]	Open-label trial	18–65	Cognitive decline in T2DM	12 wk	Initial sample size = 50, 2 patients in control group and 1 patient in GLP-1 group quit the trial. Control group (n = 23), GLP-1 group (n = 24)	Initial liraglutide dose = 0.6 mg/day and a maximum dose = 1.8 mg/day adjusted once a week when hyperglycemia was uncontrolled	MMSE, Digit Span Test (including forward and backward), RAVLT (total learning, long-delay free recall and recognition), TMT, Clock Drawing test, Animal Naming test, Memory and Executive Screening	12 wk of treatment with liraglutide significantly improved the cognitive function in patients with T2DM compared to regular hypoglycemic treatment	No side effects were reported
Mansur et al[23]	Secondary analysis of open-label trial	18–55	MDD and bipolar disorder	4 wk	101 individuals were screened, and of those 19 were enrolled; 17 individuals completed the trial	Initial liraglutide dose = 0.6 mg/day, increased to 1.2 mg/day for the 2nd wk, and then titrated to 1.8 mg/day for the final 2 wk	TMTB, DSST, RAVLT, Stroop test, TMTA, HDRS, YMRS, SHAPS, GAF, CGI-S	The 4-wk trial was associated with significantly improved cognitive performance with increased TMTB standard score from baseline (age and education corrected) (Cohen $d = 0.64$, $P = .009$) and in a composite Z-score comprising multiple cognitive tests (ie, Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, Stroop test) (Cohen $d = 0.77$, $P < .001$)	Nausea (36.8%), dizziness (10.6%), and indigestion (10.6%). Two participants (10.6%) discontinued liraglutide due to severe nausea
Battini et al[24]	Nested case-noncase study	No specific age range	Depression and T2DM	54 y of data for 1 database, 53 y of data from second database	Database 1 = 121,368; database 2 = 85,267	None	Standardized MedDRA queries	All signal detection methodologies and disproportionality statistics investigating the GLP-1 analogs agreed on its potential antidepressant effect and showed values <1	No side effects were mentioned
Järvinen et al[25]	Case report	20	OCD associated with autism	36 wk	1	Initial liraglutide dose = 0.6 mg/day at week 1, 1.2 mg/day at week 2, 1.8 mg/day at week 4, and gradually increased to 2.4 mg/day during the following 8 wk	OCI-R	Immediate positive response was observed in the patient's food-related behavior manifesting as subsided obsessive food-related thoughts, craving for food, and compulsive eating. Obsessions, compulsions, and behavioral problems not related to food, including aggressive behavior, decreased significantly	No adverse side effects were observed

Abbreviations: CGI-S = Clinical Global Impressions–Severity of Illness, C-SSRS = Columbia-Suicide Severity Rating Scale, FDG = fluorodeoxyglucose, GAF = Global Assessment of Functioning, GLP-1 RA = glucagon-like peptide 1 receptor agonist, HDRS = Hamilton Depression Rating Scale, MedDRA = Medical Dictionary for Regulatory Activities, MMSE = Mini-Mental State Examination, OCD = obsessive-compulsive disorder, OCI-R = Obsessive-Compulsive Inventory-Revised, PDQ = Perceived Deficits Questionnaire, PHQ-9 = 9-item Patient Health Questionnaire, PIB = Pittsburgh Compound B, REY = Rey-Osterreith complex figure test, SHAPS = Snaith-Hamilton Pleasure Scale, TMTA = Trail-Making Test A, TMTB = Trail-Making Test B, WMS-IV = Wechsler Memory Scale, YMRS = Young Mania Rating Scale.

Table 2.

Articles on Exenatide

Author	Study design	Age, y	Diagnosis	Duration	Group, n	Dose range	Scales to measure the clinical outcome	Clinical Outcome	Common side effects
Athauda et al[26]	Post hoc analysis of an RCT	No specific age range	Parkinson disease	60 wk	31	2 mg once weekly	NMSS, PDQ-39, MDS-UPDRS Part 1, MADRS scores	Compared to placebo, patients treated with exenatide once weekly had greater improvements in individual domains assessing mood/depression across all observer-rated outcome measures after 48 wk including the "mood/apathy" domain of the NMSS, −3.3 points (95% CI −6.2 to −0.4), *P* = .026; the "mood" score (Q1.3 + Q1.4 of the MDS-UPDRS Part 1), −0.3 points (95% CI, −0.6 to −0.1), *P* = .034; and a trend in the MADRS total score, −1.7 points (95% CI, −3.6 to 0.2), *P* = .071. At 48 weeks, these changes were of a magnitude that would be subjectively meaningful to patients and were not associated with changes in motor severity or other factors, suggesting exenatide may exert independent effects on mood dysfunction. The proportion of patients reporting depressive symptoms (as defined by the total MADRS score > 7) in the placebo group increased from 17% at baseline to 25% at 48 wk, while in the exenatide group, the proportion of patients reporting depressive symptoms reduced from 23% at baseline to 6% of patients at 48 wk	None reported
Angarita et al[15]	RCT, crossover study	30–55	Cocaine use disorder	44 mo	13	5 µg, 0.02 mL exenatide or placebo (saline) 3 h before cocaine administration	VAS self-ratings for subjective outcomes, number of infusions of cocaine for behavioral outcomes	Pretreatment with exenatide (8.5 ± 1.2) did not change the number of cocaine infusions in comparison to pretreatment with placebo (9.1 ± 1.2) (F[1, 12] = 0.76, *P* = .39). Exenatide did not change primary subjective outcomes of cocaine-induced subjective effects of euphoria/"high" (4.4 ± 0.8 vs 4.0 ± 0.8; F[1, 12] = 1.73, *P* = .21) nor wanting cocaine (5.5 ± 0.9 vs 5.4 ± 0.9; F[1, 12] = 0.58, *P* = .46), compared to placebo. Pretreatment with exenatide had an effect on levels of GLP-1 (F[1, 55] = 4.65, *P* = .03) and insulin (F[1, 55] = 5.69, *P* = .02), but not amylin (F[1, 50] = 1.17, *P* = .28). Both GLP-1 and insulin were lower following exenatide during cocaine self-administration (GLP- 1 = 22.6 ± 3.3 pg/mL; insulin = 9.5 ± 1.4 uIU/mL) as compared to placebo during cocaine self-administration (GLP-1 = 26.6 ± 4.3; insulin = 13.8 ± 2.1 uIU/mL)	No adverse effects were reported

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Table 2 (continued).

Author	Study design	Age, y	Diagnosis	Duration	Group, n	Dose range	Scales to measure the clinical outcome	Clinical Outcome	Common side effects
Klausen et al[37]	RCT	Mean = 52	Alcohol use disorder	26 wk	Exenatide (n = 62), placebo (n = 65)	2 mg subcutaneously once weekly for 26 wk	AUDIT, Fagerström Test for Nicotine Dependence, SF-36, Symptom Checklist-92	Exenatide did not significantly reduce the number of heavy drinking days compared with placebo. Exploratory analyses revealed that exenatide significantly reduced heavy drinking days by 23.6 percentage points (95% CI, −44.4 to −2.7, *P* = .034) and total alcohol intake per 30 d by 1,205 g (95% CI, −2,206 to −204, *P* = .026) in a subgroup of obese patients (BMI > 30 kg/m2).The mean (SD) number of injections was 22.6 (2.2) in the exenatide group and 22.1 (2.8) in the placebo group. In patients with a BMI less than 25 kg/m^2 (n = 52), treatment with exenatide increased the number of heavy drinking days by 27.5 percentage points (95% CI, 4.7–50.2, *P* = .024) relative to the placebo group	Gastrointestinal side effects were higher in the exenatide compared with the placebo group (nausea, 37.1% vs 15.4%; decreased appetite, 24.2% vs 9.2%; vomiting, 22.6% vs 7.7%; overall weight loss, 67.7% vs 40.0%; fatigue, 12.9% vs 4.6%; injection site reaction, 41.0% vs 0.0%)
Ishøy et al[28]	RCT	Exenatide = 19–65 vs placebo = 19–56	Schizophrenia spectrum disorder	28 mo	Exenatide (n = 20), placebo (n = 20)	2 mg once weekly	BACS, REY, SF-36, PSP, PANSS	Three-month treatment with the GLP-1 receptor agonist, exenatide 2 mg once weekly, did not improve cognition or psychosocial function in patients with schizophrenia spectrum disorder. In Short-Form 36, the parameter "functioning limitations due to emotional problems" showed an effect of "Time" (*P* = .01) and no effect of "Group" (*P* = .43), but a significant "Time × Group" interaction (*P*=.02) with exenatide treated patients scoring higher than the placebo group	Gastrointestinal side effects were reported
Mullins et al[29]	RCT	>60	Alzheimer disease	6 years 9 months	Exenatide (n = 13) Placebo (n = 14)	5 mcg twice daily and then after 1 wk 10 mcg twice daily	CDR, OGTT, MRI	Exenatide treatment produced no differences in clinical and cognitive measures	Nausea was reported
Eren-Yazicioglu et al[30]	Cross-sectional Study	18–65	Obesity with T2DM	3 mo	Exenatide 23, placebo = 20	0.01 mg twice daily	PHQ-9, GAD-7, PRT, SHAPS, CFQ, LNB, CSS, PSS, CTQ	Patients taking exenatide reported higher PHQ-9 scores (9.70 ± 4.92 vs 6.70 ± 4.66; *P* = .026). Patients with exenatide use also reported higher GAD-7 scores; it was not at a significant level (8.04 ± 5.69 vs 4.70 ± 2.54;*P* = .055. Exenatide did not show statistically significant effect on cognitive measures (*P* = .066), anhedonia, and reward learning assessment	No side effects were reported

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, BACS = Brief Assessment of Cognition in Schizophrenia, CDR = Clinical Dementia Rating, CFQ = Cognitive Failures Questionnaire, CSS = Chronic Stress Scale, CTQ = Childhood Trauma Questionnaire**,** GAD-7 = Generalized Anxiety Disorder-7, GLP-1 RA = glucagon-like peptide 1 receptor agonist, LNB = Letter-N-Back Task, MADRS = Montgomery-Asberg Depression Rating Scale, MDS-UPDRS = Movement Disorder Society-Unified Parkinson Disease Rating Scale, MRI = magnetic resonance imaging, NMSS = Non-Motor Symptoms Scale for Parkinson Disease, OGTT = oral glucose tolerance test, PANSS = Positive and Negative Syndrome Scale, PDQ-39 = Parkinson`s Disease Questionnaire, PHQ-9 = 9-item Patient Health Questionnaire, PRT = probabilistic reward task, PSP = Personal and Social Performance Scale, PSS = Perceived Stress Scale, REY = Rey-Osterreith complex figure test, SF-36 = 36-Item Short Form Survey, SHAPS = Snaith-Hamilton Pleasure Scale, T2DM = type 2 diabetes mellitus, VAS = visual analog scale.

Table 3.

Articles on Miscellaneous Drugs

Author	Study design	Age, y	Diagnosis	Duration	Pharmacologic intervention	Group, n	Dose range	Scales to measure the clinical outcome	Clinical outcome	Common side effects
Nørgaard et al[31]	3 RCTs and 1 nested case-control study	No specific age range	T2DM	RCT 1: 3.8 y, RCT 2: 2.1 y, RCT 3: 1.3 y; for the case-control study, the median follow-up time was 7.4 y between 2009 and 2017	Liraglutide and semaglutide	RCT 1: n = 9,340, RCT 2: n = 3,297, RCT 3: n = 3,183, case control: n = 120,054	None	Standardized MedDRA queries for RCT	For RCTs, patients randomized to GLP-1 RAs had a lower rate of developing dementia compared to those randomized to placebo (HR: 0.47; 95% CI, 0.25–0.86) and in the nationwide cohort (HR: 0.89; 95% CI, 0.86–0.93 with yearly increased exposure to GLP-1 RAs). For the case-control study, the result was a reduced rate of dementia with increasing exposure to GLP-1 RAs compared to other second-line diabetes treatments	None
Wium-Andersen et al[32]	Case-control study	No specific age range	Dementia in T2DM	17 y with a median follow-up of 7.2 y	GLP-1 analog, metformin, DPP4 inhibitors, SGLT2 inhibitors	Total (n = 170,417), cases with dementia (n = 11,619), cases without dementia (n = 46,476)	NA	*ICD-10* codes DE10–14, DH36.0, DO24	Use of metformin, DPP4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors were associated with lower odds of dementia after multiple adjustments (ORs of 0.94 [95% CI, 0.89–0.99], 0.80 [95% CI, 0.74–0.88], 0.58 [95% CI, 0.50–0.67], and 0.58 [95% CI, 0.42–0.81], respectively), with a gradual decrease in odds of dementia for each increase in daily defined dose	Side effects are not mentioned in the study
Wium-Andersen et al[33]		Cohort study (range, 35–103), case-control study (depression cases: 35–99, cases: 35–100)	T2DM	12 y	Insulin, metformin, sulfonylureas and glinides combined, glitazones, DPP-4i, GLP-1 analogs, sodium-glucose transport protein 2 (SGLT2) inhibitors and acarbose	116,699 patients with diabetes and a matched reference group of 116,008 individuals without diabetes	NA	*ICD-10* diagnosis of depression (DF32, DF33) in the Danish National Patient Registry	Low doses of metformin, DPP4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors were associated with a lower risk of depression in patients with diabetes compared to non-users, with the lowest risk for sodium-glucose transport protein 2 inhibitor users (OR of 0.55 [0.44–0.70]	
Wium-Andersen et al[34]	Cohort and self-controlled case series	GLP-1 receptor agonists (57.8 [12.1]) or DPP-4 inhibitors (65.1 [12.5])	Alcohol use disorder	8 y	GLP-1 RA or DPP-4 inhibitors	GLP-1 (n = 38,454) and DPP-4i (n = 49,222)	NA	*ICD-10* code DF10	GLP-1 treatment was associated with a lower risk of an alcohol-related event (HR = 0.46 [95% CI, 0.24–0.86]) compared with initiation of DPP4 during the first 3 months of follow-up and after 1 y of follow-up ($HR_{365+\text{ days after initiation}}$ 0.62 [95% CI, 0.45–0.85]). Self-controlled analysis showed the highest risk of alcohol-related events in the 3-month pretreatment period (incidence rate ratio [IRR] = 1.25 [1.00–1.58]), whereas the risk was lowest in the first 3-month treatment period (IRR = 0.74 [0.56–0.97])	
Tsai et al[16]	Cohort study	53.33 ± 13.04	T2DM	7 y	GLP-1 RA (liraglutide, dulaglutide, exenatide)	10,690 DM patients prescribed GLP-1 RA and 42,766 comparisons with nonusers	NA	*ICD-10-CM* codes	The cumulative incidence of anxiety was 2.13% lower in GLP-1 RA users than non-users (Log-rank test $P < .001$), whereas depression was not significantly different between the 2 groups. The overall incidence of depression and/or anxiety was lower in GLP-1 RA users than non-users (6.80 vs 9.36 per 1,000 person-	

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Table 3 (continued).

Author	Study design	Age, y	Diagnosis	Duration	Pharmacologic intervention	Group, n	Dose range	Scales to measure the clinical outcome	Clinical outcome	Common side effects
									years), with an aHR of 0.8 (95% CI, 0.67–0.95) for users, after controlling for demographic factors, comorbidities and medications. The difference in incidence rates between the 2 groups was more significant for anxiety than depression. The aHRs of developing anxiety and depression for the GLP-1 RA group, compared to non-users, were 0.78 (95% CI, 0.64–0.95) and 0.94 (95% CI, 0.72–1.23), respectively. After taking the medicine for 180 d or longer, rates of incidence of depression or anxiety reduced to 2.19 and 2.93 per 1,000 person-years, respectively	
Secnik et al[35]	Cohort study	Dementia cohort (metformin = 78.1 [7.6]; insulin = 80.0 [7.0]; sulfonylurea = 79.3 [7.1]; DPP-4i = 79.7 [7.0]; GLP-1a = 75.7 [7.0]; SGLT-2i = 75.7 [6.3]). Dementia-free cohort (metformin = 76.3 [7.1]; insulin = 81 [6.7]; sulfonylurea = 77.3 [7.4]; DPP-4i = 78.5 [7.4]; GLP-1a = 72.7 [8.1]; SGLT-2i = 75.5 [7.2])	Diabetes with and without dementia		Metformin, insulin, sulfonylurea, DPP-4i, GLP-1a, and sodium-glucose cotransporter-2 inhibitors	132,402 subjects with diabetes (11,401 with dementia, 121,001 without dementia)	NA	Mortality data obtained from Death Registry	GLP-1a was associated with lower mortality in the dementia cohort (0.44 [0.25–0.78]) but not in the dementia-free cohort (0.68 [0.41–1.10]). While increased mortality was observed among insulin users with dementia (HR 1.34 [95% CI, 1.24–1.45]) as well as in dementia-free subjects (1.54 [1.10–1.55]), conversely, sulfonylurea was associated with higher mortality only in dementia subjects (1.19 [1.01–1.42]). GLP-1a (0.44 [0.25–0.78]) and SGLT-2i users with dementia (0.43 [0.23–0.80]) experienced lower mortality compared to non users	
Gamble et al[36]	Cohort study	DPP-4i (58 [12.2]), sulfonylurea (60.5 [13.8]); GLP-1 RA (49.4 [11.3]), sulfonylurea (57.8 [12.9])	T2DM	15 y	First cohort: DPP-4i and sulfonylurea; Second cohort: GLP-1 RA and sulfonylurea	First cohort: DPP-4i (n = 6,206) and sulfonylurea (n = 22,128); Second cohort: GLP-1 RA (n = 501) and sulfonylurea (n = 16,409)	NA	Clinical Practice Research Datalink, Hospital Episode Statistics, or Office for National Statistics data sources	DPP-4 inhibitor users had 8.2 per 1,000 person-years of depression or self-harm, while sulfonylurea users had 11.7 (unadjusted HR 0.70, 95% CI, 0.51–0.96). DPP-4 inhibitor users also had lower crude incidence rates (10.0 vs 10.8 per 1,000 person-years for TZDs; 9.8 vs 20.7 for insulin users). After adjusting for potential confounders, DPP-4 inhibitor use was not associated with depression or self-harm in any comparator group. GLP-1 receptor users had a nonsignificantly higher rate of depression or self-harm than sulfonylurea (18.2 vs 13.6 per 1,000 person-years; unadjusted HR 1.36, 95% CI, 0.72–2.58; adjusted HR 1.25, 95% CI, 0.63–2.50), TZDs (16.4 vs 12.5 per 1,000 person-years; unadjusted HR 1.32, 95% CI, 0.72–2.42; adjusted HR 1.18, 95% CI, 0.53–2.65) and insulin users (13.6 vs 20.7 per 1,000 person-years; unadjusted after confounder adjustment; all measured associations were nonsignificant	

Abbreviations: DPP-4i = dipeptidyl-peptidase-4 inhibitors, GLP-1 RA = glucagon-like peptide 1 receptor agonist, HR = hazard ratio, MedDRA = Medical Dictionary for Regulatory Activities, NA = not applicable, T2DM = type 2 diabetes mellitus, TZD = thiazolidinediones.