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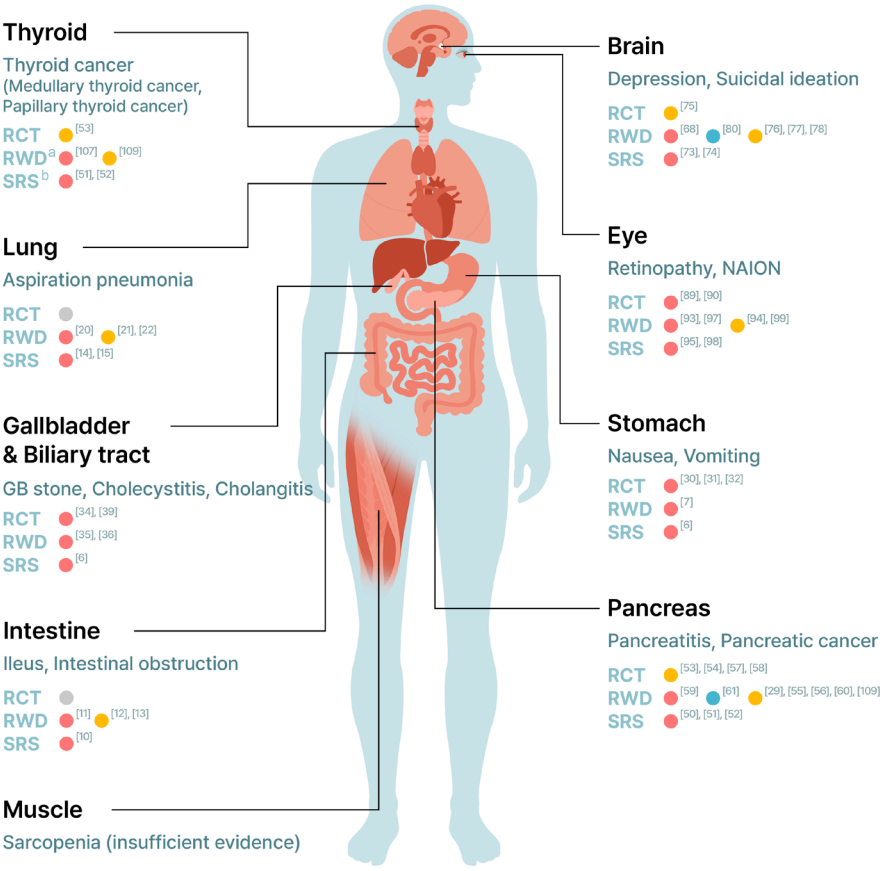

Highlights

- **GLP-1 RAs demonstrate metabolic efficacy but present diverse adverse events.**
- **GI effects are common; obstruction or perioperative aspiration are major concerns.**
- **GLP-1 RAs link to gallbladder/biliary diseases without increasing pancreatitis risk.**
- **Close monitoring is essential for depression and suicidal ideation during therapy.**
- **Retinopathy, NAION, cancer, and sarcopenia warrant careful consideration.**

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Exploring the Side Effects of GLP-1 Receptor Agonist: To Ensure Its Optimal Positioning

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Although glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated considerable efficacy in the treatment of diabetes and obesity, it is essential to recognize that their use is associated with certain intrinsic risks that must not be disregarded. The incidence of adverse effects, particularly gastrointestinal complications, psychiatric disorders, and ocular problems, highlights the critical need for thorough patient assessment and continuous monitoring to ensure both the safety and effectiveness of treatment. Despite the possibility of adverse events, GLP-1 RAs continue to represent a crucial therapeutic modality for metabolic disturbances. This highlights the significance of ongoing research initiatives aimed at optimizing their safe utilization and refining current treatment protocols to improve patient outcomes. This review summarizes updated research findings regarding the adverse effects of GLP-1 RAs, their mechanisms of action, and guidelines for clinical application.

Keywords: Biliary tract diseases; Drug-related side effects and adverse reactions; Eye diseases; Gastrointestinal diseases; Glucagon-like peptide-1 receptor agonists; Mental disorders; Pancreatic diseases; Sarcopenia

INTRODUCTION

The first incretin hormone, gastric inhibitory peptide, was identified in the early 1970s, followed by the discovery of glucagon-like peptide 1 (GLP-1) in the 1980s [1]. In the 1990s, exendin-4, a GLP-1 receptor agonist (GLP-1 RA) structurally similar to endogenous GLP-1, was isolated from Gila monster venom, which subsequently led to the approval of exenatide for type 2 diabetes mellitus (T2DM) management in 2005 [2]. Since then, GLP-1 RAs have attracted considerable academic interest, leading to the continuous introduction of innovative analogs into the pharmaceutical industry. These pharmacological agents exhibit beneficial effects on glycemic regulation, weight management, and cardiovascular outcomes, thereby establishing their essential roles in contemporary diabetes management [3-5]. To date, dulaglutide, semaglutide, and tirzepatide have been the three predominant GLP-1 therapeutics employed in the treatment of T2DM, and their applications have been broadened to include weight management. In December 2014, the Food and Drug Administration (FDA) approved liraglutide for weight loss, and semaglutide was approved for diabetes in 2017 and obesity in 2021, opening a new era of obesity treatment. Currently, intense media attention and influencer promotion, coupled with robust marketing tactics, have led to an increase in the demand for GLP-1 RAs, resulting in global shortages of these medications. Despite their considerable benefits, GLP-1 RAs are associated with various adverse reactions (Fig. 1). This study aimed to critically assess the existing literature on the adverse effects of GLP-1 RAs to formulate appropriate risk-benefit prescription practices for their optimal utilization as metabolic disease therapeutics.

GASTROINTESTINAL ADVERSE EFFECTS

The most prevalent adverse effects associated with GLP-1 RAs include gastrointestinal disturbances, such as nausea, vomiting,

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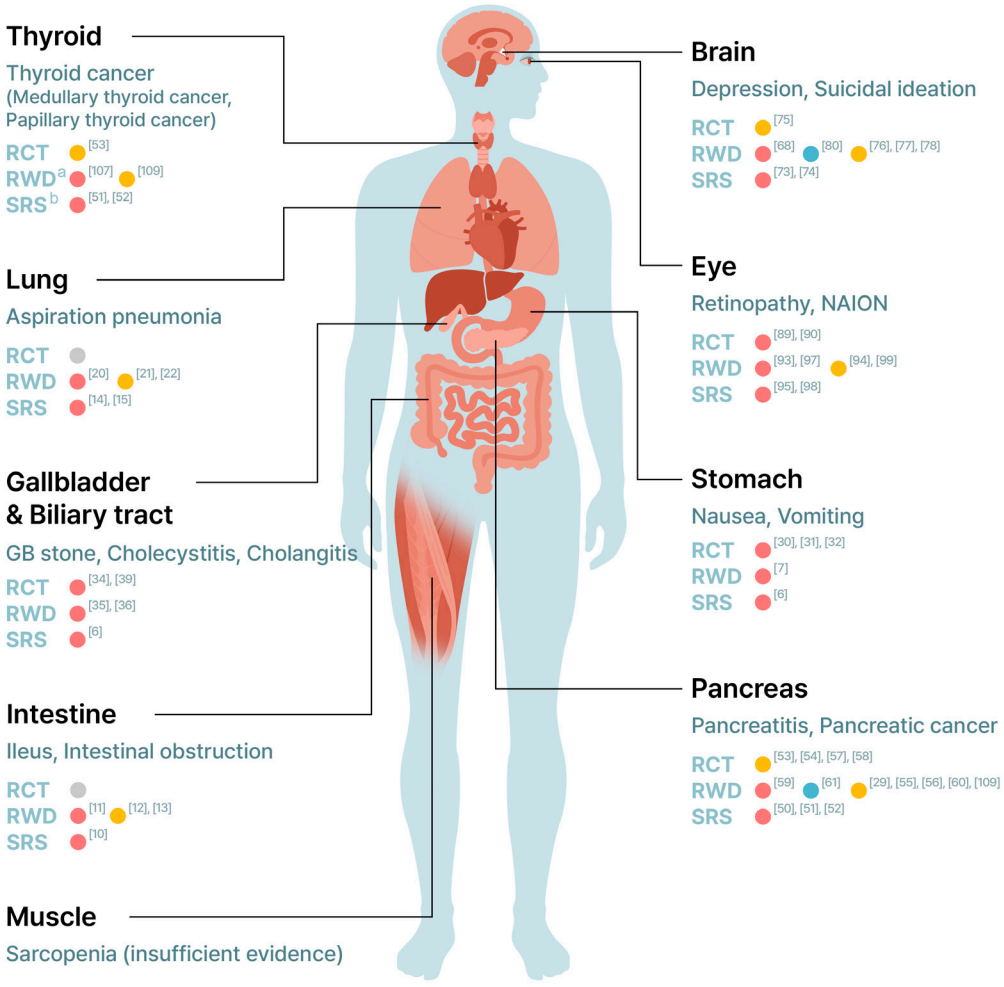

Fig. 1. An overview of the existing literatures on the adverse effects linked to glucagon-like peptide-1 receptor agonists (GLP-1 RAs) across diverse research methodologies: Pink circle (●) denotes the existence of research indicating that GLP-1 RAs increased the incidence of such adverse effects; Blue circle (●) denotes the existence of research indicating that GLP-1 RAs decreased the incidence of such adverse effects; Orange circle (●) denotes the existence of research indicating that GLP-1 RAs was not significantly associated with such adverse effects; Grey circle (●) denotes an absence of research concerning the correlation between GLP-1 RAs and such adverse effects. The superscript numerals of each circular element indicate the corresponding referenced studies. RCT, randomized controlled study; RWD, real-world data; SRS, spontaneous-reporting system; NAION, non-arteritic ischemic optic neuropathy; GB, gallbladder. [a]RWD: real-world data from cohort or registry studies (electronic health records, insurance-claims databases), [b]SRS: adverse drug reaction evidence from case reports and spontaneous-reporting systems, such as the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and World Health Organization (WHO) VigiBase.

diarrhea, and constipation [6,7]. These symptoms frequently manifest during the initial treatment phase, affecting approximately 50% to 60% of patients [8], but they generally diminish over time, with their occurrence being dose-dependent. The capacity of GLP-1 RAs to decelerate gastric emptying to levels indicative of gastroparesis raises concerns regarding potential intestinal obstruction and perioperative aspiration risk.

Evidence based on recent studies

Intestinal obstruction

Initially, cases of intestinal obstruction associated with GLP-1 RAs were reported by the European Medicines Agency (EMA) in 2013 [9], and this safety signal is currently being monitored by the United States (US) FDA. Based on VigiBase, the World Health Organization's (WHO) adverse drug reaction database,

intestinal obstructions are reported over 4.5 times more frequently with incretin-based drugs than with other diabetes medications [10]. Similarly, an analysis utilizing the UK Clinical Practice Research Datalink (CPRD) revealed that GLP-1 RAs were linked to an increased incidence of intestinal obstruction requiring hospitalization, compared to sodium-glucose cotransporter-2 (SGLT-2) inhibitors (1.9 vs. 1.1 per 1,000 person-years; hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.04 to 2.74) [11]. In contrast to these results, a study using nationwide registry data from Sweden, Denmark, and Norway—involving 121,254 new GLP-1 RA users and 185,027 new SGLT-2 inhibitor users— documented 557 intestinal obstruction events, with no significant correlation between GLP-1 RA use and increased intestinal obstruction risk, thereby refuting earlier safety concerns [12]. Nielsen et al. [13] recently reported that GLP-1 RAs are not associated with an increased risk of intestinal obstruction in patients with inflammatory bowel disease using Danish health registries. While some studies suggest a possible correlation between GLP-1 RAs and intestinal obstruction, others report no significant association, with discrepancies likely due to variations in study demographics, methodologies, and GLP-1 RA formulations. Therefore, more extensive randomized controlled trials (RCTs) are essential to elucidate these relationships and inform clinical practice.

Aspiration occurring during procedural anesthesia

The correlation between delayed gastric emptying and GLP-1 RAs raises concerns about the possible negative effects in the periprocedural setting, as evidenced by case reports of aspiration events occurring during procedural anesthesia in patients administered GLP-1 RAs [14,15]. Studies on patients taking GLP-1 RAs have demonstrated increased gastric residue on esophagogastroduodenoscopy [16]. A prospective study involving individuals initiated on semaglutide, evaluated via ultrasound after an overnight fast, demonstrated that 70% of those receiving semaglutide exhibited retained solid gastric content, in contrast to 10% in the control group [17]. Nersesian et al. [18] also reported that preoperative semaglutide use within 10 days of elective surgery was independently associated with increased residual gastric content, as assessed by gastric ultrasound. In the semaglutide group, 40% of patients exhibited increased residual gastric content, compared to only 3% of non-semaglutide users [18]. Another cross-sectional study prospectively recruited patients adhering to preprocedural fasting protocols before elective anesthesia revealed that, after controlling for confounding variables, the use of GLP-1 RAs was associated with a 30.5% increase in the prevalence of increased residual gastric contents. This finding indicate that current fasting guidelines may be insufficient for patients on GLP-1 RAs, thereby increasing their aspiration risk [19]. A retrospective cohort study using the TriNetX dataset revealed a significant correlation between GLP-1 RAs use and elevated aspiration pneumonia risk in patients undergoing gastrointestinal endoscopy, particularly among those receiving propofol sedation [20]. However, a recent retrospective cohort study using a nationwide commercial administrative claims database—including 6,806,046 patients with T2DM who underwent outpatient upper endoscopy from 2005 to 2021—reported contrasting findings. It showed that the relative risks for aspiration, aspiration pneumonia, pneumonia, or respiratory failure were not elevated in patients prescribed GLP-1 RA compared to those receiving dipeptidylpeptidase-4 (DPP-4) inhibitors [21]. A comprehensive analysis of 43,365 individuals from two US healthcare databases indicated that GLP-1 RAs do not elevate the risk of pulmonary aspiration during upper gastrointestinal endoscopy in patients with T2DM when compared to SGLT-2 inhibitors, yielding a pooled risk ratio of 0.98 (95% CI, 0.73 to 1.31) among GLP-1 RA users. However, these agents were linked to an increased likelihood of procedure discontinuation, presumably due to aggravated gastric retention [22].

Mechanism

Gastric emptying results from a sophisticated interaction between gastric pacemaker cells, gastrointestinal smooth muscle dynamics, and neurohormonal regulatory mechanisms. Both animal and human studies have shown that increased GLP-1 activity reduces intestinal motility [23]. GLP-1 inhibits intestinal contractions through mechanisms that may involve the central nervous system via vagal pathways or direct action on central receptors [24], as well as the enteric nervous system by modulating neurotransmission through presynaptic receptors affecting nitric oxide release [25,26]. This may be further pronounced in patients with diabetes with compromised gastrointestinal function due to autonomic neuropathy. More comprehensive insight into the effects of GLP-1 RAs on gastrointestinal and central nervous system functions is required.

Clinical implication

Considering the potential for gastric food retention and aspiration risks associated with surgical or endoscopic interventions,

the American Society of Anesthesiologists recommends the discontinuation of short-acting GLP-1 RAs one day and long-acting formulations at least 1 week before surgical procedures [27]. However, insufficient evidence exists to justify the discontinuation of GLP-1 RAs before the procedure, and the ideal cessation timing for these agents remains indeterminate. A recent cross-sectional study involving 124 participants indicated that 56% of patients still exhibited elevated residual gastric contents despite halting incretin agonists for a minimum of 7 days, thus challenging the practice of discontinuing long-acting GLP-1 RAs solely for this duration prior to surgery [19]. Postponing GLP-1 RAs before endoscopic intervention or surgery may hinder diabetes management and increase cancellation rates without significant advantages. Consequently, the 2024 American Gastroenterology Association (AGA) Rapid Clinical Practice Update recommends that management should depend on upper gastrointestinal symptoms. An 8-hour fast from solids and a 2-hour fast from liquids for individuals on GLP-1 RAs is considered sufficient in the absence of such symptoms [28]. Although data are lacking to justify the cessation of GLP-1 RAs therapy preoperatively, additional precautions should be taken due to aspiration risk. Thus, if gastrointestinal symptoms exist, assessing gastric emptying through solid tests or employing gastric ultrasound to detect retained contents may be warranted.

HEPATOBILIARY ADVERSE EFFECTS

Evidence based on recent studies

Several RCTs have demonstrated a significantly higher prevalence of gallbladder disorders among patients treated with GLP-1 RAs compared to placebo [29-32], as initially evidenced by the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, which reported acute gallstone disease rates of 3.1% in the liraglutide group versus 1.9% in the placebo cohort ($P<0.001$) [33]. *Post hoc* analysis of LEADER data revealed a persistent increase in the overall risk of biliary tract-related events and gallbladder diseases, consistently observed across four categories: uncomplicated gallbladder stones, complicated gallbladder stones, cholecystitis with/without gallbladder stones, and biliary obstruction [34]. Faillie et al. [35] conducted the first population-based study linked the UK CPRD with the Hospital Episodes Statistics database, examining the relationship between incretin-based medications and the incidence of hospitalization due to bile duct and gallbladder diseases. They found that current DPP-4 inhibitor usage did not correlate with an increased risk of these conditions compared to at least two oral antidiabetic drugs predominantly comprising metformin and sulfonylurea (3.6 vs. 3.3 per 1,000 person-years; adjusted HR, 0.99; 95% CI, 0.75 to 1.32), whereas the use of GLP-1 analogues was linked to an increased risk (6.1 vs. 3.3 per 1,000 person-years; adjusted HR, 1.79; 95% CI, 1.21 to 2.67) [35]. Extending the findings from the UK cohort study, additional real-world data derived from the Taiwan National Health Insurance Database—which encompasses Asian populations characterized by lower gallstone prevalence, low-fat and high-fiber dietary patterns, and lower body mass index—also documented an elevated risk of biliary-related diseases linked to GLP-1 RAs compared with SGLT-2 inhibitors [36]. In that study, liraglutide (HR, 1.33; 95% CI, 1.00 to 1.77) exhibited a significantly elevated risk, whereas dulaglutide did not. Liraglutide has a significantly lower molecular weight than dulaglutide (3.8 kDa albumin binding heptamer vs. 59.7 kDa immunoglobulin G4-fusion molecule), a shorter half-life (11–15 hours vs. 5 days), is partially metabolized and excreted via the biliary route, and exerts a stronger weight-reducing effect; these factors may contribute to a higher incidence of hepatobiliary adverse events [2,37]. The differential impact of various GLP-1 RAs on biliary disorders remains ambiguous; nonetheless, the Researching cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial indicated no significant hepatobiliary adverse events in the dulaglutide cohort vs. placebo (2.4% vs. 2.1%, $P=0.450$) [38]. Additional research is required to ascertain the variability in the risk of biliary diseases associated with GLP-1 RAs. A recent systematic review and meta-analysis encompassing 76 RCTs demonstrated that GLP-1 RA therapy considerably elevated the probability of gallbladder and biliary disorders (pooled relative risk, 1.37; 95% CI, 1.23 to 1.52) [39]. This augmented risk was particularly pronounced in the context of weight loss interventions compared to diabetes management (P for interaction <0.001), when using higher rather than lower dosages (P for interaction $=0.006$), and with extended treatment duration compared to shorter intervals (P for interaction $=0.030$).

Mechanism

Although the biological rationale for GLP-1 RA-induced biliary toxicity is not clear, the current findings indicate potential weight-loss-dependent mechanisms. Cholelithiasis is a common complication associated with weight reduction interven-

tions, with the incidence of new gallstone formation exceeding 30% after gastric bypass surgery in obese populations [40]. Weight reduction results in cholesterol supersaturation in the bile, thereby increasing the risk of gallstone formation [40]. Another pathway contribute to gallbladder-related complications independently of weight reduction. GLP-1 hinders gallbladder motility and postpones gallbladder evacuation by inhibiting cholecystokinin secretion [40-44]. Small-scale clinical trials have reported that exenatide and liraglutide can diminish gallbladder emptying or extend the time to reach the peak postprandial gallbladder ejection fraction [42,45]. Compounded gallbladder motility results in sludge accumulation and gallstone development [46]. Further, direct stimulation of the GLP-1 receptor on cholangiocytes can lead to enhanced cellular proliferation and an elevated likelihood of cholestasis [47]. Experimental investigations have demonstrated that cholangiocytes are sensitive to GLP-1 and respond with augmented proliferation, potentially increasing the risk of duct obstruction [47,48].

Clinical implication

Although the association between GLP-1 RAs and gallbladder/biliary diseases has been supported by multiple studies, causality has not been definitively established. To reduce these potential risks, healthcare providers are advised to closely monitor patients, particularly those with a history of gallbladder or biliary disease [49].

PANCREAS ADVERSE EFFECTS

Evidence based on recent studies

Acute pancreatitis following exenatide administration has been documented in case reports since 2006 [50]. This concern was further highlighted by an analysis of the US FDA adverse events database. From 2004 to 2009, an analysis of the database revealed a six-fold increase in pancreatitis incidents linked to the DPP-4 inhibitor sitagliptin and the GLP-1 mimetic exenatide, the first two GLP-1-based medications marketed in the US [51]. In that report, the incidence of pancreatic cancer was also 2.9 and 2.7 times greater with exenatide and sitagliptin, respectively, compared to other oral antidiabetic medications. A recent analysis of FDA adverse event reporting system (FAERS) data from 2004 to 2020 revealed a notable association between GLP-1 RAs and malignant pancreatic neoplasms (proportional reporting ratio [PRR], 9.86) [52]. Although the FAERS database aids in detecting rare adverse events via spontaneous reporting, its propensity to overestimate unexpected adverse events linked to new therapies makes it inappropriate for comparative analysis of adverse event frequencies among pharmaceuticals.

Initial concerns regarding the possible link between the use of GLP-1 RAs and the development of pancreatitis or pancreatic cancer have not been supported by the results of RCTs [53,54], or real-world data [29,55,56]. Most RCTs failed to demonstrate a significant association between GLP-1 RAs and the occurrence of pancreatitis or pancreatic cancer, primarily because of their short duration and insufficient design for evaluating such risks. Based on an analysis of 68 RCTs encompassing 60,720 participants, Shihab et al. [57] demonstrated that GLP-1 based agents were associated with a three-fold increased risk of pancreatic enzyme elevation relative to controls, yet did not indicate a significant rise in pancreatitis or pancreatic cancer. A meta-analysis of 113 RCTs comprising 33,167 patients in the GLP-1 RA cohort and 26,683 in the comparator cohort revealed no significant elevation in pancreatitis or pancreatic cancer risk relative to control groups (Mantel-Haenszel odds ratio [MH-OR] of 0.93 and 0.94, respectively), but identified a notable increase in cholelithiasis risk (MH-OR, 1.30) [58]. A recent meta-analysis of 11 cardiovascular outcome trials involving 55,921 patients treated with GLP-1 RAs and 43,306 patients treated with DPP-4 inhibitors also revealed no significant association between either drug class and pancreatic cancer risk. However, while GLP-1 RAs did not exhibit an increased risk of acute pancreatitis, DPP-4 inhibitors demonstrated a notable risk elevation (rate ratio, 1.75) [53]. It is important to note that randomized trials typically involve a highly selective group of individuals who do not accurately reflect the general population with T2DM. For instance, clinical trials on pancreatitis rarely include individuals with a history of heavy alcohol consumption. Therefore, if GLP-1 RA treatment specifically increases the risk of pancreatitis in this vulnerable population, such an effect would likely remain undetected in randomized trials.

In contrast to RCTs, retrospective observational studies offer the benefit of capturing extensive patient data in real-world settings. In a comprehensive US administrative database from 2005 to 2008, GLP-1-based treatments, particularly sitagliptin and exenatide, were associated with a significantly increased risk of acute pancreatitis-related hospitalization in adults with T2DM [59], thereby reinforcing prior mechanistic experimental studies and spontaneous reports to the FDA suggesting a

potential causal relationship. Nonetheless, investigators from the Canadian Network for Observational Drug Effect Studies (CNODES) reported contradictory results. They concluded that incretin-based medications did not correlate with an increased risk of acute pancreatitis or pancreatic cancer compared to other oral anti-diabetic agents, which remained consistent across drug classification and duration of use [29,55]. Furthermore, a recent extensive cohort study involving over 33,000 GLP-1 RA users diagnosed with diabetes over a 9-year period indicated no significant increase in pancreatic cancer risk associated with GLP-1 RA use, as evidenced by an HR of 0.50 compared to basal insulin [60]. In the Veterans Health Administration (VHA) national dataset, an adjusted OR indicated no significant difference in pancreatitis occurrences between thiazolidinedione and incretin groups (adjusted OR, 0.94; 95% CI, 0.75 to 1.18) [56]. Despite the limitations of real-world observational studies—including the absence of randomization, control for confounding variables, and inability to establish causality—researches offer confidence regarding the pancreatic safety profiles of GLP-1 RAs [55,61].

Mechanism

In response to a previous FDA inquiry, two short-term mechanical studies were conducted using exenatide and liraglutide in a diabetic rat model, wherein one rat administered with exenatide died of pancreatic necrosis, while the others exhibited acinar-to-ductal metaplasia and ductal hyperplasia, indicative of potential premalignant alterations [62,63]. Persistent activation of GLP-1 receptors in exocrine pancreatic cells may lead to localized hyperplasia in the exocrine pancreas, consequently accelerating the formation of dysplastic lesions and pancreatitis [64]. Although experimental studies suggest potential pancreatic harm from GLP-1 RAs, robust clinical evidence demonstrates that these drugs do not increase the incidence of pancreatitis or pancreatic cancer in diverse human populations. This contrasts with controlled animal model findings, which may not accurately reflect real-world complexities.

Clinical implication

Clinicians are encouraged to perform comprehensive evaluations prior to prescribing GLP-1 RA therapy in patients with a history of pancreatic disorders or other pancreatitis risk factors. However, past pancreatitis is not a contraindication for these agents, and contrary to the previous warning, recent studies have not shown an increased pancreatic risk associated with GLP-1 RAs, leading to ongoing revisions in treatment guidelines. In cases where pancreatitis is suspected, discontinuation of GLP-1 RA and appropriate medical intervention are recommended according to the risks and benefits for each patient [65].

PSYCHIATRIC ADVERSE EFFECTS

Evidence based on recent studies

The prevalence of various neuropsychiatric disorders is high in individuals with obesity [66]. Suicidal ideation is associated with the use of various weight reduction drugs [67,68]. Certain anti-obesity drugs, including selective serotonin reuptake inhibitors and naltrexone/bupropion combinations, have been linked to adverse psychological outcomes such as mood alterations and suicidal ideation [69]. Furthermore, the EMA has withdrawn the weight loss medication rimonabant, a selective cannabinoid type 1 receptor antagonist, due to its reported links to increased risks of depression and suicide [70].

In 2017, a *post hoc* pooled analysis of RCTs on liraglutide demonstrated comparably low incidences of depression and anxiety in both the liraglutide and placebo cohorts. However, a slight numerical increase in suicidal ideation was observed among liraglutide recipients, with nine cases (0.3%) in the liraglutide group compared to two cases (0.1%) in the placebo group [71]. In July 2023, the EMA initiated an inquiry into safety concerns after receiving approximately 150 spontaneous reports indicating potential links between drugs and suicide ideation or self-harm [72]. The WHO's VigiBase identified a notable disproportionality signal for suicidal ideation linked to semaglutide (reported odds ratio [ROR], 1.45; 95% CI, 1.18 to 1.77), absent for liraglutide, especially in patients concurrently using antidepressants (ROR, 4.45; 95% CI, 2.52 to 7.86) [73]. McIntyre et al. [74] analyzed the FAERS data from 2005 to October 2023, revealing a notable incidence of suicidal ideation and depression linked to semaglutide and liraglutide, with no recorded cases of suicidal behaviors or completed suicides. The primary limitation of FAERS is its dependence on voluntary adverse event reporting, which restricts its ability to comprehensively document all occurrences. However, the recent heightened social media attention on GLP-1 RAs, notably semaglutide and liraglutide, may have resulted in an imbalanced surge in reporting relative to other pharmaceuticals.

RCTs evaluating GLP-1 RA have not identified indicators of suicidality. The *post hoc* analysis of pooled data from the Semaglutide Treatment Effect in People with Obesity (STEP) 1, 2, 3,

and 5 trials indicated that semaglutide treatment at 2.4 mg did not increase the risk of depressive symptoms or suicidal ideation compared to placebo, while demonstrating a statistically significant yet clinically negligible decrease in depressive symptoms [75]. Nonetheless, these clinical trials were underpowered to detect rare events such as suicidal ideation and self-injurious behavior, and they systematically excluded patients with psychiatric comorbidities commonly seen in clinical settings.

Retrospective cohort studies using real-world data have indicated a neutral or reduced impact of GLP-1 RAs on suicidal ideation. Hurtado et al. [76] found no evidence of increased risk of suicidal ideation and self-injury associated with GLP-1 RAs compared to SGLT-2 inhibitors in individuals with T2DM and obesity, based on data from the Valencia Health System Integrated Database (VID) (per-protocol analysis: HR, 1.04; 95% CI, 0.35 to 3.14). Nationwide retrospective studies utilizing register data from Sweden and Denmark (2013–2021) and the UK CPRD (2007–2020) have revealed consistent findings, indicating that GLP-1 RAs are not associated with an elevated risk of suicidality relative to DPP-4 or SGLT-2 inhibitors [77,78]. A recent meta-analysis encompassing 11 observational and case-control studies across various countries revealed no statistically significant disparity in suicidal outcomes between GLP-1 RA users and those utilizing alternative antihyperglycemic medications (relative risk, 0.57; 95% CI, 0.08 to 4.21) [79]. On the other hand, in the retrospective cohort study using TriNetX Analytics Network electronic health records, semaglutide significantly lowered the risk of both new (HR, 0.27; 95% CI, 0.20 to 0.32) and recurrent (HR, 0.44; 95% CI, 0.32 to 0.60) suicidal ideation compared to non-GLP-1 RAs anti-obesity treatments [80]. However, the limited follow-up duration of 6 months raised concerns about potential reverse causality, as undetected suicidal ideation and medical conditions might have influenced the choice of particular anti-obesity or anti-diabetic drugs. Furthermore, such a retrospective design inherently limits the identification of causal relationships, and unmeasured residual confounding variables—such as glycemic control, hypoglycemic episodes, familial suicide history, and socioeconomic status—may persist. Therefore, given the rarity of suicidal or self-harming behaviors, the limited sample size of the RCT, and the inherent limitations of retrospective studies, comprehensive research with long-term follow-up and rigorous mental health assessments is needed to clarify the potential risks and benefits.

Mechanism

The precise mechanisms underlying these adverse psychiatric effects remain unclear. The interplay between obesity, weight loss, anti-obesity medication, and suicidal ideation is complex. The timing of suicidal ideation in relation to ongoing drug administration or cessation remains unclear. Sudden weight reduction or maladaptation to an altered body perception may elicit biological and psychological reactions that can potentially impact suicidal thoughts. GLP-1 receptors are distributed in multiple brain regions implicated in mood regulation, such as the hypothalamus, hippocampus, amygdala, and pancreas. This suggests that GLP-1 RAs may directly influence these areas, thereby affecting emotional and behavioral states [81]. Moreover, GLP-1 receptors interact with various neurotransmitter systems such as serotonin, dopamine, and glutamate, which are essential for mood regulation and may contribute to the onset of depression and other psychological disorders [82]. The role of GLP-1 in the nervous system remains inconclusive, yet indicates its potential for alleviating neuroinflammation, safeguarding neurons and glial cells from oxidative damage, and optimizing neurotransmitter equilibrium [83]. GLP-1 RAs not only ameliorate insulin resistance and microvascular injury [84], which are significant determinants of depression in T2DM, but also enhance dopamine metabolism and stimulate growth factor signaling pathways, suggesting potential neuroprotective functions [85,86]. Further studies are required to clarify the complex interactions between GLP-1 RAs and various neuropsychiatric processes.

Clinical implication

The updated FDA labeling for liraglutide and semaglutide highlights the importance of monitoring depressive symptoms or suicidal thoughts, suggesting treatment discontinuation if such ideations occur [87,88]. However, current evidence does not strongly justify the cessation of GLP-1 RAs based on suicidality concerns. Consequently, it is essential to prioritize shared decision-making and individualized risk-benefit assessments for prescribing GLP-1 RAs, while avoiding misuse with off-label indications.

OCULAR ADVERSE EFFECTS

Evidence based on recent studies

While GLP-1 RAs have demonstrated potent glucose-lowering effects, their impact on diabetic retinopathy remains incom-

pletely elucidated. In 2016, concerns regarding retinopathy associated with GLP-1 were first raised in the Semaglutide Unabated Sustainability in Treatment of T2DM (SUSTAIN) 6 trial with semaglutide [89]. Patients receiving semaglutide (0.5 or 1.0 mg) for 104 weeks demonstrated a significantly higher risk of diabetic retinopathy complications, including vitreous hemorrhage, blindness, or required procedural treatment compared to those receiving placebo (HR, 1.76; 95% CI, 1.11 to 2.78). Similarly, the LEADER trial with liraglutide showed a numerically higher, though non-significant, rate of diabetic retinopathy events compared to placebo (HR, 1.15; 95% CI, 0.87 to 1.52) [33]. The REWIND cardiovascular outcome trial also revealed that dulaglutide administration resulted in inferior ocular outcomes, leading to an increased need for interventions such as photocoagulation, anti-vascular endothelial growth factor (VEGF) therapy, or vitrectomy compared to placebo recipients [38]. As a result, a meta-analysis of 13 RCTs revealed that GLP-1 RAs, including liraglutide, semaglutide, and dulaglutide, are associated with a 23% increased risk of rapid worsening of diabetic retinopathy in T2DM (OR, 1.23; 95% CI 1.05 to 1.44), with longer treatment periods associated with a greater risk [90]. However, these trials concentrated on cardiovascular outcomes rather than ocular ones, with inconsistent definitions and grading, rendering them insufficient for evaluating the long-term stabilization or enhancement of retinal pathology following an acute reduction in glycosylated hemoglobin (HbA1c). *Post hoc* evaluations of the SUSTAIN 6 trial revealed that semaglutide markedly increased the incidence of diabetic retinopathy complications in individuals with a history of retinopathy, especially among insulin users, presumably due to the swift deterioration of pre-existing retinopathy following rapid glycemic control [91]. Similarly, a meta-analysis of six placebo-controlled trials indicated that the worsening of diabetic retinopathy correlated with reductions in average HbA1c rather than with GLP-1 RA treatment [92].

Real-world studies have shown heterogeneous findings. A retrospective cohort studies using the TriNeX database found that GLP-1 RA therapy combined with insulin was associated with a higher risk of diabetic retinopathy (HR, 1.21; 95% CI, 1.15 to 1.26) and diabetic macular edema (HR, 1.13; 95% CI, 1.06 to 1.21) compared to SGLT-2 inhibitor therapy with insulin [93]. Conversely, a retrospective study with 981 patients with T2DM showed no difference in diabetic retinopathy progression between GLP-1 RAs and SGLT-2 inhibitors [94]. Analysis of FAERS data from 2003 to 2024 showed significant associations between diabetic retinopathy and semaglutide (PRR, 19.43), dulaglutide (PRR, 9.01), and liraglutide (PRR, 4.4) [95].

Non-arteritic anterior ischemic optic neuropathy (NAION) is characterized by optic nerve ischemia leading to abrupt vision loss, yet its pathophysiology remains inadequately understood [96]. In 2024, Hathaway et al. [97] observed a potential association between semaglutide and NAION, with incidence rates of 4.28 and 7.64 per 1,000 person-years in patients with T2DM and those who were overweight or obese, respectively, over 36 months. The FAERS database also revealed 41 reported cases for semaglutide with an ROR of 11.36 (95% CI, 8.33 to 15.49) and a PRR of 11.36 (95% CI, 8.32 to 15.47), suggesting a potential causal relationship between semaglutide and NAION [98]. However, Abbas et al. [99] showed different results using a retrospective matched cohort study that utilized the TriNetX, found no increased risk of NAION or ischemic optic neuropathy among patients with T2DM or elevated BMI prescribed semaglutide over 5 years. Because these findings are based on limited, recently published datasets with conflicting results, ongoing pharmacovigilance and large-scale prospective studies are needed.

Mechanism

Although the exact mechanisms underlying GLP-1 RA-induced diabetic retinopathy remain unclear, several hypotheses have been proposed. The early deterioration of diabetic retinopathy observed with GLP-1 RAs may reflect rapid glucose decline that affects osmotic pressure rather than direct retinal toxicity [91]. This rapid glucose lowering can also induce hypoxia, which may modulate the effect of GLP-1 RAs on retinal VEGF expression [100]. Additionally, GLP-1 has been shown to enhance the proliferation and differentiation of endothelial progenitor cells through upregulation of VEGF, potentially promoting angiogenesis that could contribute to retinal complications [101,102].

However, GLP-1 RAs may also confer neuroprotective benefits to the retina. Recent studies have demonstrated abundant GLP-1 receptors in human retinal tissue, suggesting potential for direct neuroprotective effects [103]. GLP-1 RAs may inhibit retinal neurodegeneration and reduce proinflammatory processes, which could protect against diabetic retinopathy progression.

While the precise mechanism of NAION remains unknown, the effects of GLP-1 on vascular function, glucose homeostasis,

and neuroprotection may potentially influence NAION development. The mechanisms of GLP-1 RAs' action in retinopathy and NAION remain incompletely understood, highlighting the need for large trials with baseline retinal grading and extended follow-up. The ongoing dedicated ophthalmic trial named as FOCUS study, which aims to evaluate semaglutide's long-term effects on diabetic retinopathy, is now ongoing and could contribute to a comprehensive understanding of the true risk-benefit profile of these agents in patients with or at risk for diabetic retinopathy (NCT03811561) [104].

Clinical implication

The potential ocular complications associated with GLP-1 RAs need careful clinical consideration. However, due to discrepancies in findings from clinical trials, real-world data, and fundamental research, definitive recommendations for diabetic retinopathy screening prior to GLP-1 RA treatment initiation remain elusive. Instead, clinicians should acknowledge this risk and consider individualized risk-benefit strategies when prescribing GLP-1 RAs, particularly for patients with pre-existing ocular manifestations and must inform patients regarding possible ocular hazards while advocating for regular retinal examinations and assessments of visual acuity.

OTHERS

Other cancers

Recent investigations have highlighted the association between various neoplasms, such as thyroid, breast, and cholangiocarcinoma, and GLP-1 RAs [105-107]. Notably, a 2020 clinical trial involving patients with nonalcoholic steatohepatitis (NASH) revealed a 15% incidence of tumors (benign, malignant, or unspecified) (35/239) among those administered semaglutide, compared to 8% (6/80) in the control group [108]. However, to date, extensive RCTs have shown no correlation between specific GLP-1 RAs and increased cancer risk. Participants in RCTs typically comprise relatively healthy individuals, excluding those with a history of medullary thyroid cancer or pancreatitis, and the duration of the RCTs is insufficient to induce cancer. Thus, spontaneous reporting may be the most effective method for identifying infrequent adverse events. Analysis of FAERS data from 2004 to 2020 revealed significant associations between GLP-1 RA and various neoplasms, notably medullary thyroid cancer (PRR, 27.43), papillary thyroid cancer (PRR, 8.68), malignant pancreatic neoplasms (PRR, 9.86), and pancreatic neuroendocrine neoplasms (PRR, 2.86) [52]. The FDA's prior warnings regarding the potential elevated risk of medullary thyroid carcinoma associated with GLP-1 RAs may encourage more patients on GLP-1 RA therapy to undergo thyroid ultrasounds, thereby enhancing tumor detection. Furthermore, certain spontaneous reports lacked validation from healthcare professionals, and there was an absence of data regarding the patients' physical conditions, familial history, and individual histories of alcohol and tobacco use, all of which could potentially affect cancer development. Therefore, the results from the FAERS database should be interpreted with caution as they can overestimate adverse events due to reporting bias and do not establish causality. Recently, a comprehensive cohort study utilizing data from the Korean National Health Insurance Service from 2004 to 2021 indicated no significant correlation between GLP-1 RAs and the incidence of new-onset malignancies, with a median follow-up of 8 years [109]. Future research is warranted to explore the prolonged implications of GLP-1 RAs on oncogenic risk. While clinicians should not limit their usage due to cancer concerns, they must maintain a thorough surveillance for possible adverse outcomes.

Sarcopenia

Approximately 40% of the weight reduction associated with GLP-1 RAs is derived from a lean body mass, which raises significant concerns regarding its potential negative impact on skeletal muscle functionality [110]. In the SUSTAIN 8 study, patients with T2DM exhibited a lean mass decrease of 2.3 kg alongside a total weight loss of 5.3 kg, resulting in 43.4% of weight loss attributable to lean mass, while the ratio of lean mass to total mass increased by 1.2% from the baseline [111]. Current evidence, including magnetic resonance imaging studies, suggests that skeletal muscle alterations resulting from GLP-1 RA-induced weight loss, such as enhanced insulin sensitivity and reduced muscle fat infiltration, are adaptive, thereby improving muscle quality despite concurrent reductions in lean mass [112]. Recently, to ensure the safety of GLP-1 RA on sarcopenia, a clinical randomized multicenter trial of bimagrumab, an antibody blockade of activin type II receptor inhibitor, alone or in addition to subcutaneous semaglutide is now ongoing (NCT05616013) [113]. While studies in mice indicate the potential direct benefits of GLP-1 on the skeletal muscle and bone, human data supporting this hypothesis are absent owing to the absence of GLP-1 receptors in the human skeletal muscle, implying that any effects on muscles are likely indirect

Table 1. Summary of key recent findings on the various side effects of GLP-1 RAs

Adverse effects	Study design	Dataset	Period	Subjects	Target	Comparators	Median follow-up duration	Results	Ref
Intestinal obstruction	Population-based cohort study	UK Clinical Practice Research Datalink	2013–2019	T2DM	GLP-1 RAs DPP-4 inhibitors	SGLT-2 inhibitors	0.9 years for GLP-1 RAs 0.5 years for SGLT-2 inhibitors	GLP-1 RAs associated with increased intestinal obstruction risk (HR, 1.69; 95% CI, 1.04–2.74). DPP-4 inhibitors also increased the risk (HR, 2.59; 95% CI, 1.52–4.42).	[11]
		Administrative and health registers in Sweden, Denmark, and Norway	2013–2021	T2DM	GLP-1 RAs DPP-4 inhibitors	SGLT-2 inhibitors	0.9 years for GLP-1 RAs 0.8 years for SGLT-2 inhibitors	Neither DPP4 inhibitors (HR, 1.13; 95% CI, 0.96–1.34) nor GLP-1 RAs (HR, 0.83; 95% CI, 0.69–1.01) increased intestinal obstruction risk.	[12]
		Danish health registries	Before 2018–2024	Irritable bowel disease	GLP-1 RAs exposure	GLP-1 RAs non-exposure	348,687 Person-years	Adjusted hazard ratios indicated no increased risk associated with GLP-1 RA exposure (aHR, 0.57; 95% CI, 0.36–0.88).	[13]
Aspiration pneumonia	Population-based cohort study	TriNetX dataset	2018–2020	Mostly T2DM	GLP-1 RAs exposure	GLP-1 RAs non-exposure		GLP-1 RA use showed a higher incidence rate of aspiration pneumonia (HR, 1.33; 95% CI, 1.02–1.74).	[20]
		Truven Health Analytics MarketScan databases	2005–2021	T2DM	GLP-1 RAs	DPP-4 inhibitors	Within 14 days after endoscopy	GLP1-RA use was not associated with an increased risk of pulmonary complications after upper endoscopy (aRR, 0.93; 95% CI, 0.60–1.43).	[21]
		US commercial healthcare databases		T2DM	GLP-1 RAs	SGLT-2 inhibitors	Within 1–3 days after endoscopy	GLP-1 RA use was not associated with an increased risk of pulmonary aspiration compared (PRR, 0.98; 95% CI, 0.73–1.31).	[22]
Hepato-biliary diseases	*Post hoc* analysis of RCTs	The LEADER trial involved 410 sites across 32 countries		T2DM with high risk for CVD	Liraglutide 1.8 mg	Placebo	3.8 years	Liraglutide increased the risk of gallbladder or biliary tract-related events (HR, 1.60; 95% CI, 1.23–2.09).	[34]
	Meta-analysis of RCTs	76 Randomized trials of GLP-1 RA medications		Mostly T2DM	GLP-1 RAs	Active and placebo		GLP-1 RAs treatment significantly increased the risk of gallbladder or biliary diseases (RR, 1.37; 95% CI, 1.23–1.52).	[39]
	Population-based cohort study	UK Clinical Practice Research Datalink	2007–2013	T2DM	GLP-1 RAs DPP-4 inhibitors	Two OHAs	3.2 years	GLP-1 RAs increased the risk of bile duct/gallbladder disease (HR, 1.79; 95% CI, 1.21–2.67) and undergoing cholecystectomy (HR, 2.08; 95% CI, 1.08–4.02).	[35]
		Taiwan National Health Insurance Database	2012–2018	T2DM	GLP-1 RAs	SGLT-2 inhibitors	1.4 years for GLP-1 RAs 1.8 years for SGLT-2 inhibitors	GLP-1 RAs increased the risk of acute cholecystitis or cholecystectomy (HR, 1.22; 95% CI, 0.92–1.62).	[36]
Pancreas diseases	Meta-analysis of RCTs	Data from 11 CVOTs with GLP-1 RAs and DPP-4 inhibitors		T2DM	GLP-1 RAs DPP-4 inhibitors	Active and placebo		Neither GLP-1 RAs (RR, 1.14; 95% CI, 0.77–1.70) nor DPP-4 inhibitors (RR, 0.94; 95% CI, 0.52–1.68) significantly elevated the risk of pancreatic cancer. DPP-4 inhibitors increased the risk of acute pancreatitis (RR, 1.75; 95% CI, 1.14–2.70).	[53]
	Meta-analysis of RCTs	28 RCTs for assessing safety of GLP-1 RAs		T2DM	GLP-1 RAs	Active and placebo		The incidence of pancreatitis (MH-OR, 0.93; 95% CI, 0.65–1.34) and pancreatic cancer (MH-OR, 0.94; 95% CI, 0.52–1.70) with GLP-1 RA was not significantly different.	[58]
	Population-based cohort study	Six CNODES database sites from Canada, the US, and the UK	2007–2014	T2DM	GLP-1 RAs DPP-4 inhibitors	Sulfonyl-urea	1.3–2.8 years	Compared with sulfonylureas, incretin-based drugs were not associated with an increased risk of pancreatic cancer (HR, 1.02; 95% CI, 0.84–1.23).	[55]
		Veterans Health Administration	2011–2021	T2DM	GLP-1 RAs DPP-4 inhibitors	TZD		An adjusted odds ratio found no statistical difference in pancreatitis cases between the TZD and incretin cohorts (aOR, 0.94; 95% CI, 0.75–1.18).	[56]
		US administrative database	2005–2008	T2DM	GLP-1 RAs DPP-4 inhibitors	Non-GLP-1 based therapy		GLP-1 based therapy was associated with an increased risk of acute pancreatitis compared with nonusers (aOR, 2.07; 95% CI, 1.36-3.13).	[59]
		TriNetX dataset	2013–2019	T2DM	GLP-1 RAs	Non-GLP-1 RA	5 years	GLP-1RAs were associated with a lower risk of pancreatic cancer compared to insulin (HR, 0.42; 95% CI, 0.33–0.53), metformin (HR,0.74; 95% CI, 0.58–0.95), DPP-4 inhibitors (HR, 0.77; 95% CI, 0.66–0.90), SGLT-2 inhibitors (HR, 0.71; 95% CI, 0.59–0.85), sulfonylurea (HR, 0.74; 95% CI 0.63–0.88), and TZD (HR, 0.82, 95% CI, 0.69–0.99).	[61]

(*Continued to the next page*)

Table 1. Continued

Adverse effects	Study design	Dataset	Period	Subjects	Target	Comparators	Median follow-up duration	Results	Ref
Psychiatric diseases	*Post hoc* analysis of RCTs	STEP 1, 2, 3, and STEP 5 trials	2018–2021	OW/OB (T2DM in STEP 2)	Semaglutide 2.4 mg	Placebo	STEP 1, 2, and 3: 68 weeks STEP 5: 104 weeks	Semaglutide, 2.4 mg, did not increase the risk of developing depressive symptoms (OR 0.63; 95% CI, 0.50–0.79) or suicidal ideation/behavior.	[75]
	Population-based cohort study	Valencia Health System Integrated Database (VID)	2015–2021	T2DM, obese	GLP-1 RAs	SGLT-2 inhibitors	992 days for GLP-1 RA 970 days for SGLT-2 inhibitors	GLP-1 RAs exhibited no increased risk of the incidence of suicidal ideation and self-injury (HR, 1.04; 95% CI, 0.35–3.14).	[76]
		Nationwide register data from Sweden and Denmark	2013–2021	Mostly T2DM	GLP-1 RAs	SGLT-2 inhibitors	2.5 years	GLP-1 RAs did not increase the risk of suicide death (HR, 1.25; 95% CI, 0.83–1.88).	[77]
		UK Clinical Practice Research Datalink	2007–2020	T2DM	GLP-1 RAs	DPP-4 inhibitors SGLT-2 inhibitors	1.3 years	GLP-1 RAs did not increase the risk for suicide death (vs. SGLT-2 inhibitor, HR, 0.91; 95% CI, 0.73–1.12) (vs. DPP-4 inhibitors, HR, 1.02; 95% CI, 0.85–1.23).	[78]
		TriNetX dataset	T2DM: 2017–2021 OW/OB: 2021–2022	T2DM, OW/OB	Semaglutide	Non-GLP-1 RA AOM	172.9 days for semaglutide 167.2 days for non-GLP-1 RA AOM	Semaglutide was associated with a lower risk for incident (HR, 0.27; 95% CI, 0.20–0.36) and recurrent (HR, 0.44; 95% CI, 0.32–0.60) suicidal ideation.	[80]
	Meta-analysis of observational cohort and case-control studies	Various 11 studies on GLP-1 RAs and their association with suicidal ideation		T2DM, OW/OB, general users of GLP-1 RAs	GLP-1 RAs	Active and placebo		No statistically significant differences were observed in suicidal outcomes between GLP-1 RAs and other antihyperglycemic drugs (RR, 0.57; 95% CI, 0.08–4.21).	[79]
Ocular diseases	*Post hoc* analysis of RCTs	SUSTAIN 6	2013	T2DM	Semaglutide 0.5/1.0 mg	Placebo	2.1 years	Semaglutide increase the risk of diabetic retinopathy complications (HR, 1.76; 95% CI, 1.11–2.78).	[89]
		LEADER	2010–2015	T2DM with high risk for CVD	Liraglutide	Placebo	3.8 years	Liraglutide exhibited no increased risk of the incidence of retinopathy events (HR, 1.15; 95% CI, 0.87–1.52).	[33]
		REWIND	2011–2018	T2DM ± CVD	Dulaglutide 1.5 mg weekly	Placebo	5.4 years	Dulaglutide resulted in inferior ocular outcomes (HR, 1.24; 95% CI, 0.92–1.68).	[38]
	Meta-analysis of RCTs	13 Studies on GLP-1 RAs	2008–2021	T2DM	GLP-1 RAs	Placebo/standard care		GLP-1 RAs increase the risk of diabetic retinopathy (HR, 1.23; 95% CI, 1.05–1.44).	[90]
	Population-based cohort study	TriNetX dataset	2010–2023	T2DM	GLP-1 RAs+insulin	SGLT-2 inhibitor+insulin		GLP-1 RA therapy combined with insulin was associated with a higher risk of diabetic retinopathy (HR, 1.21; 95% CI, 1.15–1.26) and diabetic macular edema (HR, 1.13; 95% CI, 1.06–1.21) compared to SGLT-2 inhibitor therapy with insulin.	[93]
		Cleveland Clinic Cole Eye Institute	2012–2023	T2DM	GLP-1 RAs	SGLT2 inhibitors	1.54 years for GLP-1 RAs; 1.38 years for SGLT-2 inhibitor	No difference in diabetic retinopathy progression between GLP-1 RAs and SGLT-2 inhibitors after propensity matching (OR, 0.33; 95% CI, 0.11–1.03)	[94]
		Neuro-ophthalmology registry	2017–2023	T2DM, OW/OB	Semaglutide	Non-semaglutide	33.3 months for semaglutide, 34.5 months for non-semaglutide	Semaglutide increased the risk for NAION in T2DM (HR, 4.28; 95% CI, 1.62–11.29) and in obesity (HR, 7.64; 95% CI, 2.21–26.36) compared to non-semaglutide.	[97]
		TriNetX dataset		T2DM, OW/OB	Semaglutide/GLP-1 RA	Non-GLP-1 RA		Semaglutide and GLP-1 RAs had no increased risk of NAION in patients with T2DM or high BMI compared to non-GLP-1 RAs.	[99]

GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus; DPP-4, dipeptidylpeptidase-4; SGLT-2, sodium-glucose cotransporter-2; HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio; aRR, adjusted relative risk; PRR, proportional reporting ratio; RCT, randomized controlled trial; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; CVD, cardiovascular disease; RR, relative risk; OHA, oral hypoglycemic agent; CVOT, cardiovascular outcome trial; MH-OR, Mantel-Haenszel odds ratio; CNODES, Canadian Network for Observational Drug Effect Studies; TZD, thiazolidinedione; aOR, adjusted odds ratio; STEP, Semaglutide Treatment Effect in People with Obesity; OW, overweight; OB, obese; AOM, anti-obesity medication; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of T2DM; REWIND, Researching cardiovascular Events with a Weekly Incretin in Diabetes; NAION, non-arteritic anterior ischemic optic neuropathy; BMI, body mass index.

[114]. Future research on GLP-1-based medicines for weight reduction must prioritize the precise evaluation of muscle mass, composition, and functionality to clarify their impact on muscular health.

CONCLUSIONS

Recent investigations have elucidated a multifaceted spectrum of adverse effects linked to GLP-1 RAs (Table 1), necessitating meticulous interpretation based on the various methodological designs employed, including RCTs and retrospective analyses. Notably, although gallbladder disorders frequently manifest, advanced gastrointestinal complications such as intestinal obstruction and periprocedural aspiration, and emergent concerns regarding suicidality and ocular problems require further longitudinal studies to refine the usage guidelines for GLP-1 RAs in susceptible populations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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