GLP-1 RAs and Suicidality: Weighing Out The Risks

Does taking Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) increase the risk of suicidality?

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Suicidality Risk in Adult Patients Taking Glucagon Like Peptide-1 Receptor Agonists (GLP-1 RAs)

ABSTRACT

Background: Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) are at the forefront of medical therapy for patients with obesity and type 2 diabetes mellitus. They are relatively new to the market, and have increased in popularity over the last few years because of their positive effects of glucose control and weight loss. In mid 2023, reports of suicidal behavior with use of GLP-1 RAs prompted the European Medicines Agency (EMA) to investigate further. Determining adverse effects of GLP-1 RAs is crucial because these medications are going to be around for the foreseeable future and continue to gain popularity. Suicide is one of the leading causes of death in the United States, and if there is an association of suicidality with GLP-1 RA use, it is important for clinicians to know when they are prescribing these medications.
Objectives: To evaluate the risk of suicidality in adult patients with obesity or type 2 diabetes mellitus who are taking GLP-1 RAs.
Design: Multi-study review
Methods: A search of the National Library of Medicine PubMed, Cochrane, and Embase was completed in December 2024 using the search terms "GLP-1 receptor agonist AND (depressi* OR suicid* OR mental health)" and yielded 246 results. The search was limited using filters such as "humans" and "within the last year". Various inclusion and exclusion criteria were applied. 4 articles were analyzed for outcomes and validity assessments, and the level of evidence of each article was made.
Results: Study #1: The authors found an 106% increase risk for suicidal behavior in patients taking GLP-1 RAs. HR=2.06 overall. *Level of evidence is of moderate quality*. **Study #2:** The authors found that semaglutide did not increase risk of suicidal ideation or behavior compared to placebo. *Level of evidence is of high quality.* **Study #3:** The authors found that suicidal ideation or behavior risk is similar and not statistically significant when comparing GLP-1 RAs to SGLT-2 inhibitors and DPP4 inhibitors. *Level of evidence is of moderate quality.* **Study #4:** The authors found that the use of semaglutide is associated with a lower risk for incident and recurrent suicidal ideation. *Level of evidence is of moderate quality.*
Conclusion: The four studies all had a primary outcome of suicidality risk with GLP-1 RAs and showed mixed results. All studies are assumed to be of adequate power due to a large sample size, but all of the studies are limited by study design flaws because they are cohort studies. Further investigation is needed to determine an association between GLP-1 RA use and increased suicidality.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of medications that are the center of attention for treating patients with overweight, obesity, and type 2 diabetes mellitus. These medications have many different mechanisms that work to lower body weight, control blood sugar, and positively impact cardiorenal outcomes, making them desirable for many patients [1,2]. Since 2018, these medications have gained popularity due to the high media presence and influencer attention for the purpose of weight loss.[3] Glucagon-like peptide 1 is an incretin in the body originating from intestinal L cells. GLP-1 stimulates insulin secretion, slows gastric emptying, and suppresses glucagon secretion. In a patient, this translates into a reduction of appetite, slowed stomach emptying which makes you feel full for longer, and better control of eating.[4] Given these mechanisms, it makes sense that GLP-1 receptor agonists such as liraglutide and semaglutide are so efficacious in weight reduction.

With these medications continuing to gain popularity, one must consider the risks associated with GLP-1 RAs, including emerging concerns about their neuropsychiatric effects. In July 2023, there were reports to the Icelandic Medicines Agency of increased suicidal behavior associated with liraglutide and semaglutide[5], which prompted an investigation by the European Medicines Agency (EMA)[3,6,7]. The FDA is also assessing this topic by reviewing events reported to the adverse event reporting system, looking at clinical trials, and reviewing observational studies. As of January 11th, 2024, the FDA reported that preliminary evaluation does not show evidence that the use of GLP-1 RAs causes suicidal thoughts[7]. However, they also reported that they cannot definitively rule out a small risk, so continued monitoring of this issue is recommended. There is still a recommendation that healthcare professionals should tell their patients to report thoughts of suicide or any other changes in mood or behavior.

Obesity and type 2 diabetes mellitus are two of the most prevalent comorbidities in the United States. According to the World Health Organization, in 2022, 1 in 8 people in the world are living with obesity[8], and 830 million people are living with T2DM[9]. These diseases pose a huge burden on patients in every aspect of their lives including physical and mental health, as well as a financial burden for the patient and hospitals. Anti-obesity medications (with the addition of lifestyle modifications) have become

key in helping reduce these numbers. Liraglutide was the first GLP-1 RA to be approved by the FDA in 2010 for the treatment of T2DM, then later in 2014 for the treatment of obesity. Semaglutide is another common GLP-1 RA that was approved for T2DM in 2017 and obesity in 2021[10].

With the emergence of new medications comes the risk of adverse events. The common adverse effects known of these medications are gastrointestinal related such as nausea, vomiting, abdominal pain, diarrhea, and constipation. More severe adverse effects include the development of pancreatic or thyroid cancer. In addition to the most common and more serious adverse effects of these medications, there has also been an increase in interest in the neuropsychiatric effects of GLP-1 RAs. There are also GLP-1 receptors in the central nervous system, and it has been shown that GLP-1 RAs can cross the blood-brain barrier[11,12,13]. Given this fact, there is a potential for GLP-1 RAs to affect mood and could potentially lead to an increased risk of suicidal ideation.

There are previous studies that report some centrally acting anti-obesity drugs can potentially cause an increased risk of suicide and self-harm[14]. For example, Rimonabant, which was the first selective central cannabinoid receptor antagonist, was not FDA-approved for weight loss because of the increased risk of depression, anxiety, and suicidal ideation. It was withdrawn from the market in 2009, and no further cannabinoid receptor 1 blockers were made for the treatment of obesity[10]. Given that GLP-1 RAs are centrally acting with CNS activity, it is reasonable to investigate whether these medications pose a similar risk.

Despite the potential for GLP-1 RAs to impact neuropsychiatric behavior, it is also important to consider confounding variables such as obesity and T2DM. It has been shown that patients with obesity have a higher rate of mental health disorders[15]. Therefore, it can be challenging to determine whether the suicidal ideation is due to the medication itself or the underlying condition of the patient.

Conversely, some studies have shown that GLP-1 RAs can exert an antidepressant effect. A systematic review conducted in 2023 showed that GLP-1 RAs had a positive antidepressant effect in adults, specifically in adults with T2DM[16]. The exact mechanism by which this occurs remains unclear, but it is important to consider that the reduction in depression symptoms may be due to improving

symptoms of diabetes. Some of the proposed mechanisms involve looking at insulin signaling and include insulin resistance in patients with depression. It has been shown that insulin resistance can develop in the brains of patients with depression, so targeting insulin resistance with GLP-1 RAs might decrease depressive symptoms[17,18]. There have also been animal studies that have looked at the neuroprotective effects of GLP-1 RAs[19,20,21]. Studies are ongoing looking at this association, and further studies are needed to determine a true association.

While these studies have looked at depression associated with GLP-1 RAs, there is not a lot of data about suicidal ideation in particular in association with GLP-1 RA use. Suicide is among one of the leading causes of death worldwide, and is a preventable public health problem[22]. In the US in 2022, the CDC states that over 49,000 people died from suicide, with one death every eleven minutes[23]. If there is a way to identify at-risk patients, such as being aware of medications that can lead to an increased risk of suicide, clinicians should be aware. There are tools in place to assess the risk of suicide, including the Columbia Suicide Severity Rating Scale (C-SSRS) which has been validated in many different settings and populations. This is a clinician-administered questionnaire that can be used to assess suicidality risk and is how many of the studies assessed this risk[24,25,26].

Before 2024, there had been few studies that looked specifically at the risk of suicidal ideation with GLP-1 RAs. Since the EMA and FDA launched their investigation, there have been more studies looking at this relationship. In this review, I intend to address the clinical question of "In adult patients with overweight, obesity, or T2DM without a prior psychiatric history/suicidal ideation, does initiation of a GLP-1 receptor agonist have a higher risk of suicidal ideation/self-harm compared to placebo or another standard of care non-GLP1-RAs?" This question is important because these drugs will likely remain a mainstay in the treatment of metabolic disorders, and the psychiatric safety of these drugs is essential as their use continues to expand.

Methods

A search of the National Library of Medicine PubMed was completed in December 2024 using the search terms "GLP-1 receptor agonist AND (depressi* OR suicid* OR mental health)" yielded 246 results. I then limited the search using filters such as "humans" and "within the last year". This yielded 72 articles. Similar searches were conducted on Embase and Cochrane but did not yield any more studies. The collected articles were then included based on the following criteria: (1) primary outcome of risk of suicide / suicidal ideation / suicidal behaviors. (2) adults >18 years old with overweight, obesity, or T2DM. (3) patient population without prior known suicide attempts or suicidal ideation at least within the prior year. Articles were excluded based on the following criteria: (1) data on depression, anxiety, or other psychiatric outcomes not related to suicide. (2) meta-analyses or systematic reviews. (3) published before 2024. (4) patient population <18 years old. (5) Review articles lacking original data. (6) Case reports. (7) Combination studies without a primary assessment of GLP-1 RAs. (8) studies not focusing on clinical outcomes. (9) Articles with populations that include patients with a previous history of suicidal ideation or attempts. (10) Mendelian randomizations.

A total of 4 studies were identified based on the above criteria. Each of these studies was evaluated individually for relevance and validity using standardized criteria. Each study was given a level of evidence rating. The primary outcome of this literature review is the incidence of suicide/suicidal ideation in adult patients with no history of suicidal ideation starting GLP-1 receptor agonists for overweight, obesity, or T2DM. Of note, since the search in December of 2024, there have been more articles published, including a systematic review about this topic in March 2025[27].

Results

Study #1: Kornelius et al. 2024[28]

This study by Kornelius et al[28]. followed 162,253 pairs (intervention and control) of adult patients 18 and older from January 1st, 2015 to December 31st, 2023 using the TriNetX network. This network includes 66 healthcare organizations in the United States. All of these patients were diagnosed with

obesity. The intervention the patients were receiving was either Victoza (liraglutide 1.8 mg), Saxenda (liraglutide 3 mg), Ozempic (semaglutide 1 mg), or Wegovy (semaglutide 2.4 mg). Of note, the Victoza, Saxenda and Wegovy doses are at their maximum. The Ozempic maximum dose is 2 mg, but these patients were given 1 mg. These 162,253 patients were paired with a control group of patients who were not taking GLP-1 RAs. The primary outcome was to assess the risk of depressive disorders, anxiety, and suicidality in patients taking GLP-1 RAs compared to patients not taking GLP-1 RAs. For this study, suicidality means suicidal ideation, suicide attempts, and intentional self-harm. The results are grouped together and termed "suicidal behaviors". Patients were followed up in this study at 6 months, 1 year, 3 years, and 5 years. Suicidal behaviors were measured via the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Patient Health Questionnaire-9 (PHQ-9), which are both validated tools for assessing suicide risk[29,30].

Validity assessment: The design of this study was a retrospective cohort study, which is acceptable given the nature of the question being asked. Due to the design of the study, the patients could not be blinded because they were already taking the medication and knew they were taking it. However, retrospective cohort studies have many limitations themselves such as selection bias and confounding variables. Because retrospective studies rely on records that already exist, the population of patients may not fully represent the population in question.

This study used propensity score matching which is a way that bias can be reduced by grouping patients based on their baseline characteristics. In this study, propensity score matching was used to group patients and compare those on GLP-1 RAs with those not on GLP-1 RAs. Grouping was based on age, sex, race, socioeconomic factors, and comorbidities such as hypertension, type 2 diabetes mellitus, ischemic heart disease, chronic kidney disease, cerebrovascular disease, neoplasms, substance abuse, and respiratory diseases. Although this can help reduce bias, there can still be unmeasured confounding variables, as well as a reduction in sample size. In this paper, the sample size of 162,253 groups is very

large, so the concern of lowering the sample size was not an issue. Due to the large sample size, one can assume there is adequate power in this study.

This study has a meaningful clinical endpoint because it assesses the psychiatric risks of GLP-1 RAs, which is very important if these medications continue to be the mainstay of treatment. There is also a meaningful comparison because the control group is patients not taking GLP-1 RAs. This can help decipher if adverse effects are truly from GLP-1 RAs or not, although a causal relationship cannot be established from a retrospective cohort study. These patients were followed up until 5 years, which is a long time. The longitudinality of this study provides further insight into possible adverse effects after being exposed to these medications for a prolonged period. This study has adequate safety because it looks at psychiatric events as a primary outcome.

Another positive of this study included the analysis of the risk of suicidal behavior in different GLP-1 RAs, including different doses of the same medication. This can help assess if the dose of a GLP-1 RA plays a role in adverse effects. The study broke the results into sections based on the dose of medication, which amplifies the quality of the data.

Regarding patient accountability, this study states that not all patients were fully accounted for. The study states that those patients lost to follow-up were included only up to their last recorded visit, and not included in follow-up visits after. Therefore, the patients included in the primary analysis included those with at least one follow-up visit after the initial index date. This is expected in a retrospective cohort study but could lead to incomplete data. In addition to a potential lack of patient accountability, there was also a lack of information about patient compliance with their medications. This means that patients could have been going to their follow-up appointments, but not taking the medication they were prescribed. This can skew results too. In summary, this article is graded as moderate quality due to retrospective cohort design study and potential lack of accountability of patients.

Results: This study grouped suicidal behavior into one category including suicide attempts or ideation. The hazard ratio for suicidal behavior on GLP-1 RAs was 2.06 with a 95% confidence interval. The

hazard ratios for each drug and dose were different as well. For Victoza, the hazard ratio is 1.32. For Saxenda, the hazard ratio is 1.67. For Ozempic, the hazard ratio is 1.66. For Wegovy, the hazard ratio is 2.42. In the Ozempic group for SI or SA, there was a 2.4 fold increase in risk. In the GLP-1 RA group, the percentage of patients with suicide ideations or attempts are as follows: 0.22% at 6 months, 0.42% at 1 year, 1.45% at 3 years, and 3.64% at 5 years. In the non-GLP-1 RA group, the percentages of patients with suicide ideations or attempts are as follows: 0.21% at 6 months, 0.35% at 1 year, 0.89% at 3 years, and 1.42% at 5 years. The calculated number needed to harm at 6 months is 10,000, 1 year is 1,428, 3 years is 178, and 5 years is 45.

This study also looked at different subgroups and found that females on GLP-1 RAs have a 105% higher risk of psychiatric disease compared to non-GLP-1 RA users. In addition, it was reported that younger patients have a high risk of suicidal behavior, as well as African American patients. This study looked at depression and anxiety as well, but this review is only focusing on suicidal behavior. Of note, the study found similar results for depression and anxiety, meaning that GLP-1 RA use was associated with an increased risk of depression and anxiety. Even though this review is not primarily looking at depression or anxiety, it is an important outcome of this study.

Conclusion: In conclusion, this study found that there is an increased risk of suicidal behavior with the use of GLP-1 RAs over time. In addition, they found that suicidal behavior varies across different demographic subgroups such as sex, age, and race. This proves that it is important to consider these factors when looking into the efficacy and safety of GLP-1 RAs. This study also looked at the effects of GLP-1 RAs over time, including different dosing. The higher doses of medications (Wegovy and Saxenda) had higher incidences of suicidal behavior, which could be an important area of research in the future.

Limitations: Some limitations of this study include the potential bias and lack of full patient accountability due to the nature of a retrospective cohort study, not looking at or following BMI during

the follow-up period, lack of information about patient compliance with treatment, and the exclusion of patients with any psychiatric diseases within one year. Also, the study combines suicidality risk into one outcome but does not separate suicidal ideation from suicide attempts.

Study #2: Wadden et al.[31]

This study by Wadden et al.[31] is a post hoc analysis of the phase 3a STEP 1, 2, and 3, trial[32,33,34] and the phase 3b STEP 5 trial[35]. The study analyzed 3,377 participants with overweight, obesity, or diabetes from the STEP 1, 2, and 3 trials, and 304 participants from the STEP 5 trial. The original STEP 1, 2, and 3 were conducted for 68 weeks from 2018-2020, and the original STEP 5 trial was conducted for 104 weeks from 2018-2021. This study looks at the intervention of semaglutide 2.4 mg and its associated risk of suicide in patients without known major psychopathology. The authors measured suicide risk via the PHQ-9 and the C-SSRS at various points throughout the trial. If at any point the participants had a PHQ-9 score of 15 or greater, or a type 4 or 5 SI or suicidal behavior on the C-SSRS, they were referred to a mental health professional. For this study, the authors looked at the initial screening done for suicidal ideation and behavior using C-SSRS. If the patients had high-risk suicidal ideation, they were excluded from the study. For this study, high-risk included patients with active suicidal ideation with intent to act with or without a specific plan. Patients who screened positive for low to moderate-risk suicidal ideation were still included in this study. Low and moderate risk includes patients who stated that they wish to be dead, if they had a nonspecific active suicidal thought, or if they have active suicidal ideation but with no plan and no intention to act.

Validity assessment: This study by Wadden et al. is a post hoc analysis, so the study itself is not blinded. However, the original trials were randomized, double-blind, placebo-controlled, and multicentered phase trials, which makes the results of this trial higher quality. There is a meaningful comparison in this study because the comparison group was treated with lifestyle changes like diet and exercise as opposed to medications. This study focused solely on semaglutide 2.4 mg and did not look at other GLP-1 RAs or

other doses of semaglutide. This makes the comparison of higher quality because the intervention is the same throughout the entire patient population. The results of this study focus on a meaningful clinical endpoint because the authors are looking specifically at the risk of suicide which is relevant. Both the STEP 1, 2, and 3 trials and the STEP 5 trial were conducted for over a year, with patient follow-up periodically throughout that time, so the follow-up time is adequate. With a patient population of 3,377 in STEP 1, 2, and 3, and 304 patients in STEP 5, the sample size is adequate to assume power is sufficient.

Regarding patient accounting, in the original studies, some of the patients were lost to follow-up. However, these patients were still included in the final analysis, but they did not have data for their last follow-up visit. This is a positive of the study and means that all patients are included in the final data. The original studies also had the intention to treat analysis which included all patients who underwent randomization. While this study focused primarily on suicide and depression, the authors also sorted out other adverse effects in a table including other psychiatric disorders and nervous system disorders. The high-quality evidence of the original articles makes the quality of evidence of this post hoc higher as well. In summary, this article is graded as high quality because of the reasons discussed above, and the design of the study itself being a post-hoc analysis of randomized control trials.

Results: The authors of this study found that there were 18 cases of suicidal ideation in total between STEP 1, 2, 3, and 5 trials. It was noted that 12/18 of these cases were resolved by the end of the trial. In terms of numbers, for STEP 1, 2, and 3 trials, 8 participants (0.4%) receiving semaglutide 2.4 mg and 7 participants (0.6%) receiving placebo reported incident suicidal ideation throughout the time randomization through the end of treatment. From STEP 5, 1 participant (0.7%) receiving semaglutide 2.4 mg and 2 participants (1.4%) receiving placebo reported incident suicidal ideation from randomization through the end of treatment.

When looking at PHQ-9 screenings from the patients, more patients acknowledged self-reported suicidal thoughts than compared to the clinician-administered C-SSRS. On the PHQ-9 question “thoughts that you would be better off dead, or hurting yourself in some way”, six participants (0.3%) on

semaglutide 2.4 mg and two participants (0.2%) on placebo reported adverse effects of suicidal ideation from STEP 1, 2, and 3. There were no reports of suicidal ideation from the PHQ-9 from STEP 5. The number needed to treat for these results cannot be calculated because the results are not statistically significant.

Conclusion: In conclusion, the authors stated that semaglutide 2.4 mg compared to placebo was not associated with increases in clinically significant symptoms of suicidal ideation. The authors attributed the fact that more patients reported suicidal thoughts in the PHQ-9 vs the C-SSRS because the PHQ-9 is self-administered, and the C-SSRS is clinician-administered. Patients might be more likely to disclose sensitive information when they are doing the questionnaire by themselves. In addition to the authors finding no elevated risk for suicide in patients taking semaglutide 2.4 mg, they found a decrease in depressive symptoms. This review is not focusing on depressive symptoms, but it is worth noting for future research.

Limitations: Some of the limitations of this study include the biases that come with a post-hoc analysis itself, excluding patients with high-risk suicidal ideation yet including patients with low to moderate-risk suicidal ideation, and a biological female predominance.

Study #3: Tang et al.[36]

This study by Tang et al.[36] is an observational cohort study using a target trial emulation approach comparing GLP-1 RAs vs SGLT2is and GLP-1 RAs vs DPP4is in two separate studies. This study was conducted from January 1st, 2017 - December 31st, 2020, and included adults older than 66 with T2DM and no history of prior suicidal ideation or attempts. This study used Medicare administrative claims data and had a requirement of at least 1 year of continuous enrollment in Medicare parts A, B, and D. After 1:1 propensity score matching, the authors ended up with 21,807 pairs of people treated with GLP-1 RAs vs. SGLT-2is, and 21,402 pairs of people treated with GLP-1 RAs vs. DPP4is. The authors do not state

specifically what GLP-1 RAs, SGLT-2is, or DPP4is were used in the treatment groups, but they included patients taking any of the class of medications. The primary outcome of this study is to look into the association between GLP-1 RAs and the risk for suicidal ideation and behaviors in adult patients with T2DM. The authors measured suicidal behaviors by patients having at least one International Classification of Diseases (ICD) diagnosis code.

Validity assessment: This study is an observational cohort study, so by design, it cannot be blinded. However, it is a target emulation trial which means that the study's goal is to mimic the design and analysis of a randomized control trial, but it uses observational data. The authors are evaluating a meaningful clinical endpoint of suicidal ideation and behaviors, and have a meaningful comparison. SGLT-2 inhibitors and DPP4 inhibitors are other common classes of medications used to treat diabetes. SGLT-2 inhibitors have similar indications to GLP-1 RAs, and DPP4 inhibitors have a similar mechanism of action to GLP-1 RAs for lowering blood sugar, so having these head-to-head comparisons is important.

This study is assumed to have adequate power due to the large sample size. The patient timeline is adequate because patients were followed throughout the entire period the study was conducted (from 2017 to 2020). The authors used Medicare administrative data to monitor the patients over time. The follow-up for patients continued in an intention to treat fashion until the outcome of the study was reached, there was a death of a patient, their enrollment in Medicare ended, or the study period ended. The average follow-up for a patient was about 1.5 years, which is an acceptable amount of time to evaluate the adverse effects of a medication.

The authors note that there was a high rate of discontinuation of treatment with GLP1- RAs (66.5% of patients) and in SGLT-2 inhibitors (63.8% of patients). Although the authors followed an intention-to-treat approach, dropout numbers this high may underestimate the true differences in outcomes between the treatment groups. This study evaluates important safety effects such as suicide, but it notes that a modest risk cannot be ruled out because of imprecise estimates and unmeasured confounding variables that might be present. In summary, this article is graded as moderate quality

evidence because of the observational cohort study design and potential lack of accountability of patients due to a high dropout rate.

Results: The results of this study found that there is not a significantly higher risk for suicidal ideation and suicidal behaviors in patients beginning treatment with a GLP-1 receptor agonist in adults with T2DM when comparing the medications with SGLT-2 inhibitors and DPP4 inhibitors. The hazard ratio (HR) of suicidal ideation and behaviors with GLP-1 RAs relative to SGLT-2 inhibitors was 1.07. The incidence rate was 2.4 per 1000 person-years for GLP-1 receptor agonists and 2.24 per 1000 person-years for SGLT-2 inhibitors. The median follow-up time was 1.56 years.

For the GLP-1 RA vs. a DPP4i study, the hazard ratio of suicidal ideation and behaviors comparing GLP-1 RAs relative to DPP4is was 0.94. The incidence rate was 2.63 per 1000 person-years for the GLP-1 RAs, and 2.81 per 1000 person-years for DPP4i, respectively. The median follow-up time was 1.64 years. The authors also looked at the results separated by age, sex, race, and comorbidities in a subgroup analysis and did not find any difference. The authors also separated suicidal ideation from suicidal behaviors and found similar results. The results are not statistically significant to calculate the number needed to treat.

Conclusion: In conclusion, this study showed that there is no significantly higher risk for suicidal ideation and behaviors in older adult patients with T2DM treated with GLP-1 RAs compared to SGLT2 inhibitors or DPP4 inhibitors. The authors do note, however, that estimates were imprecise. They found consistent results across all demographics including age, sex, race, and comorbidities like obesity and depression. They also found similar results when separating suicidal ideation and suicidal behavior. The authors state that their confidence intervals were wide, so they could not rule out a moderate increased risk of suicide.

Limitations: This study is limited by the low rate of suicidal ideation and behavior, the use of the ICD codes to determine if patients have suicidal ideation or behavior, the high rate of treatment discontinuation in the GLP-1 RA group and SGLT-2 group, and confounding variables such as body mass index (BMI) and hemoglobin A1c that were not available.

Study #4: Wang et al.[37]

This study by Wang et al.[37] is a retrospective cohort study of electronic health records from the TriNetX Analytics Network conducted from June 1st, 2021 - December 31st, 2022 that looked at the risk of suicidal ideation with semaglutide use. The population included adults with overweight or obesity, who had no prior history of suicidal ideation. After propensity scoring, 52,783 pairs of patients were included. The groups included patients taking semaglutide, and patients not taking a GLP-1 RA. Similar methods were performed with adults with type 2 diabetes mellitus from December 1st, 2017 - May 31st, 2021. After propensity scoring, 27,726 pairs of patients taking semaglutide vs. a non-GLP-1 RA for T2DM were observed for suicidal ideation. The primary outcome of this study was to assess the association of semaglutide with the incidence and recurrence of suicidal ideation, but this review focuses on the incidence of suicidal ideation in patients without a previous history of SI. The study used ICD codes to identify suicidal ideation.

Validity assessment: This study is a retrospective cohort study, so by the nature of the design, it cannot be blinded. This study looked at a meaningful clinical endpoint of suicidal ideation which is very important. It also had a good comparison because this study compares semaglutide, a commonly prescribed GLP-1 RA, to non-GLP-1 RA treatments for obesity such as bupropion, topiramate, orlistat, naltrexone, and phentermine, and to non-GLP-1 RA treatments for T2DM such as insulin, metformin, sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors. These are all commonly prescribed medications for their indications of anti-obesity or anti-diabetes, so having this information to compare GLP-1 RAs to non-GLP-1 RAs is clinically useful.

In the group with overweight and obesity, the timeline for follow-up was about 6 months on average. For the group with T2DM, the follow-up times were at 6 months, 1 year, 2 years, and 3 years, giving more of a longitudinal analysis of the effects of semaglutide. The power of this study is assumed to be adequate due to the large sample size. Because this study is a retrospective cohort study, the intention to treat cannot be determined because the patients have already been treated. This study has an adequate safety analysis because the primary endpoint is looking at a safety concern. This study can only measure what has been reported to the TriNetX Analytics Network, so it cannot report adverse effects comprehensively, but it is adequate due to the nature of the study. In summary, this article is graded as moderate quality evidence because of the retrospective cohort design study, and the lack of an adequate follow-up time for the overweight and obesity group.

Results: In the overweight or obesity group, the authors found that semaglutide had a significantly lower risk for incident suicidal ideation than the non-GLP-1 RA group. The semaglutide group had a 0.11% incidence of suicidal ideation compared to a 0.43% incidence in the non-GLP-1 RA group (NNT: 313). The hazard ratio for this was 0.27 with a 95% confidence interval. The authors found these low rates no matter the sex, age, or ethnicity. In addition to suicidal ideation, the authors also looked at suicide attempts at the follow-up visit. During the 6-month follow-up, 0/52,783 patients taking semaglutide reported suicide attempts, and 14/52,783 patients in the non-GLP-1 RA group reported suicide attempts (NNT: 3,774).

In the T2DM group, the authors found that the semaglutide group had a significantly lower risk for incident suicidal ideation than the non-GLP-1 RA group at each of the follow-up periods (6 months, 1 year, 2 years, and 3 years). The incidence of suicidal ideation for the semaglutide group vs. the non-GLP-1 RA group, respectively, is 0.13% vs 0.36% at the 6-month mark (NNT: 435), 0.19% vs. 0.48% at the 1-year mark (NNT: 345), 0.37% vs. the 0.69% at the 2-year mark (NNT: 313), and 0.47% vs. the 0.85% at the 3-year mark (NNT: 263). The hazard ratios for each follow-up are 0.36 at the 6-month mark, 0.39 at the 1-year mark, 0.53 at the 2-year mark, and 0.58 at the 3-year mark. The authors could not

report an actual number of patients with suicide attempts at the 6-month follow-up due to privacy concerns, but they state that the number for the semaglutide group and the non-GLP-1 RA group was between 1 and 9.

Conclusion: In conclusion, the authors of this study found that semaglutide is not associated with an increased risk of suicidal ideation or attempts. They found that semaglutide, in fact, lowers the risk of incident suicidal ideation. The authors found similar results when looking across demographics like age, sex, and ethnicity. The authors were not looking specifically at suicide attempts, but they did for the overweight or obesity group. The sample sizes for the T2DM group were too small to evaluate statistically, so one cannot make a conclusion from this data.

Limitations: Some limitations of this study include the retrospective observational study design, using the TriNetX database as the population, shorter follow-up for the overweight and obesity group, no dosage of semaglutide included, inability to decipher medication adherence, inclusion of patients with depression anxiety and mood disorders, reliance on ICD codes to diagnose suicidal ideation.

Summary of study characteristics

Study + design	Number of patients	Treatment	Comparison	Patient timeline	Outcome	Safety outcome
Kornelius et al. "The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon-like peptide-1 receptor agonist therapy" Retrospective cohort study	162,253	GLP-1 receptor agonists (liraglutide and semaglutide in various doses)	Non GLP-1 receptor agonists	Patient follow up at 6 months, 1 year, 3 years, 5 years	Using the columbia suicide severity rating scale, they found an 106% elevated risk for suicidal behavior	GLP1-RA users had elevated risk of psychiatric disease Females had 105% higher risk of psychiatric disease compared to non GLP-1 RA users

Wadden et al. "Psychiatric safety of semaglutide for weight management in people without known major psychopathology: a post hoc analysis of the STEP 1, 2, 3, and 5 trials" Post Hoc analysis	STEP 1, 2, 3 = 3,377 STEP 5 = 304	Semaglutide 2.4 mg	Placebo: Lifestyle changes	68 weeks from STEP 1,2,3 104 weeks from STEP 5	Using the columbia suicide severity rating scale, they found that semaglutide did not increase risk of suicidal ideation / behavior compared to placebo	Psychiatric adverse events were similar between active treatment and placebo Small but statistically significant reduction in depression symptoms seen with semaglutide, however not clinically meaningful
Tang et al. "Glucagon-like peptide-1 receptor agonists and risk for suicidal ideation and behaviors in US older adults with type 2 diabetes: a target trial emulation study" Observational cohort study: Target emulation trial	21,807 pairs treated with GLP-1 RA vs SGLT2i 21,402 pairs treated with GLP-1 RA vs DPP4i	GLP-1 receptor agonists	SGLT-2 inhibitors and DPP4 inhibitors	Median follow up 1.56 years for SGLT2 group and 1.64 years for GPP4i group	Results are similar and not statistically significant for an increased risk of suicidal ideation or behavior	N/A
Wang et al. "Association of Semaglutide with risk of suicidal ideation in a real-world cohort" Retrospective cohort study	27,726 pairs with T2DM and no prior history of SI 52,783 pairs with overweight or obesity and no previous history of SI	Semaglutide	Other non GLP-1 RA medications for diabetes or obesity	6 month follow up for both overweight or obesity and T2DM groups, an additional 1, 2, and 3 year follow up for T2DM group	Overweight or obesity and diabetes: semaglutide associated with lower risk for incident and recurrent suicidal ideation	Safety outcomes similar between semaglutide patients and those on other treatments

GLP-1 RA = Glucagon Like Peptide-1 Receptor Agonists. SGLT-2i = Sodium-Glucose Cotransporter-2 Inhibitor. DPP-4i = Dipeptidyl Peptidase-4 Inhibitor. N/A = Not Applicable.

Validity assessment table

Study	Clinical endpoint	Blinded	Meaningful comparison	Adequate patient follow up (>1 year)	Intention to treat analysis	Patient accounting	Adequate power	Adequate safety	Level of Evidence
Kornelius et al.	A	N/A	A	A	N/A	M	A	A	MQ
Wadden et al.	A	N/A	A	A	N/A	A	A	A	HQ
Tang et al.	A	N/A	A	A	N/A	M	A	A	MQ
Wang et al.	A	N/A	A	M	N/A	A	A	A	MQ

A = Adequate M = Marginal I = Inadequate

Grade: HQ = High Quality. MQ = Moderate Quality. LQ = Low Quality. IQ = Inadequate Quality

Summary of study results

Study	Suicidality Risk Overall	Suicidal Ideation	Suicide Attempts	Non Suicidal Self Injury / Suicidal Behavior
Kornelius et al.	Combined # events for GLP-1-RA = 1,901 Combined # events for non-GLP-1 RAs = 1,559 **6 months** GLP-1 RA: 0.22% non-GLP-1RA: 0.21% NNH: 10,000 **1 year** GLP-1 RA: 0.42% non-GLP-1RA: 0.35% NNH: 1,428 **3 years** GLP-1 RA: 1.45% non-GLP-1RA: 0.89% NNH: 178 **5 years** GLP-1 RA: 3.64% non-GLP-1RA: 1.42% NNH: 45 HR of 2.06 overall (1.92-2.21) <u>By medication</u> Victoza: HR 1.32 Saxenda: HR 1.67 Ozempic: HR 1.66 Wegovy: HR 2.42	NR	NR	NR

Wadden et. al	N/A	**From the C-SSRS** STEP 1, 2, 3 Semaglutide: 8 patients (0.4%) Placebo: 7 patients (0.6%) STEP 5: Semaglutide: 1 patient(0.7%) Placebo: 2 patients (1.4%) **From the PHQ-9** STEP 1, 2, 3 Semaglutide: 6 patients (0.3%) Placebo: 2 patients (0.2%) STEP 5: Semaglutide: 0 patients Placebo: 0 patients None of these results are statistically significant	NR	NR
Tang et al.	N/A	**GLP-1 RA vs. SGLT2i** - GLP-1 RA: 83/21,807 - SGLT2i: 79/21,807 **GLP1-RA vs. DPP-4i** - GLP-1 RA: 94/21,402 - DPP-4i: 98/21,402 Not statistically significant	NR	**GLP-1 RA vs. SGLT2i** - GLP-1 RA: 14/21,807 - SGLT2i: 17/21,807 **GLP1-RA vs. DPP-4i** - GLP-1 RA: 12/21,402 - DPP-4i: 13/21,402 Not statistically significant
Wang et al.	N/A	**Overweight or obesity** 6 months - semaglutide group: 0.11% - non GLP-1 RA group: 0.43% HR = 0.27 NNT: 313 **T2DM** 6 months - semaglutide group: 0.13% - non GLP-1 RA group: 0.36% HR = 0.36 NNT: 435 1 year - semaglutide group: 0.19% - non GLP-1 RA group: 0.48% HR = 0.39 NNT: 345 2 years - semaglutide group: 0.37% - non GLP-1 RA group: 0.69% HR = 0.53 NNT: 313 3 years - semaglutide group: 0.47% - non GLP-1 RA group: 0.85%	**Overweight or obesity** - semaglutide group: 0% (0/52,783) - non GLP-1 RA group: 0.00026% (14/52,783) NNT: 3,774 **T2DM** - semaglutide group: between 1-9 patients* - non GLP-1 RA group: between 1-9 patients* *actual number not reported because sample sizes were too small for statistical evaluation, and the main outcome was SI not SA	NR

		HR = 0.58 NNT: 263		

GLP-1 RA = Glucagon Like Peptide-1 Receptor Agonists. NNH = number needed to harm. NNT = number needed to treat. NR = Not reported. N/A = not applicable. C-SSRS = Columbia-Suicide Severity Rating Scale. PHQ-9 = Patient Health Questionnaire-9. SGLT-2i = Sodium-Glucose Cotransporter-2 Inhibitor. DPP-4i = Dipeptidyl Peptidase-4 Inhibitor. HR = Hazard Ratio. T2DM = Type 2 Diabetes Mellitus.

Discussion

Each of the articles discussed had a primary endpoint of assessing the risk of suicidality with the use of GLP-1 RAs. The articles had varying results with study #1 showing an elevated risk of suicidal behavior, studies #2 and #3 showing no increased risk of suicidal ideation or behavior, and #4 showing that semaglutide is associated with a lower risk of incident and recurrent suicidal ideation. All four studies were conducted similarly in the sense that they are all observational studies due to the nature of the question being asked. This provides some utility in comparing the results of the study, but there are limitations when it comes to cohort studies. Limitations include selection bias because the patients selected might not represent an entire population. For example, all of the studies reviewed here looked at patients with no prior suicide risk within the last year, so one cannot apply these results to patients who already have suicide risk at baseline.

Also, it is important to look at the demographics of the patients chosen in the analysis. For example, study #2 was heavily female-dominant, so it is possible that the results found cannot be applied to biological males. In addition to selection bias, there is also a riks of the quality of data in a cohort study because one relies on existing healthcare data, most of which is reported by patients. If the patients did not report suicidality as an adverse effect, but experienced it while taking GLP-1 RAs, they might have been missed in this data analysis. Three of the studies used propensity scoring to help decrease the confounding variables, but this method is not perfect and there is still room for confounding variables to exist.

In addition to the limitations of cohort studies in general, there are also specific limitations of each study. Study #1 is limited because it does not follow BMI during the follow-up period. This is important because while there was an increase in suicide risk over time (throughout five years), it is

unknown whether these patients were losing weight or not. If patients were losing weight during this follow-up time, it may show a dose-dependent effect of GLP-1 RAs. However, if patients were not losing weight and or gaining weight, the increased risk of suicidality might not be able to be explained. This is because obesity can contribute to psychiatric disorders and worsen someone's mental health, possibly leading to an increased risk of suicide[38,39]. It is also unknown whether the patients were compliant with their treatment during the follow-up period because that is not stated.

In study #2, there are also several limitations. Firstly, this study included patients with low/moderate-risk of suicidal ideation but excluded patients with high-risk suicidal ideation. This can provide bias because patients might be less likely to report suicidal behavior in a clinician-administered survey, so some patients who have a higher risk of suicidal behavior might have been included. Also, the fact that patients who already have a low/moderate risk of suicidality are included in this study makes the data less significant for answering the clinical question of whether GLP-1 RAs cause an increased risk of suicidality in patients with no known history. Another limitation is that this study was biologically female-predominant, with 70.5% of patients in the semaglutide group from STEP 1, 2, and 3 being female, and 80.9% of the semaglutide group in STEP 5 being female. This can limit the ability to apply the results of this study to other demographic groups and make generalizations.

In study #3, a limitation is the low rate of suicidal behavior reported in the study, which can lead to imprecise measurements of the true association between GLP-1 RA use and suicide risk. Also, this study used ICD codes for the determination of suicidal ideation or behavior, which could pose a problem because patients might be mislabeled on their diagnostic codes. This could lead to an over or underrepresentation of true rates of suicide risk. Another limitation includes the high treatment discontinuation rate in the GLP-1 RA group and the SGLT-2 inhibitor group, which can make the final results less convincing. The authors do not state why the dropout rate was so high, which is another limitation. Also, this study only includes patients over 66, which leaves out a significant age group. Older people are at the highest risk of suicide[40], which is important to consider when looking at the results.

Lastly, the authors did not know the patient's body mass index (BMI) or their hemoglobin A1c values, which could change the results as mentioned before.

Study #4 had limitations as well, including the use of the TriNetX database for the population, which does not represent the entire population, making it hard to generalize the findings. Also, the obesity and overweight group had a shorter follow-up of only 6 months, which might not be adequate time to determine the effects of a medication. This study fails to include the dose of semaglutide, which makes determining a dose-related effect not possible, and also we cannot standardize the results. There is also a limitation in the sense that the study does not state that they were able to decipher the medication adherence of patients. This means that at the follow-up visits, patients may not have been taking their medication. Even though this study excluded patients with prior suicidal ideation and attempts, patients with depression, anxiety, and mood disorders were included. This might change the data because patients with depression might be more likely to be suicidal, and could contribute to why the control group had higher rates of suicidal ideation. Lastly, this study relies on ICD codes to determine who has suicidal ideation, which, as was already discussed, can lead to mislabeling of a patient.

In addition to these limitations, there is also a lack of standardization in the classification and definition of suicidality. Some of the articles specified suicidal ideation vs suicide attempts, one of the studies separated results for suicidal ideation and attempts, one combined the results as suicidality risk, and one reported the outcome as suicide behavior without specifying what that meant. This makes it hard to generalize the results of the studies. Also, two of the studies used the C-SSRS score to quantify suicidality, while the other two studies used ICD codes for suicidality. This can make it challenging to compare the results because results are more subjective rather than objective, given the nature of the patient-reported screening tests like C-SSRS and PHQ-9.

Despite the many limitations of these articles, there were also strengths specific to each study. Study #1 had the added benefit of tracking the effects of different GLP-1 RAs at different doses over time. A time frame of five years for a follow-up is a long time, and this data can be helpful to see a potential dose-related effect of the medications. Study #2 also had strengths such as gathering data from already

conducted randomized control trials that were double-blind and placebo-controlled. In addition, they had a high retention rate in both treatment arms, which decreased the risk of bias due to discontinuation of the medication.

Study #3 had strengths such as the design of the study itself. This study was a trial emulation study which takes into consideration the desirable features of RCTs but is an observational study. Another strength is that this study separated both suicidal ideation and suicidal behaviors and found similar results. This further validates the findings because they have different sets of data both showing similar results. This study also had good comparators of SGLT-2 inhibitors and DPP4 inhibitors, which are both common medications with similar indications, making this a good head-to-head study. Study #4 had strengths such as a large and diverse patient cohort. Also, while the TriNetX database could be a limitation, it can also be a strength because the authors are using real-world data from the electronic health record. Another strength includes the consistent findings across all subgroups such as age, ethnicity, and sex.

As a whole, from the articles that were evaluated in this literature review, an answer to the clinical question of the risk of suicide with GLP-1 RAs cannot be fully answered. Each of the articles had large sample sizes and, thus, are adequately powered, yet the results cannot be compared to one another due to the lack of standardization and comparison in each study. The studies used different placebos, different ways of measuring suicidality, followed up patients for different time periods, and looked at different dosages of GLP-1 RAs. All of these differences make it difficult to establish a causative relationship between the use of GLP-1 RAs and the risk of suicide. Due to the lack of similarities between studies, it makes sense why each of the results of the studies was different. Further research is needed, specifically on the neuropsychiatric effects of GLP-1 RAs. This paper focuses solely on suicidality, but many other aspects need to be considered such as depression and anxiety[41,42], substance use disorders[43,44] mood disorders[45], eating disorders[46], and conditions like Parkinson's disease[47] and Alzheimer's[48]. These neuropsychiatric effects are important to consider, especially because of the elevated suicide risk in these groups[27].

Conclusion

Overall, this review found varying results regarding the association between GLP-1 RA use and an increased risk of suicidal ideation or behavior. Most of the studies found no statistically significant risk of increased suicide when taking GLP-1 RAs. One study found that there was an increased risk of suicidal ideation with the use of GLP-1 RAs. One study found that GLP-1 RA use lowers the risk of suicide. Each of these studies has its limitations which warrants a cautious interpretation of the results of these studies. Given the mixed results and inability to fully conclude the suicidality risk of GLP-1 RAs, continued monitoring is warranted. Further research should include patients who have a history of psychiatric diseases such as suicidal ideation. Further research should also look into the potential neuroprotective effects of GLP-1 RAs, as evidenced by one of the studies. Other areas of research worth looking into are the dose-related effects of GLP-1 RAs and the long-term effects of these medications. In summary, clinicians should be careful and vigilant when prescribing GLP-1 RAs and should educate their patients on the potential adverse effects.

References

1. Popoviciu MS, Păduraru L, Yahya G, Metwally K, Cavalu S. Emerging role of GLP-1 agonists in obesity: A Comprehensive review of randomised controlled trials. International Journal of Molecular Sciences. 2023;24(13):10449. doi:10.3390/ijms241310449
2. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. New England Journal of Medicine. 2023;389(24):2221-2232. doi:10.1056/nejmoa2307563
3. Hurtado I, Robles C, Peiró S, García-Sempere A, Sanfélix-Gimeno G. Association of glucagon-like peptide-1 receptor agonists with suicidal ideation and self-injury in individuals with diabetes and obesity: a propensity-weighted, population-based cohort study. Diabetologia. 2024;67(11):2471-2480. doi:10.1007/s00125-024-06243-z
4. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Molecular Metabolism. 2021;57:101351. doi:10.1016/j.molmet.2021.101351
5. EMA statement on ongoing review of GLP-1 receptor agonists | European Medicines Agency (EMA). European Medicines Agency (EMA). https://www.ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists. Published July 11, 2023.
6. McIntyre RS, Mansur RB, Rosenblat JD, Kwan ATH. The association between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: reports to the Food and Drug Administration Adverse Event Reporting System (FAERS). Expert Opinion on Drug Safety. 2023;23(1):47-55. doi:10.1080/14740338.2023.2295397
7. Research C for DEA. Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity. U.S. Food And Drug Administration. https://www.fda.gov/drugs/fda-drug-safety-podcasts/update-fdas-ongoing-evaluation-reports-suicidal-thoughts-or-actions-patients-taking-certain-type. Published March 8, 2024.
8. World Health Organization: WHO. Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Published March 1, 2024.
9. World Health Organization: WHO, World Health Organization: WHO. Diabetes. https://www.who.int/news-room/fact-sheets/detail/diabetes. Published November 14, 2024.
10. Tobaiqy M, Elkout H. Psychiatric adverse events associated with semaglutide, liraglutide and tirzepatide: a pharmacovigilance analysis of individual case safety reports submitted to the EudraVigilance database. International Journal of Clinical Pharmacy. 2024;46(2):488-495. doi:10.1007/s11096-023-01694-7
11. Chen C, Zhou R, Fu F, Xiao J. Postmarket safety profile of suicide/self-injury for GLP-1 receptor agonist: a real-world pharmacovigilance analysis. European Psychiatry. 2023;66(1). doi:10.1192/j.eurpsy.2023.2474
12. Trapp S, Brierley DI. Brain GLP‐1 and the regulation of food intake: GLP‐1 action in the brain and its implications for GLP‐1 receptor agonists in obesity treatment. British Journal of Pharmacology. 2021;179(4):557-570. doi:10.1111/bph.15638
13. Dong M, Wen S, Zhou L. The relationship between the Blood-Brain-Barrier and the central effects of Glucagon-Like peptide-1 receptor agonists and Sodium-Glucose cotransporter-2

inhibitors. Diabetes Metabolic Syndrome and Obesity. 2022;Volume 15:2583-2597. doi:10.2147/dmso.s375559
14. Coulter AA, Rebello CJ, Greenway FL. Centrally Acting Agents for Obesity: past, present, and future. Drugs. 2018;78(11):1113-1132. doi:10.1007/s40265-018-0946-y
15. Rajan T, Menon V. Psychiatric disorders and obesity. Journal of Postgraduate Medicine. 2017;63(3):182-190. doi:10.4103/jpgm.jpgm_712_16
16. Chen X, Zhao P, Wang W, Guo L, Pan Q. The Antidepressant Effects of GLP-1 Receptor Agonists: A Systematic Review and Meta-Analysis. American Journal of Geriatric Psychiatry. 2023;32(1):117-127. doi:10.1016/j.jagp.2023.08.010
17. De M Lyra E Silva N, Lam MP, Soares CN, Munoz DP, Milev R, De Felice FG. Insulin resistance as a shared pathogenic mechanism between depression and Type 2 diabetes. Frontiers in Psychiatry. 2019;10. doi:10.3389/fpsyt.2019.00057
18. Hamer JA, Testani D, Mansur RB, Lee Y, Subramaniapillai M, McIntyre RS. Brain insulin resistance: A treatment target for cognitive impairment and anhedonia in depression. Experimental Neurology. 2019;315:1-8. doi:10.1016/j.expneurol.2019.01.016
19. Batista AF, Forny‐Germano L, Clarke JR, et al. The diabetes drug liraglutide reverses cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non‐human primate model of Alzheimer's disease. The Journal of Pathology. 2018;245(1):85-100. doi:10.1002/path.5056
20. Yan W, Pang M, Yu Y, et al. The neuroprotection of liraglutide on diabetic cognitive deficits is associated with improved hippocampal synapses and inhibited neuronal apoptosis. Life Sciences. 2019;231:116566. doi:10.1016/j.lfs.2019.116566
21. Zhang H, Chu Y, Zheng H, Wang J, Song B, Sun Y. Liraglutide improved the cognitive function of diabetic mice via the receptor of advanced glycation end products down-regulation. Aging. 2020;13(1):525-536. doi:10.18632/aging.202162
22. World Health Organization: WHO. Suicide. https://www.who.int/news-room/fact-sheets/detail/suicide. Published March 25, 2025.
23. Suicide data and statistics. Suicide Prevention. https://www.cdc.gov/suicide/facts/data.html. Published October 29, 2024.
24. Brown LA, Boudreaux ED, Arias SA, et al. C‐SSRS performance in emergency department patients at high risk for suicide. Suicide and Life-Threatening Behavior. 2020;50(6):1097-1104. doi:10.1111/sltb.12657
25. Bjureberg J, Dahlin M, Carlborg A, Edberg H, Haglund A, Runeson B. Columbia-Suicide Severity Rating Scale Screen Version: initial screening for suicide risk in a psychiatric emergency department. Psychological Medicine. 2021;52(16):3904-3912. doi:10.1017/s0033291721000751
26. Ji Y, Liu X, Zheng S, et al. Validation and application of the Chinese version of the Columbia-Suicide Severity Rating Scale: Suicidality and cognitive deficits in patients with major depressive disorder. Journal of Affective Disorders. 2023;342:139-147. doi:10.1016/j.jad.2023.09.014
27. Ebrahimi P, Batlle JC, Ayati A, et al. Suicide and Self-Harm events with GLP-1 receptor agonists in adults with diabetes or obesity. JAMA Psychiatry. March 2025. doi:10.1001/jamapsychiatry.2025.0091

28. Kornelius E, Huang JY, Lo SC, Huang CN, Yang YS. The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon like peptide-1 receptor agonist therapy. Scientific Reports. 2024;14(1). doi:10.1038/s41598-024-75965-2
29. Na PJ, Yaramala SR, Kim JA, et al. The PHQ-9 Item 9 based screening for suicide risk: a validation study of the Patient Health Questionnaire (PHQ)−9 Item 9 with the Columbia Suicide Severity Rating Scale (C-SSRS). Journal of Affective Disorders. 2018;232:34-40. doi:10.1016/j.jad.2018.02.045
30. Chung TH, Hanley K, Le YC, et al. A validation study of PHQ-9 suicide item with the Columbia Suicide Severity Rating Scale in outpatients with mood disorders at National Network of Depression Centers. Journal of Affective Disorders. 2022;320:590-594. doi:10.1016/j.jad.2022.09.131
31. Wadden TA, Brown GK, Egebjerg C, et al. Psychiatric safety of semaglutide for weight management in people without known major psychopathology. JAMA Internal Medicine. September 2024. doi:10.1001/jamainternmed.2024.4346
32. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. New England Journal of Medicine. 2021;384(11):989-1002. doi:10.1056/nejmoa2032183
33. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. The Lancet. 2021;397(10278):971-984. doi:10.1016/s0140-6736(21)00213-0
34. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity. JAMA. 2021;325(14):1403. doi:10.1001/jama.2021.1831
35. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nature Medicine. 2022;28(10):2083-2091. doi:10.1038/s41591-022-02026-4
36. Tang H, Lu Y, Donahoo WT, et al. Glucagon-Like peptide-1 receptor agonists and risk for suicidal ideation and behaviors in U.S. older adults with type 2 diabetes. Annals of Internal Medicine. 2024;177(8):1004-1015. doi:10.7326/m24-0329
37. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with risk of suicidal ideation in a real-world cohort. Nature Medicine. 2024;30(1):168-176. doi:10.1038/s41591-023-02672-2
38. Ninla-Aesong P, Puangsri P, Kietdumrongwong P, Jongkrijak H, Noipha K. Being overweight and obese increases suicide risk, the severity of depression, and the inflammatory response in adolescents with major depressive disorders. Frontiers in Immunology. 2023;14. doi:10.3389/fimmu.2023.1197775
39. Haynes A, Kersbergen I, Sutin A, Daly M, Robinson E. Does perceived overweight increase risk of depressive symptoms and suicidality beyond objective weight status? A systematic review and meta-analysis. Clinical Psychology Review. 2019;73:101753. doi:10.1016/j.cpr.2019.101753
40. Suicide statistics. American Foundation for Suicide Prevention. https://afsp.org/suicide-statistics/. Published August 26, 2024.
41. De Paiva IHR, Da Silva RS, Mendonça IP, De Souza JRB, Peixoto CA. Semaglutide attenuates anxious and Depressive-Like behaviors and reverses the cognitive impairment in a type 2 diabetes

mellitus mouse model via the Microbiota-Gut-Brain axis. Journal of Neuroimmune Pharmacology. 2024;19(1). doi:10.1007/s11481-024-10142-w

42. Chen X, Zhao P, Wang W, Guo L, Pan Q. The Antidepressant Effects of GLP-1 Receptor Agonists: A Systematic Review and Meta-Analysis. American Journal of Geriatric Psychiatry. 2023;32(1):117-127. doi:10.1016/j.jagp.2023.08.010
43. Lengsfeld S, Burkard T, Meienberg A, et al. Effect of dulaglutide in promoting abstinence during smoking cessation: a single-centre, randomized, double-blind, placebo-controlled, parallel group trial. EClinicalMedicine. 2023;57:101865. doi:10.1016/j.eclinm.2023.101865
44. Probst L, Monnerat S, Vogt DR, et al. Effects of dulaglutide on alcohol consumption during smoking cessation. JCI Insight. 2023;8(22). doi:10.1172/jci.insight.170419
45. Whicher CA, Price HC, Phiri P, et al. The use of liraglutide 3.0 mg daily in the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first episode psychosis: Results of a pilot randomized, double‐blind, placebo‐controlled trial. Diabetes Obesity and Metabolism. 2021;23(6):1262-1271. doi:10.1111/dom.14334
46. Richards J, Bang N, Ratliff EL, et al. Successful treatment of binge eating disorder with the GLP-1 agonist semaglutide: A retrospective cohort study. Obesity Pillars. 2023;7:100080. doi:10.1016/j.obpill.2023.100080
47. Mulvaney CA, Duarte GS, Handley J, et al. GLP-1 receptor agonists for Parkinson's disease. Cochrane Library. 2020;2020(7). doi:10.1002/14651858.cd012990.pub2
48. Rubin R. Could GLP-1 receptor agonists like semaglutide treat addiction, Alzheimer disease, and other conditions? JAMA. 2024;331(18):1519. doi:10.1001/jama.2024.1017