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Trends in Reporting of Psychiatric Adverse Events Including Suicidal Ideation for GLP-1 Receptor Agonists

By Anish Ghosh

AUTHOR BIOGRAPHY

Anish Ghosh is a junior at the North Carolina School of Science and Mathematics with a 5.0 GPA and a strong passion for medical research. He has conducted research at Wake Forest School of Medicine, Levine Cancer Institute, and Harvard University, with work published in the Journal of Student Research and presented at the 2025 BMES Annual Conference. Outside the lab, he is a violinist in the Charlotte Youth Symphony, a 2025 Carson Scholar, and aspires to a career in academic medicine.

ABSTRACT

Numerous glucagon-like peptide 1 (GLP-1) receptor agonists, such as liraglutide, semaglutide, and tirzepatide, have been developed to prolong the activity of GLP-1 and resist degradation by dipeptidyl peptidase 4 (DPP4) thus leading to sustained glycemic control and weight loss. The objective of this study is to characterize trends in reporting of overall adverse events, psychiatric adverse events, and suicidal ideation for the three GLP-1 receptor agonists liraglutide, semaglutide, and tirzepatide. The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) contains all submitted reports of adverse events associated with prescription and over-the-counter pharmaceuticals in the United States. The FAERS database was searched using the search terms tirzepatide, semaglutide, and liraglutide for the years 2010 to 2025. The number of adverse events for GLP-1 receptor agonists has increased exponentially since 2021, however there were differences in reporting trends between the 3 drugs studied, with increased adverse effects reported for semaglutide and tirzepatide but not for liraglutide. This corresponds to increased numbers of practitioners using semaglutide and tirzepatide compared to liraglutide. The number of psychiatric adverse events were highest for semaglutide followed by tirzepatide and liraglutide. The percentage of reported adverse events involving suicidal ideation for liraglutide peaked in 2023, where the percentage for liraglutide was 1.69 times greater than the percentage for semaglutide, and 13 times greater than the percentage for tirzepatide. Because suicidal ideation is such a serious adverse event, further research into this effect of these GLP-1 receptor agonists is needed.

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Keywords: *GLP-1, GLP-1 Receptor Agonists, Semaglutide, Liraglutide, Tirzepatide, Diabetes, Psychiatric, Adverse Events, Suicidal, FAERS, CMS*

INTRODUCTION

Glucagon-like peptide 1 (GLP-1) is primarily secreted by the intestinal enteroendocrine cells in response to oral glucose intake (Drucker, 2018). GLP-1 increases insulin secretion, improves insulin sensitivity, and suppresses glucagon release, thereby lowering blood glucose concentrations (Drucker, 2018). Additionally, GLP-1 leads to increased glucose uptake by the muscles, and decreased glucose production by the liver. Finally, GLP-1 leads to satiety by direct action on the hypothalamus and delayed gastric emptying (Tang- Christensen, 2001). However, endogenous GLP-1 is degraded by dipeptidyl peptidase 4 (DPP4) within 2–3 min resulting in a very short-lived action and ineffective glycemic control (Mulvihill et al., 2014). Numerous GLP-1 receptor agonists have been developed to prolong the activity of GLP-1 and resist degradation by DPP4 thus leading to sustained glycemic control and weight loss (Drucker, 2018). Moreover, GLP-1 receptor agonists can decrease apoptosis and increase the proliferation of pancreatic β cells which are crucial for insulin secretion (Rea, 2025).

In type 2 diabetes, the secretion of endogenous GLP-1 is blunted, leading to poor blood sugar control in response to ingestion of glucose (Holst, Rev 2007). Patients with prediabetes have higher levels of GLP-1 than those with type 2 diabetes but the levels are lower than normal individuals (Salamah et al., 2024). Pharmacologic administration of GLP-1 receptor agonists can restore the process leading to glycemic control without the risk of hypoglycemia. In a study by Zander et al, (2002) 20 patients with type 2 diabetes received either a subcutaneous continuous infusion of normal saline or a subcutaneous continuous infusion of GLP-1 for a period of 6 weeks (Zander et al., 2002). Individuals who received subcutaneous GLP-1 infusion demonstrated significant falls in fasting and postprandial glucose and slowed gastric emptying. Those who received GLP-1 infusion also reported satiety and weight loss observed throughout the study (Zander et al., 2002). Although this study supported the benefits of GLP-1 receptor agonists in the management of blood glucose, it was limited by continuous infusion which is cumbersome for the management of diabetes. Extensive research has been conducted to develop GLP-1 receptor agonists which overcome the short half-life of GLP-1 and harness the multimodal benefits with these drugs in patients with diabetes. Several GLP-1 receptor agonists have been developed which include dulaglutide, liraglutide (Figure 1A), semaglutide (Figure 1B), exenatide and tirzepatide (Figure 1C) (Katz, 2025). These drugs are rapidly absorbed and achieve peak concentration within hours. These agents have specific affinity for pancreatic cells but also target GLP-1 receptors in other tissues (Zhao et al., 2021). These drugs are metabolized by proteolytic cleavage into smaller inactive peptide and excreted by the kidneys (Jensen et al., 2017). The American Diabetes Association guidelines recommend use of GLP-1 receptor agonists for lowering cardiovascular risk (American Diabetes Association, 2022). Moreover, these drugs have also been demonstrated

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to reduce the progression of chronic kidney disease which is a known complication of diabetes (Badve et al., et al., 2025).

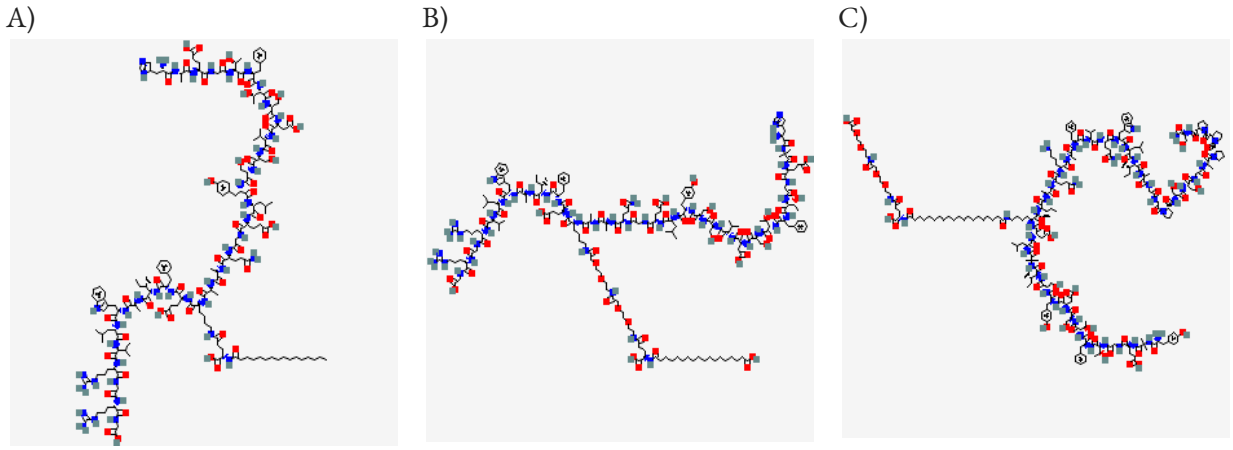

Figure 1: *Chemical Structures for A) Liraglutide, B) Semaglutide, and C) Tirzepatide (PubChem, National Institutes of Health). The figure demonstrates the peptide backbone for the GLP-1 receptor agonists with the peptide backbone and fatty acid moiety acylation at position 26; C16 for Liraglutide, CD18 for Semaglutide and C20 for fatty acid.*

Obesity is associated with insulin resistance and has been associated with the development of type 2 diabetes, hypertension, and cardiovascular disease. By delaying gastric emptying and direct action on the hypothalamus, GLP-1 receptor agonists promote decreased food intake and promote weight loss (Moiz et al., 2025). In a meta-analysis those receiving GLP-1 receptor agonists showed a significant reduction in weight compared to various controls (Visbøll, 2012). Liraglutide was the first GLP-1 receptor agonist specifically approved for weight loss in patients without a history of type 2 diabetes. It is US Food and Drug Administration (FDA) approved in adult patients with a body mass index greater than 30 kg/m^2 alone or greater than 27 kg/m^2 in the presence of at least one weight-related comorbidity, such as hypertension, diabetes, or dyslipidemia (Jackson, 2010). The approval for this indication was based on a double-blind, placebo-controlled trial comparing the weight loss drug orlistat, placebo, and different doses of liraglutide (Astrup et al., 2009). Those who received liraglutide lost significantly more weight than those on orlistat or placebo. Pre-diabetes was also significantly reduced in the reduced liraglutide group (Astrup et al., 2009). Liraglutide was approved for diabetes

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in January 2010 and for weight loss in December 2014. Semaglutide was approved for diabetes in December 2017, for weight loss in June 2021 and reduction of kidney disease progression in 2025 (Anderer, 2025). Tirzepatide was approved for diabetes in May 2022 and weight loss in November 2023 and in December 2024 for moderate to severe sleep apnea (Anderer, 2025).

The most common side effects of GLP-1 receptor agonists are gastrointestinal side effects which include nausea, diarrhea, vomiting, abdominal pain, dyspepsia and constipation (Sun, 2015). Other side effects include injection site reactions such as rash, erythema or itching (Astrup, 2012). A real-world pharmacovigilance study reported the incidence of psychiatric adverse events such as nervousness, stress, eating disorders, insomnia from the FDA Adverse Event Reporting System (FAERS) database (Chen W et al., 2024). However, a recent systematic review and meta-analysis demonstrated that treatment with GLP-1 receptor agonists was not associated with risk of psychiatric effects (Aureliane et al., 2025). Moreover, no increase in suicide and self-harm was found in patients taking GLP-1 receptor agonists compared to placebo. (Ebrahimi et al., 2025). The objective of this study is to characterize trends in reporting of overall adverse events, psychiatric adverse events, and suicidal ideation for the three GLP-1 receptor agonists liraglutide, semaglutide, and tirzepatide. The study further characterizes differences between the three approved GLP-1 receptor agonists with regard to psychiatric adverse events including suicidal ideation.

METHODS

The FAERS database includes information such as the active ingredient that is suspected to have caused the adverse event, the reason for the use, adverse reactions, as well as demographic information such as patient sex, age, and weight. (U.S. Food and Drug Administration 2026). The FAERS database was searched using the search terms tirzepatide, semaglutide, and liraglutide for the years 2010 to 2025. The data was imported for the FAERS website into Microsoft Excel, where pivot tables and analytical tools were used to produce trend graphs, histograms and pie charts. The adverse event reports were further classified according to sex and psychiatric adverse events which included anxiety, depression, insomnia, suicidal ideation, sleep disorder, attention disorder and psychotic disorder. The data regarding prescribers for semaglutide and liraglutide were obtained from the Centers for Medicare and Medicaid Services (CMS) website (CMS, 2025). The specific dataset used in the CMS database was the Medicare Part D Prescribers - by Geography and Drug. The searched terms used for the dataset were semaglutide, liraglutide, and tirzepatide.

RESULTS

Trends in total adverse events for GLP-1 receptor agonists

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The number of adverse events for GLP-1 receptor agonists tirzepatide, semaglutide, and liraglutide that have been reported to FAERS has increased dramatically from 2021 to 2024, especially in the most recent 3 years analyzed (Figure 2). The number of adverse events more than doubled from 2021 to 2022, from 2022 to 2023 and again from 2023 to 2024.

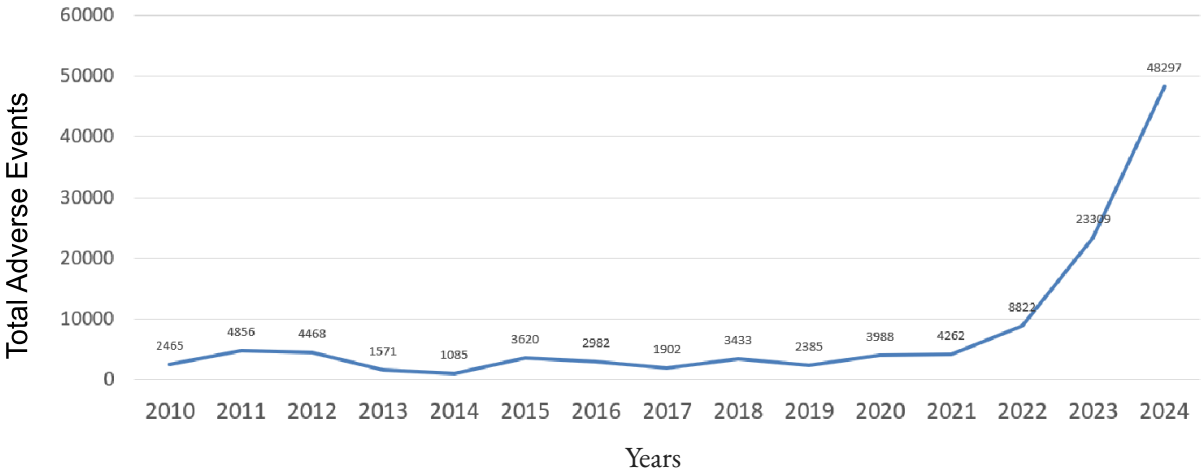

Figure 2. *Total Adverse Events reported to the FAERS website for GLP-1 receptor agonists tirzepatide, semaglutide, and liraglutide from 2010-2024 demonstrating significant increase in reporting of total adverse events since 2021.*

Figure 3 shows the overall number of adverse events reported to FAERS from 2010 to 2024 for each drug, liraglutide, semaglutide, and tirzepatide. While the number of adverse events for liraglutide has stayed low throughout its use from 2010 to 2024, the number of adverse events for semaglutide has been increasing consistently from 2018 to 2024, and the number of adverse events for tirzepatide has increased dramatically, from 3112 cases in 2022 to 35731 cases in 2024.

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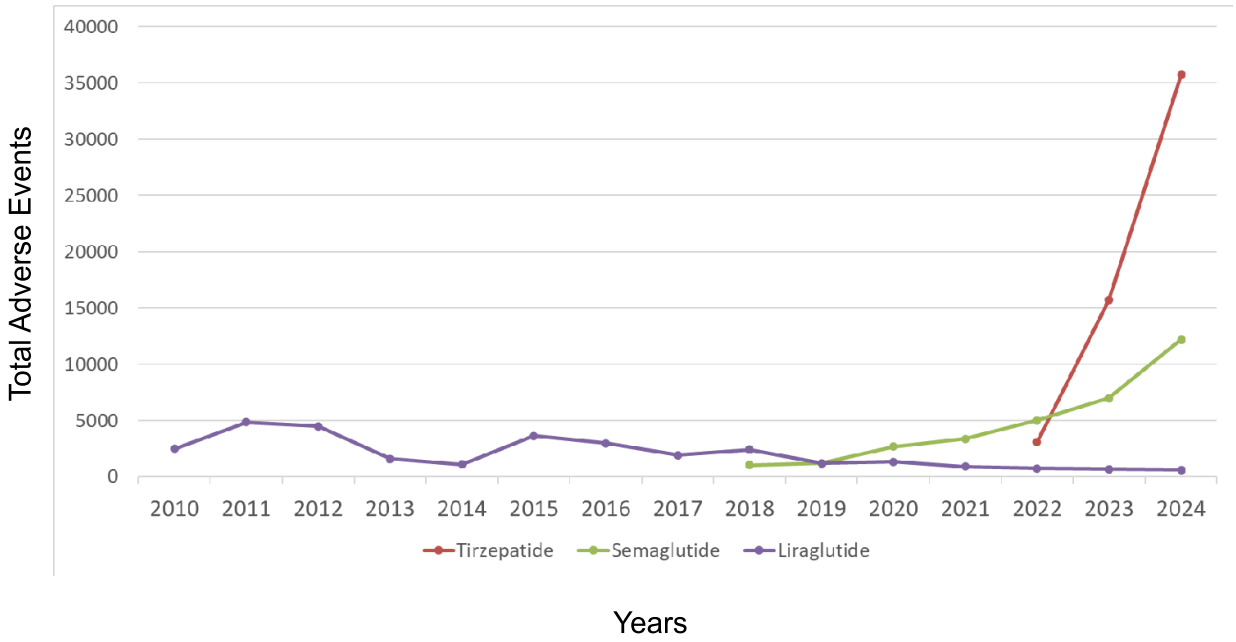

Figure 3. *Total Adverse Events reported to the FAERS website for GLP-1 receptor agonists separated by drug from 2010 to 2024. The reported adverse events for liraglutide stayed low, however the adverse events reported for semaglutide increased steadily since 2020 and there was a dramatic increase in reporting of adverse events for tirzepatide.*

Prescribers for GLP-1 receptor agonists:

The number of prescribers in the US for semaglutide and liraglutide were obtained from the CMS prescriber database. For semaglutide, the trend for total prescribers for Ozempic was examined, and for liraglutide, the trend for Victoza 2-pak and 3-pak were observed. Only two points were present for tirzepatide, in 2022 and 2023. However, there was still a large increase between the two years, from 30,007 prescribers in 2022 to 118,860 prescribers in 2023. There was an approximately linear increase in the number of prescribers for Ozempic from 2018 to 2023 (Figure 4A). In 2018, there were 13,608 prescribers for Ozempic, which increased to 254,476 in 2023. The number of prescribers for Victoza increased linearly from 2013 till 2019 and has declined between 2019 and 2023 (Figure 4B). At the time of the data capture, there was no information available for 2024 and 2025.

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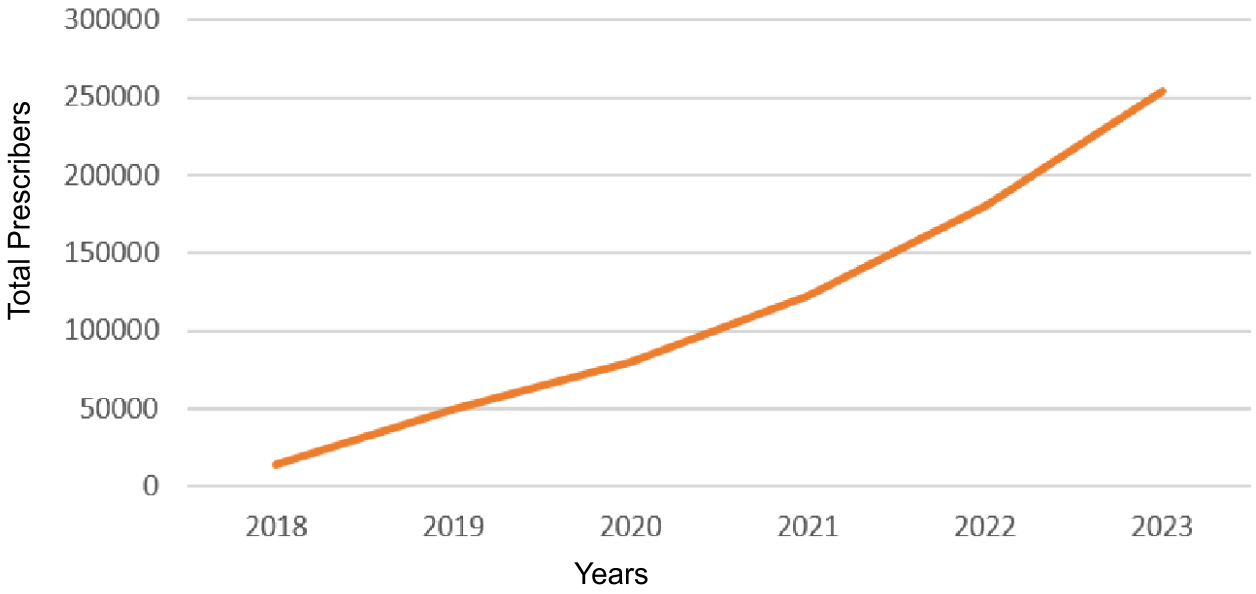

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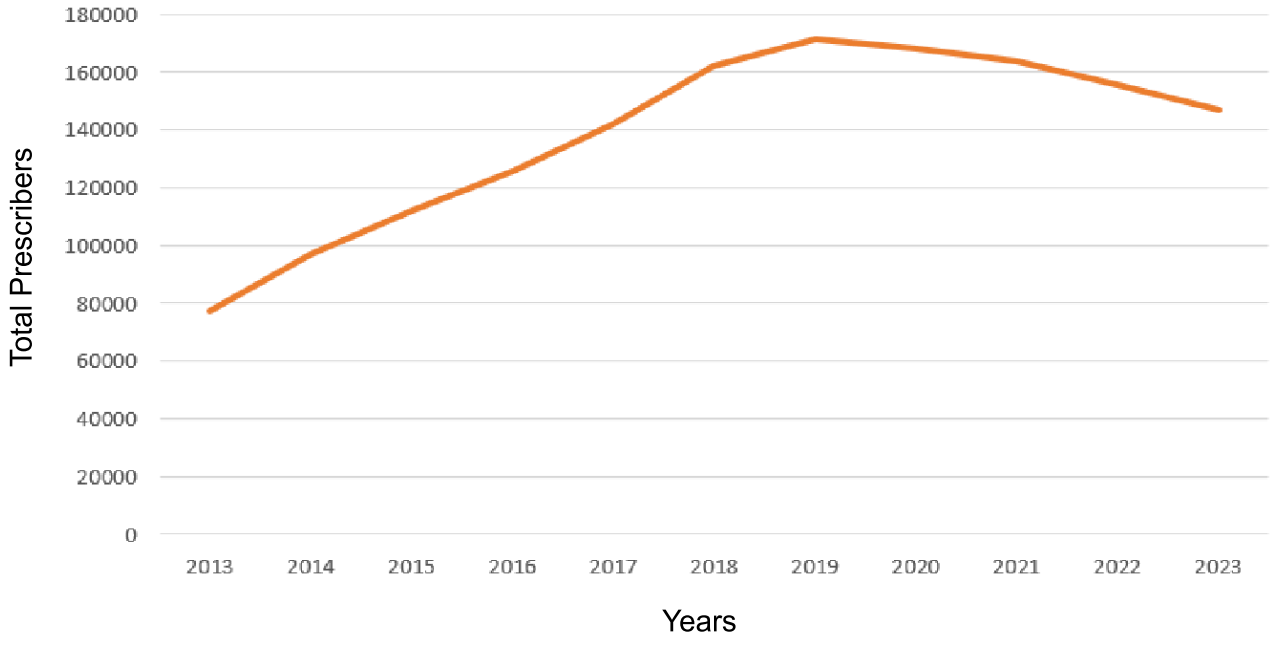

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Figure 4. *Total prescribers reported to the CMS database 2013 to 2023 A) Semaglutide (Ozempic), B) Liraglutide (Victoza). The total number of prescribers for Ozempic have been increasing steadily since 2018 and for Victoza the number of prescribers increased from 2013 to 2019 and then declined.*

Incidence of total reported adverse events based on sex:

There were more adverse events reported by women compared to men for the semaglutide, tirzepatide and liraglutide (Figure 5). For example, almost 75% of the total adverse events for tirzepatide are from females.

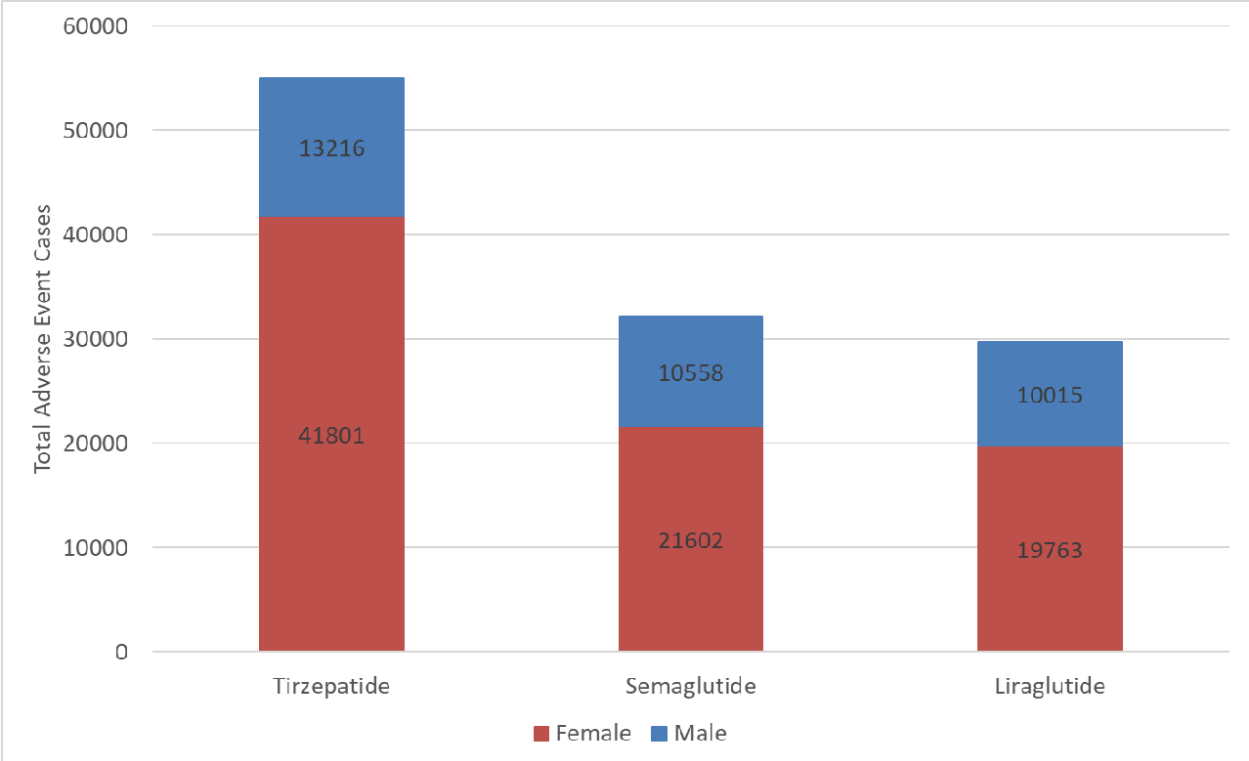

Figure 5. *Total reported adverse events for GLP receptor agonists for males versus females, 2010-2024 demonstrating higher number of adverse events reported by females compared to males for all 3 GLP-1 receptor agonists.*

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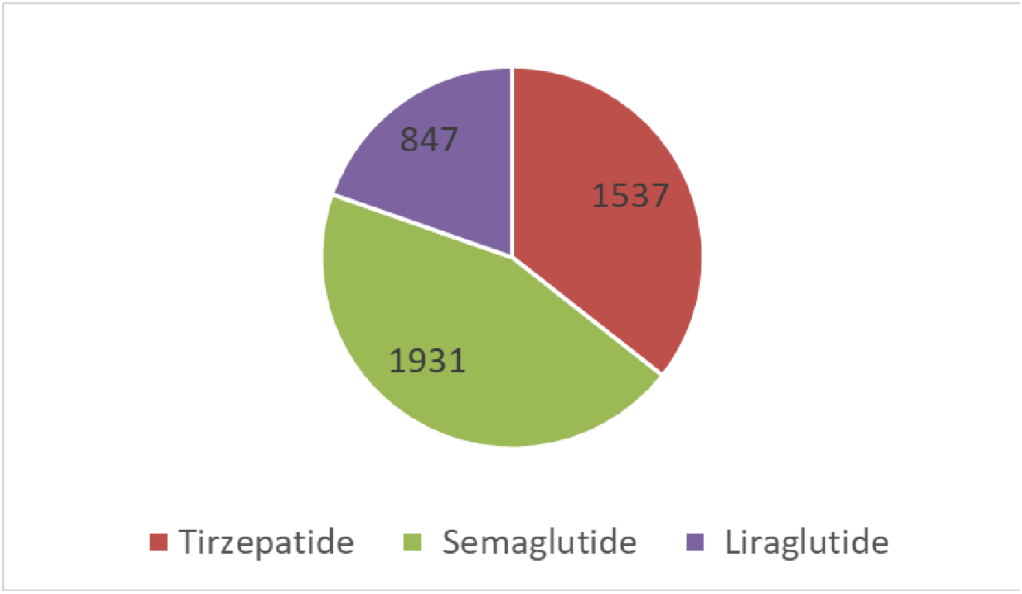
Incidence of reported psychiatric adverse events with GLP-1 receptor agonists:

The reported psychiatric adverse events for semaglutide were higher compared to tirzepatide and liraglutide (Figure 6A). Moreover, the incidence of reported psychiatric side effects with semaglutide was higher in every psychiatric category except for sleep disorder and insomnia (Figure 6B). Regarding suicidal ideation, semaglutide had more than two times the amount of reported adverse events compared to tirzepatide (302 vs 131) (Figure 6B).

A)



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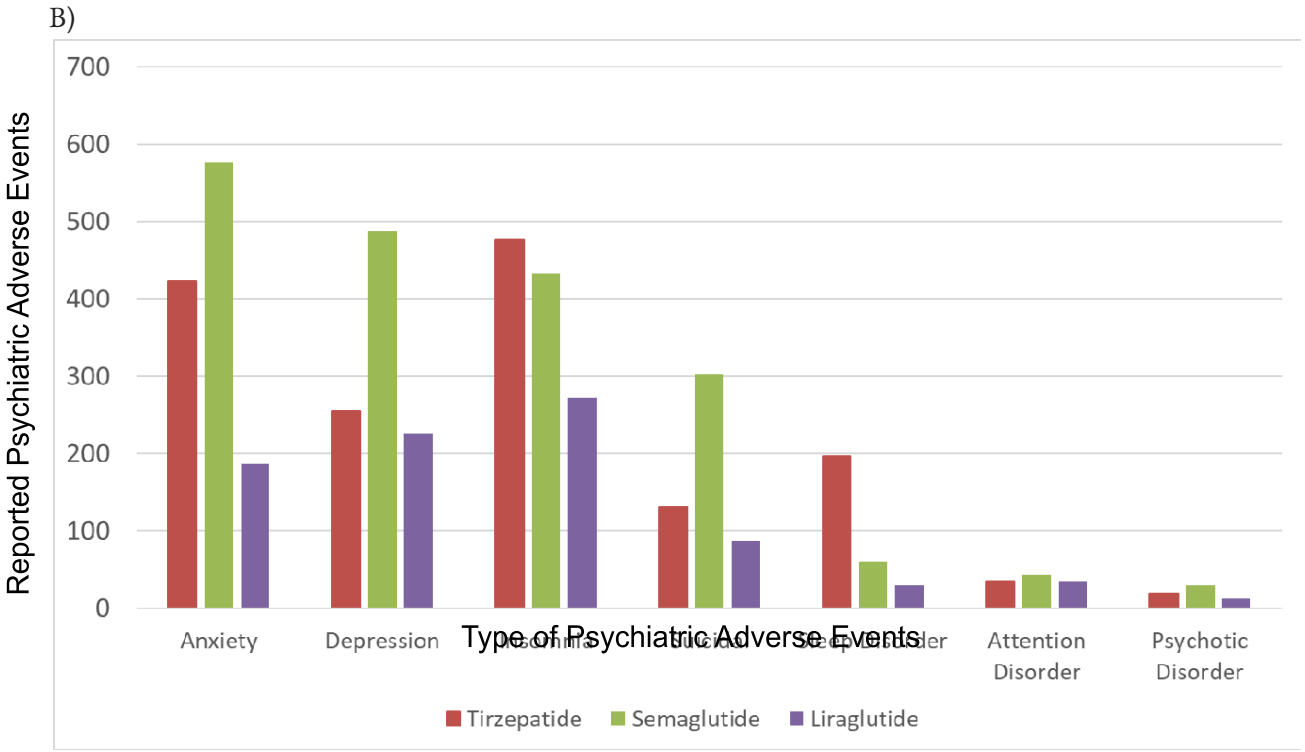

Figure 6. *A) Cumulative reported psychiatric adverse events for GLP-1 receptor agonists, 2010-2025. B) Reported psychiatric adverse events for GLP-1 receptor agonists by reaction type, 2010-2025. There were higher cumulative psychiatric adverse events reported for semaglutide compared to tirzepatide and liraglutide. There was higher reporting of anxiety, depression and suicidal ideation with semaglutide compared to tirzepatide and liraglutide. Tirzepatide was associated with higher reporting of sleep disorders compared to the other two drugs.*

There were differences in the reported psychiatric adverse events between the 3 GLP- 1 receptor agonists between the period of 2010 to 2024 (Figure 7). Tirzepatide has the least percentage of total adverse events being psychiatric related, although its overall event reporting is the most recent of the three drugs. Liraglutide had relatively low percentages, from 1%-3% until 2020, where the percentage increased to 4.4%, and then again sharply increased in 2021 to 8.2%. The peak for liraglutide interestingly corresponds with the pandemic, which may be related to the peak of liraglutide's percentage. Semaglutide is the only drug of the three that has a clear, concerningly increasing pattern. By 2023, semaglutide's percentage has crossed liraglutide's percentage. Semaglutide's percentage was also 2.85 times that of tirzepatide in 2023 and 2.88 times that of tirzepatide in 2024.

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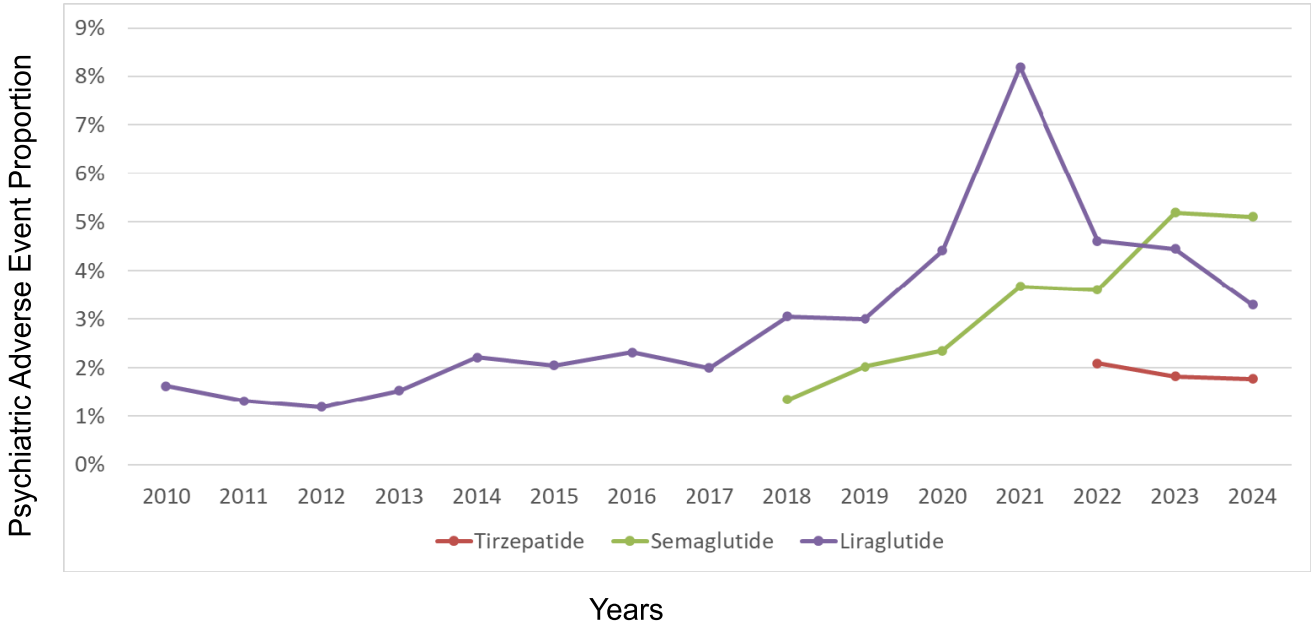

Figure 7. *Percent of total reported adverse events involving psychiatric symptoms for GLP-1 receptor agonists, 2010-2024. There was a sharp increase in percentage of psychiatric adverse events associated with liraglutide from 20202 to 2021 and a relatively steady increase in the percentage of psychiatric adverse events associated with semaglutide from 2018 to 2023. The percentage of psychiatric adverse events associated with tirzepatide has been steady since 2022.*

Trends in reporting suicidal ideation for GLP-1 receptor agonists:

The percentage of reported adverse events involving suicidal ideation for liraglutide interestingly peaked in 2023, where the percentage for liraglutide was 1.69 times greater than the percentage for semaglutide (2.23% vs. 1.32%), and the percentage for liraglutide was almost 13 times greater than the percentage for tirzepatide (2.23% vs 0.17%) (Figure 8). Meanwhile, the percentage of reported psychiatric events involving suicidal ideation for semaglutide increased dramatically from 2022 to 2023, from 0.16% to 1.32%. In 2023, the suicidal ideation percentage for semaglutide was 7.65 times greater than the percentage for tirzepatide (1.32% vs. 0.17%).

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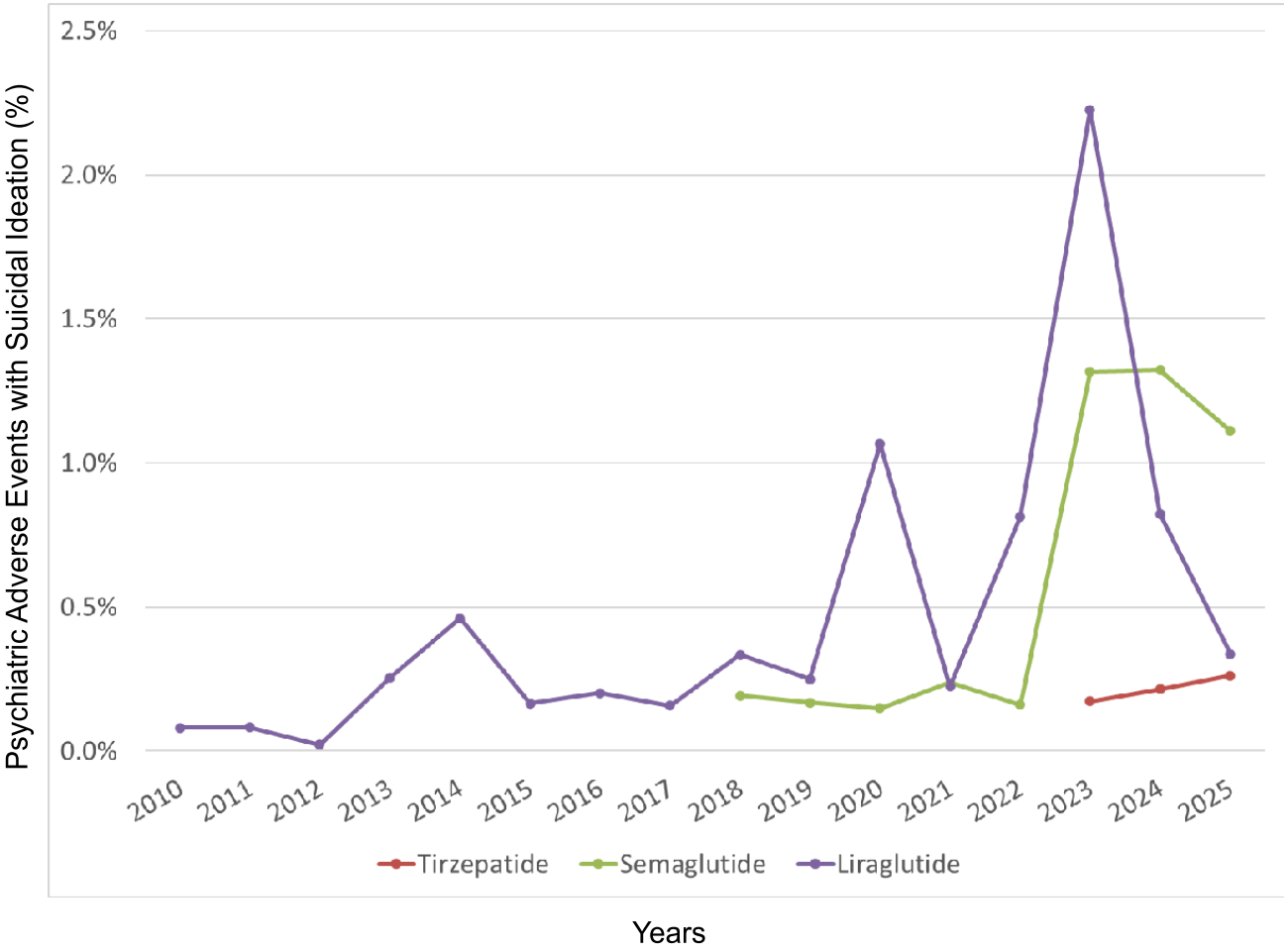

Figure 8. *Percentage of psychiatric adverse events reported as involving suicidal ideation for GLP-1 receptor agonists, 2010-2025. The percentage of psychiatric adverse events reported as suicidal ideation for liraglutide and semaglutide peaked in 2023.*

DISCUSSION

GLP-1 receptor agonists are being widely used for treatment of diabetes and obesity. While gastrointestinal side effects are common and have been well described, psychiatric side effects are rare and not well described in clinical trials. We report real world data from the FAERS database exploring the association of psychiatric adverse events including suicidal ideation with GLP-1 receptor agonists.

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The number of adverse events from GLP-1 receptor agonists reported to FAERS has increased significantly since 2021. Specifically, the number of adverse events for tirzepatide has increased exponentially since 2022, and the number of adverse events for semaglutide has been increasing rapidly since 2018. We also note increased adoption of these drugs by prescribers over the last 4 to 5 years, based on data from the CMS prescriber database. Although the increase in the use of tirzepatide and semaglutide appears to be involved in the increase of the adverse events, there may be other reasons that are contributing to the increase in adverse events reported to the FAERS website for the two drugs. One possible reason may be that the drugs are being distributed to more people who are vulnerable to certain side effects of the drugs, leading to more reports of such adverse events.

When looking at the male vs. female statistics for these drugs, it is clear that more adverse events have been reported for women than men for all three drugs. This may be due to the increased use of the drugs by females, but there may be other factors involved as well. For instance, it may be possible that females are more sensitive to the side effects of the drugs or that females may be more likely to report adverse events compared to males.

Psychiatric adverse events reported for semaglutide were higher than for liraglutide and tirzepatide, for all psychiatric adverse events except sleep disorders. This trend in psychiatric adverse events is in sharp contrast to trends in all adverse events where the reporting is much higher for tirzepatide. Semaglutide has almost 400 psychiatric event cases more than tirzepatide and more than two times that of liraglutide. This statistic could suggest that semaglutide has a larger psychiatric effect compared to tirzepatide and liraglutide. However, this interpretation is limited to reported adverse events. Therefore, the findings reflect reporting patterns and are subject to underreporting or reporting bias. The percentage of reported adverse events involving suicidal ideation for semaglutide was 3.5 times higher than liraglutide and 2.3 times higher than tirzapatide. This is even more alarming because semaglutide has had less overall adverse events than tirzepatide since 2022. Additionally, there is an increasing trend for the percentage of adverse events that are psychiatric for semaglutide, while tirzepatide and liraglutide do not have a clearly increasing pattern. The total reported side effects of the drugs are mostly driven by the total number of people exposed to each drug. Although it is difficult to make assumptions regarding causality from the FAERS database, the recent trend in higher reporting of suicidal ideation with semaglutide warrants further investigation, especially since it is a serious life-threatening adverse event. The findings of the current study contrast with those of a recent systematic review and meta-analysis from randomized clinical trials, which reported low incidence of suicidal ideation with GLP-1 receptor agonists and no differences based on the type of GLP-1 receptor agonist used (Ebrahami, 2025). However, the findings of the current study are in concordance with a report from the World Health Organization global database of suspected adverse reactions, which noted significant disproportionality for semaglutide-associated suicidal

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ideation (Schoretsantis, 2024). Although further studies need to be performed to confirm or dispute this association, clinicians prescribing GLP-1 receptor agonists may want to consider their patients' psychiatric history and psychiatric risk factors when choosing which drug to prescribe, as semaglutide may have a larger psychiatric effect on people.

The findings of the current study are important not only for clinical decision making but also for the development and design of new GLP-1 receptor agonists. One drug currently in development is retatrutide. The drug is in phase 3 of clinical trials and is not approved yet by the FDA for prescription drug use. Reatrutide is a triple receptor agonist and targets GLP-1, Glucose-Dependent Insulinotropic Polypeptide, and glucagon receptors (Katsi et al., 2025). A drug that has three targets requires more thorough examination. Phase I and phase II trials demonstrated promising results in regard to weight loss, but psychiatric effects were not mentioned (Katsi et al, 2025). The psychiatric effects may need to be evaluated considering the adverse events caused by the approved drugs.

LIMITATIONS

It is extremely important to note that there are limitations to the research methods applied. In describing FAERS, the FDA has explicitly warned that there may be duplicate reports and incomplete reports, as some of the reports may not contain all the necessary information (U.S. Food and Drug Administration, 2023). Moreover, the FAERS database relies on voluntary reporting of adverse events and is therefore subject to reporter bias, as not all adverse events are reported to the FAERS website. Although increased usage of these drugs by prescribers are reported from the CMS database, it is not possible to estimate the total prescriptions for these drugs to generate the true incidence of psychiatric adverse events in the real-world population. Moreover, it is challenging to assess if the increased prescriptions for these drugs is because of increased number of prescriptions per prescriber or increase in the number of prescribers for this drug class. Nevertheless, the findings of the current study suggest that further research is urgently needed to discern the risk of adverse events, particularly psychiatric adverse events involving suicidal ideation, associated with GLP-1 receptor agonists. The current analyses rely on the FAERS public dashboard. Future analysis can be performed using the FDA Quarterly Data Files which may enable more detailed analysis.

CONCLUSION

The trends in psychiatric adverse event reporting for semaglutide, tirzepatide and liraglutide are different from the trends in total adverse events from these drugs. There is a trend in higher reporting of suicidal ideation with semaglutide which warrants further investigation. Additionally, the trends across the three GLP-1 receptor agonists call for a need to investigate psychiatric effects of newer developing drugs.

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