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-	

(continued)

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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.