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Factors Associated with the Serious Adverse Effects and Misuse of GLP-1 Receptor Agonists

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APPROVAL PAGE

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FACTORS ASSOCIATED WITH THE SERIOUS ADVERSE EFFECTS AND MISUSE OF GLP-1 RECEPTOR AGONISTS

BY

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FACTORS ASSOCIATED WITH THE SERIOUS ADVERSE EFFECTS AND MISUSE OF GLP-1 RECEPTOR AGONISTS

BY

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07/09/2024

INTRODUCTION: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a prominent treatment for type-2 diabetes (T2D) and obesity since the FDA's approval of Exenatide in 2005. The utilization of these medications is projected to increase substantially by 2025, with reports of shortages due to high demand. Concurrently, there are growing concerns about their potential misuse, including use without proper indications and the use of counterfeit products. Despite their therapeutic benefits, GLP-1RAs have been associated with various adverse events, ranging from mild gastrointestinal symptoms to serious events including hospitalization and pancreatitis. As their utilization increases, there is an urgent need for comprehensive research into the factors associated with the serious adverse events (SAEs) and misuse of these medications.

AIM: To investigate factors associated with SAE outcomes and misuse of GLP-1RAs using data from the FDA Adverse Event Reporting System (FAERS).

METHODS: This study employed a retrospective observational analysis using FAERS quarterly data files from 2005 to 2023. Multinomial logistic regression was used to examine factors associated with SAE outcomes, while logistic regression was employed to analyze factors related to misuse. The sample included 20,704 reports after applying inclusion and exclusion criteria.

RESULTS: The multinomial logistic regression analysis revealed that compared to death/life-threatening events, each additional year of age decreased the odds of hospitalization/required immediate intervention by 1.2% (OR = 0.988 [0.985 – 0.992]). Female gender and consumer reports were associated with lower odds of fatal SAEs. Semaglutide was associated with higher odds of death/life-threatening outcomes compared to other GLP-1RAs, except for liraglutide in some instances. Misuse of GLP-1RAs was associated with higher odds of hospitalization/required immediate intervention (OR = 1.419 [1.266 – 1.589]). Logistic regression analysis of misuse factors showed that being female (OR = 1.341 [1.262 - 1.425]) and consumer-reported events (OR = 1.468 [1.377 - 1.566]) were associated with higher odds of misuse, while older age (OR = 0.995 [0.993 - 0.997]) was associated with lower odds.

DISCUSSION: This study is the first to investigate factors associated with SAE outcomes and misuse of GLP-1RAs using FAERS data. The findings have significant implications for clinical practice, as these suggest a need for age- and gender-specific risk assessment in GLP-1RA therapy. The study's strengths include its relatively large sample size, the use of multinomial logistic regression, and the inclusion of misuse as an explanatory variable . However, limitations include potential reporting bias and lack of control for certain confounding factors. Future research should address these limitations using more comprehensive data sources and advanced statistical techniques. The increasing utilization of GLP-1RAs and associated SAEs warrant attention from public health agencies, especially with the ongoing development of more convenient administration methods and potential for misuse.

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AUTHOR'S STATEMENT PAGE

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1. INTRODUCTION

1.1 The Diabetes and Obesity Epidemic

The global burden of diabetes has reached epidemic proportions as the condition affects millions of individuals worldwide and places a significant strain on healthcare systems. In 2021, approximately 529 million people of all ages were living with diabetes worldwide, with a global age-standardized diabetes prevalence of 6.1% (Aloke et al., 2022; Ong et al., 2023). This number is projected to more than double to about 1.31 billion by 2050. Furthermore, individuals with diabetes are at a higher risk of developing other comorbidities such as obesity, cardiovascular disease, kidney disease, and certain types of cancer (Centers for Disease Control and Prevention [CDC], 2021).

Obesity, a major risk factor for type-2 diabetes (T2D), has also become a global health concern. The prevalence of obesity has more than doubled since 1990, with over 890 million adults classified as obese in 2022 (World Health Organization [WHO], 2024). In addition, obesity contributes to the development of insulin resistance, which can lead to the onset of T2D. The combined adverse health effects of obesity and diabetes, often referred to as "diabesity," have become increasingly common and pose a significant challenge to the global health system (Ng et al., 2021).

These chronic conditions are associated with numerous comorbidities, reduced quality of life, and increased mortality rates. The current treatments for diabetes and obesity consist of dietary and lifestyle modifications, pharmacological interventions, and bariatric surgery, all of which aim to improve glucose homeostasis, reduce body weight, and prevent the development of complications (Aloke et al., 2022; Chakhtoura et al., 2023; Ruban et al., 2019). These therapies target various physiological mechanisms such as recovering insulin sensitivity, reducing glucose absorption, and controlling appetite-regulating hormones (Aloke et al., 2022; Chakhtoura et al., 2023; Weinberg Sibony et al., 2023). However, the complex nature of these disorders and the limitations of existing treatments highlight the need for novel therapeutic strategies that can effectively manage diabetes and obesity while minimizing adverse effects.

1.2 Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a promising class of medications for managing type 2 diabetes (T2D) and obesity (Drucker, 2024). In 2005, Exenatide became the first GLP-1RA to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of diabetes (FDA, 2024b). Since then, several similar GLP-1RA analogs have been developed, with improved

efficacy and expanded indications such as treating obesity (Latif et al., 2023). The use of GLP-1RAs is projected to increase significantly in 2025, with reports of potential shortages due to inadequate supply to support the high demand (Matthews et al., 2024; Sheppard, 2024; Watanabe et al., 2024). Consequently, this has led to an increase in misuse and the emergence of counterfeit products as consumers seek alternative treatments (Lowe, 2024).

Despite their therapeutic benefits, the usage of GLP-1RAs for the treatment of T2D has been associated with various adverse events, ranging from mild severity such as nausea, dyspepsia, and vomiting, to more serious events such as death, disability, and hospitalization (Filippatos et al., 2014). When used as a treatment for obesity, there have been reported cases of serious medical events such as pancreatitis and gastroparesis (Sodhi et al., 2023). As the utilization of GLP-1RAs continues to rise, it is important to understand the risks associated with serious adverse events (SAEs) related to these medications (Filippatos et al., 2014; Watanabe et al., 2024).

1.3 Pharmacogivilance

As new therapies are developed and introduced into clinical practice, there exists a need to monitor their safety and adverse event profiles using various pharmacovigilance systems. Global regulatory agencies have developed monitoring systems such as the FDA Adverse Event Reporting System (FAERS) and the European Medicines Agency EudraVigilance (EV) to ensure patients' well-being and identify potential safety concerns (*EudraVigilance*, n.d.; FDA, 2023b).

The FAERS is a database that collects and manages reports of adverse events associated with pharmaceutical products. It has become a valuable data source identifying SAEs in postmarketing surveillance settings, as signals detected can be evaluated to support the FDA’s regulatory decision-making processes (FDA, 2024a). For instance, a signal for hypersensitivity was detected from the usage of Mounjaro (tirzepatide). As a result, the FDA updated the label in July 2023 to include serious hypersensitivity reactions, including anaphylaxis and angioedema (FDA, 2023a). By analyzing reports collected through FAERS, it is possible to detect rare or unexpected adverse events, evaluate the safety profile of a particular drug, and identify factors that may contribute to the occurrence of adverse events (Fang et al., 2014; FDA, 2018). This information can help guide clinical decision-making, inform regulatory actions, and guide future research to optimize the use of medications and minimize the risk of harm to patients.

1.4 Study Objectives

Although recent studies have utilized FAERS to explore the postmarketing trends of GLP-1RAs, to date, none have specifically investigated the factors associated with the severity of these outcomes or the odds of misuse (Chiappini et al., 2023; Liu et al., 2022; Zhou et al., 2024). This study aims to address this knowledge gap by utilizing data from the FAERS to examine the predictors of SAE outcome severity and the odds of misuse associated with GLP-1RAs. Furthermore, this study seeks to explore and investigate factors that contribute to the severity of SAEs and the likelihood of misuse, which can provide valuable insights for the research and development of new interventions and risk mitigation strategies to ensure the safe and appropriate use of GLP-1RAs.

2. REVIEW OF THE LITERATURE

2.1 Overview of GLP-1RA and its mechanisms of action

The regulation of glucose homeostasis, energy metabolism, and overall metabolic health is a complex process involving multiple organs, hormones, and signaling pathways (Nakrani et al., 2023). Among the key players in this intricate network are the pancreatic islets, which produce hormones essential for maintaining normal blood glucose levels and energy balance. The islets are composed of several cell types, including A-cells, which produce glucagon, and B-cells, which produce insulin (Hædersdal et al., 2023). In addition to these pancreatic hormones, the enteroendocrine system of the gastrointestinal tract plays a crucial role in regulating glucose homeostasis and appetite through the secretion of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucagon-dependent insulinotropic polypeptide (GIP) (Hædersdal et al., 2023). The discovery and characterization of these hormones have not only advanced our understanding of metabolic disorders but have also paved the way for the development of novel therapeutic strategies targeting the glucagon and GLP-1 pathways (Drucker, 2024; Drucker et al., 2017).

Glucagon and GLP-1 are two essential hormones in the regulation of glucose homeostasis, energy metabolism, and overall metabolic health (Drucker et al., 2017; Hædersdal et al., 2023; Jakubowska et al., 2024). Both are derived from the protein proglucagon, which is encoded by the proglucagon gene. The tissue-specific processing of proglucagon gives rise to distinct peptides with unique biological functions

(Hædersdal et al., 2023). Despite their similar roles in regulating glucose homeostasis, they are activated by different metabolic and hormonal pathways and exert their effects through distinct mechanisms.

Glucagon, a 29-amino acid peptide primarily produced by the pancreatic alpha cells, acts as the main counter-regulatory hormone to insulin. During fasting or hypoglycemic states, glucagon maintains blood glucose levels by stimulating hepatic glycogenolysis and gluconeogenesis (Hædersdal et al., 2023; Jakubowska et al., 2024). Additionally, glucagon promotes lipolysis in adipose tissues by triggering the release of free fatty acids that can be utilized as an alternative fuel source during fasting or prolonged exercise. Moreover, it stimulates amino acid catabolism in the hepatocytes to supply substrates for gluconeogenesis and increase urea production (Hædersdal et al., 2023).

Several factors, such as blood glucose concentration, amino acids, fatty acids, and hormonal signals from neighboring pancreatic cells regulate the secretion of glucagon. Low blood glucose levels are the primary stimulus for glucagon release, while high glucose levels suppress its release. This glucose-dependent regulation is mediated by direct effects on the A-cells and by hormonal factors from B-cells and D-cells (Hædersdal et al., 2023).

GLP-1, a 30-amino acid incretin hormone, is secreted by the enteroendocrine L-cells of the small intestine in response to nutrient ingestion, specifically glucose and fat (Drucker et al., 2017; *Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Dual Agonists*, 2024; Müller et al., 2019). The discovery and characterization of GLP-1 and its related peptides have advanced the understanding of metabolic disorders and their treatment (Drucker et al., 2017; Jakubowska et al., 2024). The identification of the proglucagon gene and the subsequent elucidation of tissue-specific processing of proglucagon by Habener, Holst, Drucker, and others discovered that proglucagon encodes multiple peptides with distinct biological functions (Drucker, 2024). Particularly, they found that GLP-1 enhances glucose-dependent insulin secretion, inhibits glucagon release, delays gastric emptying, and promotes satiety. These discoveries established the foundation for the development of GLP-1 as a therapeutic target for T2D and obesity. One of the key functions of GLP-1 is to enhance glucose-dependent insulin secretion from the pancreatic B-cells. By binding to the GLP-1 receptors on pancreatic β-cells, GLP-1 triggers a signaling cascade that leads to increased insulin biosynthesis and exocytosis (Drucker et al., 2017; Müller et al., 2019). This insulinotropic effect is glucose-dependent, meaning that GLP-1 stimulates insulin secretion more potently when blood glucose levels are elevated. This mechanism helps to reduce the risk of hypoglycemia, as insulin secretion is reduced when blood glucose levels are low. In addition to its insulinotropic effect, GLP-1 also suppresses glucagon secretion from pancreatic A-cells in a

glucose-dependent manner. This glucagon-suppressive effect helps prevent excessive hepatic glucose production in the postprandial state, which helps to improve glucose homeostasis (Müller et al., 2019).

Besides the presence of macronutrients in the intestine, the secretion of GLP-1 occurs through direct interactions with the L-cells and via indirect mechanisms involving neural and hormonal pathways. In the large intestine, vagus nerve stimulation triggers GLP-1 release while vagotomy inhibits nutrient-induced GLP-1 secretion (Hædersdal et al., 2023; Müller et al., 2019). Appetite-mediating hormones such as leptin and ghrelin are involved in the regulation of GLP-1 secretion, with ghrelin counteracts GLP-1's insulinotropic effect and leptin enhances GLP-1 secretion and GLP-1's appetite-regulating effect (Ronveaux et al., 2015).

Due to the multiple beneficial effects of GLP-1, GLP-1 receptor agonists (GLP-1RAs) were developed as a novel class of medications for the treatment of T2D and obesity. GLP-1RAs are engineered peptides that mimic the actions of native GLP-1 while exhibiting improved pharmacokinetic properties, such as prolonged half-life and resistance to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) (Drucker, 2024; Jakubowska et al., 2024). The susceptibility to DPP-4 was one of the major obstacles in developing GLP-1-based therapies. The first GLP-1RA, exenatide, was developed by modifying the structure of exendin-4, a peptide isolated from the saliva of the Gila monster lizard. Exendin-4 shares approximately 50% sequence homology with human GLP-1 but is resistant to DPP-4 degradation (Aroda, 2018; Drucker, 2024). The approval of exenatide by the US Food and Drug Administration (FDA) in 2005 marked a significant milestone in the treatment of T2D, paving the way for other GLP-1 analogs (Drucker, 2024; Jakubowska et al., 2024).

Further progress in pharmacological research has led to the development of once-weekly GLP-1RAs, such as exenatide extended-release, liraglutide, dulaglutide, albiglutide, lixisneatide, semaglutide. These drugs utilize various technologies, such as microsphere encapsulation or fusion to immunoglobulin G4 (IgG4) Fc fragments, to prolong their half-lives and allow for less frequent administration (Aroda, 2018; Drucker, 2024; Drucker et al., 2017; Jakubowska et al., 2024). Liraglutide (brand names Victoza, Saxenda, Xultophy), a once-daily GLP-1RA, has a half-life of 13 hours due to its fatty acid side chain that binds with high affinity to serum albumin. Victoza and Xultophy were approved by the FDA in 2010 for the treatment of T2D and Saxenda in 2014 for the treatment of obesity (Aroda, 2018; FDA, 2024b). Dulaglutide (brand name Trulicity), a once-weekly GLP-1RA, has a half-life of 5 days due to its binding mechanism of GLP-1 analogs to the IgG4 Fc fragments. The superior efficacy and safety of dulaglutide have been demonstrated in several clinical trials, which led to its approval in 2014 for treating T2D (Aroda, 2018; FDA, 2024b).

Semaglutide (brand names Ozempic, Rybelsus, Wegovy), another once-weekly GLP-1RA, is a modified version of human GLP-1 with a fatty side chain and substituted amino acids. Although its GLP-1R binding affinity is lower than that of Liraglutide, its structure allows for much greater binding to serum albumin, which improves its resistance to the degradation of DPP-4 (Aroda, 2018; Jakubowska et al., 2024; Latif et al., 2023). The FDA approved Ozempic and Rybelsus in treating T2D in 2017 and 2019, and Wegovy in treating obesity in 2021 (FDA, 2024b). Other GLP-1RAs such as lixisenatide and albiglutide were withdrawn from the markets due to commercial considerations (FDA, 2024b; Latif et al., 2023).

2.2 GLP-1 Signaling in T2D and Obesity

The relationship between GLP-1 and T2D has been extensively studied (Andersen et al., 2018; Drucker, 2024; Weinberg Sibony et al., 2023). In patients with T2D, the secretion and action of GLP-1 are impaired, which significantly contributes to the pathogenesis of the disease. This impairment is characterized by reduced postprandial GLP-1 secretion and a diminished insulinotropic response to GLP-1. Consequently, targeting the GLP-1 pathway has become an attractive therapeutic strategy for the management of T2D (Andersen et al., 2018; Jakubowska et al., 2024).

In addition to its role in glucose homeostasis, GLP-1 has been shown to regulate appetite and body weight through its signals to the hypothalamus to induce satiety (Drucker, 2024; Drucker et al., 2017). In obese individuals, GLP-1 secretion in response to nutrient ingestion is inadequate, which suggests a potential relationship between impaired GLP-1 signaling and obesity. The weight loss effects of GLP-1RAs observed in clinical trials have further highlighted the potential of targeting the GLP-1 pathway for the management of obesity (Aroda, 2018).

2.3 Adverse effects and safety concerns of GLP-1RAs

Despite their many benefits, GLP-1RAs are associated with various risks and adverse effects. The most common are gastrointestinal symptoms like nausea, vomiting, and diarrhea, which are typically transient and dose-dependent. Other less common non-gastrointestinal effects include injection site reactions (bruises and rashes) and headaches (Filippatos et al., 2014).

In rare cases, GLP-1RAs have been suspected to be associated with the development of acute pancreatitis and gastroparesis although the causal relationship remains unestablished (Brady et al., 2016; Filippatos et al., 2014; Kalas et al., 2021). While these side effects are hypothesized to result from GLP-1's impact on

gastric emptying and intestinal motility, and GLP-1 receptor expression in the pancreas, the specific mechanisms and causal pathways remain unclear.

Recent studies have reported unexpected effects of GLP-1RAs, including acute cholecystitis, paralysis of the abducens nerve, and positional vertigo (Woronow et al., 2022; Xiong et al., 2024). Furthermore, Sodhi et al. (2023) reported that GLP-1 agonist use for weight loss was linked to increased risks of pancreatitis, gastroparesis, and bowel obstruction compared to bupropion-naltrexone use. Furthermore, Lisco et al. (2023) found a potential association between GLP-1RA use and increased risk of thyroid cancer, particularly after 1-3 years of exposure. However, the evidence regarding these adverse effects is mixed, as several reviews on randomized controlled trials and cohort studies found no evidence of GLP-1RA's increased risk of pancreatitis in patients with T2D (Ayoub et al., 2024; Storgaard et al., 2017).

The growing concerns about these potential adverse effects have led to legal actions against manufacturers of GLP-1RAs. As of June 2024, there have been 101 personal injury lawsuits for gastroparesis, ileus, and intestinal blockage or obstruction filed against Novo Nordisk and Eli Lilly, the manufacturer of Ozempic and Mounjaro (Llamas, 2023). The plaintiff argued that the manufacturers failed to provide sufficient warnings about the risk of developing these severe gastrointestinal adverse effects from GLP-1RA use. These legal actions have brought increased scrutiny to the safety profile of GLP-1RAs and raised questions about the adequacy of current public health communication strategies. Thus, there exists a need for additional research into the associated adverse events and contributing factors, especially in light of growing concerns about the potential misuse of GLP-1RAs.

3. METHODS AND PROCEDURES

3.1 Study Design and Rationale

This study employed a retrospective observational design using publicly available and accessible real-world data from the FAERS database (FDA, 2018) . The database was chosen for its large sample size and its suitability for examining SAE associated with GLP-1RA usage. The study was approved by the Institutional Review Board (IRB) of Georgia State University (IRB number: H24577) and classified as "Determination of Not Human Subject Research" since the data did contain only depersonalized records and the reported cases could not be linked to individuals**.** The study period included data from the first quarter of 2005 (coinciding with the approval of exenatide) through the fourth quarter of 2023, the most recent data available at the time of the study.

3.2 Inclusion and Exclusion Criteria

The study utilized multiple FAERS quarterly datasets, which include: demographics ("DEMO", containing demographic and administrative information), drug information ("DRUG", containing drug information), outcome ("OUTC", containing patient adverse event outcome information), adverse reaction ("REAC", containing recorded adverse events), report source (RPSR, containing information on the source of the reports), indications for use ("INDI"), and deleted cases (DELE, containing cases removed by the FDA or drug manufacturers for various reasons including combining cases) (FDA, 2019). Data preprocessing involved downloading and merging these datasets using the key variables "primaryid" and "caseid", then filtering out the deleted observations found in the DELE datasets. Deduplication was performed following FDA recommendations, retaining only the most recent and/or most severe SAE for each individual report (Khaleel et al. 2022). To retain the most clinically significant and relevant outcome event, the most severe SAE for each individual, followed by the most recent event in cases of equal severity was prioritized. The severity ranking of outcomes was as follows (from most to least severe): Death, Life-Threatening, Congenital Anomaly, Disability, Hospitalization, Required Intervention to Prevent Permanent Impairment/Damage, and Other Serious (Important Medical Event). For each "primaryid", the most severe outcome (variable "outc_cod") was selected based on the ranking above. If multiple records had the same severity ranking, the most recent event was retained, determined by the latest recorded report dates (variable "rept_dt" or recorded event date (variable "event_dt"). Additionally, age values were converted to years, and sex was limited to male and female categories due to the low number of reports with other classifications.

The inclusion criteria were FAERS reports where a GLP-1RA was listed as the primary suspected concomitant medication. Observations were limited to those classified as serious adverse events (i.e. those identified as non-NA values in the "outcome" variable found in the OUTC dataset).

The exclusion criteria were reports involving lixisenatide (withdrawn from the market for commercial reasons) and Zepbound (due to low sample size, $n < 5$ in some categories). In addition, reports with missing or undetermined age or sex information, and report source were omitted, as well as reports where age exceeded 117 years (the age of the oldest living person on Earth) were excluded due to most likely reporting errors.

A "misuse" variable was created by searching for text strings in the "pt" variable in the "REAC" dataset that contained phrases such as "medication misuse", "incorrect dosage", "administration errors", "unapprove", "confusion", "inappropriate" as well as examining missing values in the "indi_pt" variable

in the “INDI” dataset. The initial sample size of 175,728 reports involving GLP-1 receptor agonists was reduced to 20,704 after removing reports with missing data and applying all exclusion criteria filters.

3.3 Variables of Interest and Operational Definition

The primary outcome variable was the type of serious adverse event, categorized as Death or Life-threatening (DE/LT), hospitalization or required immediate intervention (HO/RI), disability or congenital anomaly, and other serious medical events (OT). This categorization was based on clinical relevance and to account for low sample sizes in some individual outcome categories. The secondary outcome was the odds of medication misuse, classified as a binary variable (yes/no). Other variables such as age, sex, and GLP-1RA class, were also included in the analysis.

3.4 Statistical Analysis Plan

Descriptive statistics were produced to summarize the characteristics of the study sample. Continuous variables, such as age, were described using mean and standard deviation. Categorical variables were reported as frequencies and percentages. Misuse and non-misuse groups were compared across demographic variables to identify any significant differences between the two groups. Chi-square tests of association were performed to compare categorical variables, and the Kruskal-Wallis rank sum tests and Wilcoxon rank sum tests were performed to compare the continuous variable.

The primary analysis employed multinomial logistic regression to examine the association between GLP-1RA use and the different SAE outcomes. The secondary analysis used logistic regression to investigate the factors associated with the misuse of GLP-1RA. The goodness of fit for the regression models was evaluated using the Akaike Information Criterion (AIC) and -2 Log-likelihood statistics, and variable selection was performed using a stepwise approach. Wald tests for coefficients were conducted to assess the significance of individual variables within the regression models. Reporting odds ratios (RORs) and 95% confidence intervals (CIs) were calculated to quantify the associations between the predictor variables and the outcomes. A p-value < 0.05 was considered statistically significant.

Data management, visualization, and preprocessing were conducted using R language v4.3.2, and statistical modeling was performed using SAS v9.4.

4. RESULTS

4.1. Study Sample Characteristics

4.1.1. Overall Sample Characteristics

The clinical characteristics of GLP-1-associated SAE are presented in **Table 1**. The majority of SAE incidence was higher in females than males, with females making up 57% of the total number of reports. The mean age of the study population was 59 years (SD = 14). Most SAEs were classified as Other Serious Medical Events (OT) (47%), followed by Hospitalization or Required Immediate Intervention (HO/RI) (39%), Death or Life-Threatening (DE/LT) (11%), and Disability or Congenital Anomaly (DS/CA) (3.2%). Most SAE reports were from consumers (59%), followed by healthcare professionals (39%), and other sources (1.8%). Of the 5 included GLP-1RA, Liraglutide was the most commonly reported GLP-1RA, with a proportion of 30%. Semaglutide made up 26% of the total sample, followed by Dulaglutide (25%), Exenatide (16%), and Tirzepatide (4.1%). The classification of misuse resulted in 66% of all reports being non-misuse and 34% being misused.

4.1.2. Characteristics of GLP-1RA associated SAE Outcomes

Table 2 details the sample characteristics for the primary analysis. The Kruskal-Wallis rank sum test was performed for the continuous variable age, while Pearson's Chi-Squared tests of association were used for the categorical variables sex, report source, GLP-1RA class, and misuse.

The mean age was similar across all SAE outcome groups, ranging from 57 (sd = 13) years in the DS/CA group to 62 (sd = 14) years in the DE/LT group. The majority of the reports in all SAE outcome groups were for females, with the highest proportion in the OT group (62%) and the lowest in the DE/LT group (45%). Regarding the report source, the consumer category made up the largest proportion of reports across all SAE outcome groups, ranging from 46% in the DE/LT group to 71% in the DS/CA group. Healthcare professionals submitted the second-highest proportion of reports, ranging from 28% in the DS/CA group to 45% in the DE/LT group. Other types of reporters made up a small proportion of reports in all SAE outcome groups, ranging from 0.7% in the OT group to 8.5% in the DE/LT group.

The distribution of GLP-1RA drug classes varied among the SAE outcome groups. Liraglutide had the highest proportion of reports in the DE/LT (31%), HO/RI (30%), and OT (30%) groups, while Semaglutide had the highest proportion in the DS/CA group (40%). Dulaglutide and Exenatide had varying proportions across all SAE outcome groups, ranging from 12% to 27%. Tirzepatide made up a

small proportion of reports in all SAE outcome groups, ranging from 3.8% in the OT group to 5.0% in the DS/CA group.

The majority of reports in all SAE outcome groups were from the non-misuse category, ranging from 61% in the OT group to 78% in the DE/LT group. The misuse category made up a smaller proportion of reports, ranging from 22% in the DE/LT group to 39% in the OT group.

4.1.3. Characteristics of GLP-1RA's Misuse Classification

The study sample for the secondary analysis is presented in **Table 3**, stratified by the misuse and non-misuse groups. The Chi-Square tests of association assessed how each categorical variable (sex, report source, GLP-1RA class) aligned with misuse classification, while the Wilcoxon rank sum test was performed for the continuous variable age.

For age, the misuse group had a mean age of 59 (sd = 14) years, while the non-misuse group had a mean age of 60 (sd = 14) years. The majority of the reports in both groups were females, with females making up 63% of the misuse group and 55% of the non-misuse group.

Regarding the report source, the misuse group had a higher proportion of consumer reports (67%) compared to the non-misuse group (55%). Healthcare professionals submitted 33% of the reports in the misuse group and 42% in the non-misuse group. Other types of reporters comprised only 0.2% of the misuse group and 2.6% of the non-misuse group.

The distribution of GLP-1RA drug classes varied between the two groups. In the misuse group, the majority of the reports were from Semaglutide (31%), while in the non-misuse group, Liraglutide was the most common (33%). Dulaglutide accounted for 28% of the misuse group and 23% of the non-misuse group. Exenatide was reported in 12% of the misuse group and 18% of the non-misuse group. Tirzepatide made up 5.4% of the misuse group and 3.2% of the non-misuse group.

4.2. Factors Associated with the SAE Outcomes of GLP-1RA usage

The Wald test statistic results from the multinomial logistic regression analysis identified several factors associated with the SAE outcomes of the usage of GLP-1RA (**Table 4**). The outcomes were categorized as Death/Life-Threatening (DE/LT), Hospitalization/Required Immediate Intervention (HO/RI), Disability/Congenital Anomaly (DS/CA), and Other Serious Adverse Events (OT), with DE/LT serving as the reference category.

Compared to the outcome DE/LT, each additional year of age significantly decreases the odds of the outcome HO/RI by 1.2% (ROR = 0.988 [0.985 – 0.992], $p < 0.001$), DS/CA by 2.3% (ROR = 0.977 [0.971 – 0.983], $p < 0.001$), and OT by 1.4% (ROR = 0.986 [0.982 – 0.989], $p < 0.001$). Sex was also found to be a significant factor, with females having a 39.9% higher likelihood of experiencing HO/RI (ROR = 1.399 [1.271 – 1.541], p), 43.0% higher likelihood of experiencing DS/CA (ROR = 1.430 [1.236 – 1.773]), and 69.1% higher likelihood of experiencing OT (ROR = 1.691 [1.537 – 1.861]) compared to males.

The source of the report significantly predicted the SAE outcomes. Compared to DE/LT, reports submitted by consumers were 30.8% more likely to be of HO/RI (1.308 [1.179 – 1.451]), almost three times more likely to be of DS/CA (ROR = 2.878 [2.352 – 3.522], $p < 0.001$), and 84.2% more likely to be of OT (ROR = 1.842 [1.661 – 2.042], $p < 0.001$) outcomes versus those submitted by healthcare professionals. In contrast, reports from other sources had an 83.3% lower likelihood of HO/RI (ROR = 0.167 [0.129 - 0.216], $p <0.001$), 66.4% lower likelihood of DS/CA (ROR = 0.336 [0.161 – 0.700], $p < 0.05$), and an 88.5% lower likelihood of OT (ROR = 0.115 [95% CI: 0.086 - 0.154], $p < 0.001$) compared to healthcare professional reports.

Among the GLP-1RA drug classes, semaglutide was found to mostly be associated with higher odds of DE/LT vs HO/RI, DS/CA, and OT compared to liraglutide, dulaglutide, exenatide, and tirzepatide (**Figure 1**). Relative to DE/LT, dulaglutide had 16.5% lower odds of HO/RI (ROR = 0.835 [0.725 – 0.962], $p < 0.05$), 63.7% lower odds of DS/CA (ROR = 0.363 [0.284 – 0.463], $p < 0.001$), and 36.3% odds of OT (ROR = 0.637 [0.553 – 0.733], $p < 0.001$) against semaglutide. Similar differences were observed when comparing exenatide and tirzepatide against semaglutide. However, liraglutide was found to not have significantly lower odds of HO/RI and OT vs DE/LT compared to semaglutide (ROR = 0.959 [0.836 – 1.099], $p > 0.05$; ROR = 0.987 [0.862 – 1.130], $p > 0.05$], and only a 59.9% lower odds of DS/CA compared to DE/LT (ROR = 0.399 [0.312 – 0.509], $p < 0.001$).

The misuse of GLP-1RA significantly predicted the SAE outcomes. More specifically, misusing was associated with higher odds of having the outcomes HO/RI and OT to DE/LT compared to not misusing (ROR = 1.419 [1.266 – 1.589], $p < 0.001$; ROR = 1.957 [1.750 – 2.188], $p < 0.001$) . This difference was not significant however for DS/CA vs DE/LT (ROR = 0.913 [0.742 – 1.122], $p > 0.05$) when comparing misusing to not misusing the medication.

4.3. Factors Associated with the Misuse of GLP-1RAs

Table 5 presents the results of the logistic regression analysis investigating factors associated with the classification of misuse of GLP-1RAs. Age was a significant predictor, with each additional year of age decreasing the odds of misuse by 0.5% (ROR = 0.995 [0.993 - 0.997], $p < 0.001$). Compared to males, females had 34.1% higher odds of misusing the medication (OR = 1.341 [1.262 - 1.425], $p < 0.001$).

The source of the report was also significantly associated with misuse. Compared to healthcare professionals, consumers had 46.8% higher odds of misusing GLP-1RA (ROR = 1.468 [1.377 - 1.566], $p < 0.001$), while other types of reporters had 85.7% lower odds of misuse (OR = 0.143 [0.085 - 0.240], $p = 0.0036$).

Among the GLP-1RA drug classes, liraglutide, dulaglutide, and exenatide were associated with significantly lower odds of misuse compared to semaglutide. Liraglutide had 42.2% lower odds (ROR = 0.578 [0.534 - 0.626], $p < 0.001$), dulaglutide had 16.2% lower odds (ROR = 0.838 [0.773 - 0.910], $p < 0.001$), and exenatide had 50.2% lower odds (ROR = 0.498 [0.451 - 0.549], $p < 0.001$) of being misused compared to semaglutide. However, tirzepatide did not show a significant difference in the odds of misuse compared to semaglutide (OR = 1.007 [0.867 - 1.168], $p = 0.932$).

5. DISCUSSION AND CONCLUSION

The multinomial logistic regression analysis of reported serious adverse events (SAEs) revealed several key factors associated with both SAE outcomes and misuse of GLP-1 receptor agonists (GLP-1RAs). Age and gender were found to be significant predictors, with female patients at higher risk for non-fatal SAEs and misuse. The source of adverse event reports significantly influenced the reported outcomes, with consumer reports more likely to be associated with non-fatal SAEs compared to healthcare professional reports. Notably, semaglutide was associated with higher odds of death/life-threatening outcomes and misuse compared to other GLP-1RAs, except for liraglutide in some instances. The indication of misuse was linked to higher odds of hospitalization, required immediate intervention, and other serious medical events. Further logistic regression analysis of misuse factors showed that increase in age and reports from other sources were associated with lower odds of misuse while being female and consumer-reported events were associated with higher odds. Liraglutide, dulaglutide, and exenatide demonstrated lower odds of being misused compared to semaglutide, while tirzepatide showed no significant difference.

This is the first study to investigate various factors associated with the SAE outcomes of GLP-1RA in FAERS. Although Chippiani et al. (2024), Liu et al. (2022), and Zhou et al. (2024) utilized FAERS to examine GLP-1RAs, they employed different analysis techniques such as data mining for disproportionate analysis and focused on other aspects of adverse events. The distribution of SAE reports in this study is consistent with findings from Chiappini et al. (2024) and Zhou et al. (2024), which showed that the majority of reports were submitted by female consumers and most reports were classified as "other SAE". However, Liu et al. (2022)'s analysis of gastrointestinal events of GLP-1RA using FAERS found that males constituted the majority of gastrointestinal adverse event reports.

The results of this study have significant implications for public health interventions and clinical practices. The observed disparities in SAE outcomes and misuse odds across different demographic groups and GLP-1RA classes indicate the need for age- and gender-specific risk assessment and management in GLP-1RA therapy. Based on these results, clinicians and providers should exercise caution when prescribing GLP-1RAs, specifically to younger patients and/or females who were identified to have a higher risk for hospitalization adverse events.

This study has several strengths which include its relatively large sample size, the use of multinomial logistic regression, and the inclusion of misuse as an explanatory variable. However, it also has several limitations that need to be acknowledged. First, the analysis was based on data from a reporting system, which is inherently prone to reporting bias and underreporting. Second, the study did not control for potential confounding factors such as race and ethnicity, comorbidities, concomitant medications, dosage, and duration of GLP-1RA, which could have influenced the observed associations. Future research should aim to address these limitations by using more comprehensive data sources, such as electronic health records (EHR) or claims databases, and employing advanced statistical techniques to control for confounding factors. Linking EHR data with pharmacy claims and social determinants of health information could provide a more comprehensive assessment of the real-world effectiveness and safety of GLP-1RA in more diverse patient populations (Patricia et al., 2023).

These significant findings could warrant further investigation through more extensive and longitudinal studies, such as prospective cohorts, to understand the underlying mechanisms of the observed disparities. Moreover, the increasing utilization of GLP-1RAs and reports of SAEs necessitate more attention from global public health agencies. In particular, the ongoing phase 2b trial of danuglipron, a full agonist oral GLP-1RA, signified the continued development of these medications toward more convenient administration methods (Saxena et al., 2023). This trend, together with the demonstrated potential for misuse and the escalating demand for GLP-1RAs, raises several concerns. These include prolonged

medication shortages affecting patients with T2D and obesity who rely on these medications for therapeutic purposes, the off-label use for weight loss, and the emergence of counterfeit products. Additionally, future research should explore the efficacy and safety of GLP-1RAs in combination with other therapeutic modalities, as such combinations may offer enhanced clinical outcomes or mitigate certain risks associated with monotherapy.

6. TABLES

Table 1. Characteristics of all relevant SAE reports from FAERS[a]

Characteristics	N = 20,704
Age	59 (14)
Sex	
Male	8,834 (43%)
Female	11,870 (57%)
Report source	
Consumer	12,217 (59%)
Healthcare professionals	8,122 (39%)
Other	365 (1.8%)
GLP-1RA class	
Liraglutide	6,171 (30%)
Semaglutide	5,304 (26%)
Dulaglutide	5,143 (25%)
Exenatide	3,242 (16%)
Tirzepatide	844 (4.1%)
Misuse	
No	13,725 (66%)
Yes	6,979 (34%)
SAE outcome	
DE/LT	2,255 (11%)
HO/RI	8,124 (39%)
DS/CA	657 (3.2%)
OT	9,688 (47%)

Abbreviations: DE/LT, Death/Life-threatening; HO/RI, Hospitalization/required Immediate Intervention; DS/CA, Disability/Congenital anomaly; OT, Other Serious Medical Events; ROR, Reporting Odds Ratio; GLP-1RA, GLP-1 Receptor Agonist; SAE, Serious Adverse Events.

[a] Data are presented as mean (sd) for age, and number (%) of reports for sex, report source, GLP-1RA class, misuse, and SAE outcomes.

Table 2. Characteristics of SAE outcomes[a]

Characteristic	DE/LT (n = 2,255)	HO/RI (n = 8,124)	DS/CA (n = 657)	OT (n = 9,688)	P value[b]
Age	62 (14)	60 (15)	57 (13)	59 (14)	< 0.001
Sex					< 0.001
Female	1,019 (45%)	4,509 (56%)	386 (59%)	5,956 (62%)	
Male	1,236 (55%)	3,615 (44%)	271 (41%)	3,712 (38%)	
Report source					< 0.001
Consumer	1,047 (46%)	4,561 (56%)	466 (71%)	6,143 (64%)	
Healthcare professionals	1,016 (45%)	3,464 (43%)	183 (28%)	3,459 (36%)	
Other	192 (8.5%)	99 (1.2%)	8 (1.2%)	66 (0.7%)	
GLP-1 class					< 0.001
Liraglutide	696 (31%)	2,401 (30%)	134 (22%)	2,940 (30%)	
Semaglutide	460 (20%)	2,011 (25%)	265 (40%)	2,568 (27%)	
Dulaglutide	582 (26%)	2,162 (27%)	147 (22%)	2,252 (23%)	
Exenatide	425 (19%)	1,196 (15%)	78 (12%)	1,543 (16%)	
Tirzepatide	92 (4.1%)	354 (4.4%)	33 (5.0%)	365 (3.8%)	
Misuse					< 0.001
No	1,767 (78%)	5,587 (69%)	491 (75%)	5,880 (61%)	
Yes	488 (22%)	2,537 (31%)	166 (25%)	3,788 (39%)	

Abbreviations: DE/LT, Death/Life-threatening; HO/RI, Hospitalization/required Immediate Intervention; DS/CA, Disability/Congenital anomaly; OT, Other Serious Medical Events; ROR, Reporting Odds Ratio; GLP-1RA, GLP-1 Receptor Agonist; SAE, Serious Adverse Events.

[a] Data are presented as mean (sd) for age, and number (%) of reports for sex, report source, GLP-1RA class, and misuse.

[b] Result from the Kruskal-Wallis rank sum test for age, and the Pearson's Chi-Squared tests of association for sex, report source, and GLP-1RA class.

Table 3. Characteristics of Misuse[a]

Characteristic	Misuse (n = 6,979)	Non-Misuse (n = 13,725)	P value[b]
Age	59 (14)	60 (14)	< 0.001
Sex			< 0.001
Female	4,371 (63%)	7,499 (55%)	
Male	2,608 (37%)	6,226 (45%)	
Report source			< 0.001
Consumer	4,659 (67%)	7,558 (55%)	
Healthcare professionals	2,305 (33%)	5,817 (42%)	
Other	15 (0.2%)	350 (2.6%)	
GLP-1RA class			< 0.001
Liraglutide	1,683 (24%)	4,488 (33%)	
Semaglutide	2,155 (31%)	3,149 (23%)	
Dulaglutide	1,965 (28%)	3,189 (23%)	
Exenatide	810 (12%)	2,432 (18%)	
Tirzepatide	377 (5.4%)	467 (3.2%)	

[a] Data are presented as mean (sd) for age, and number (%) of reports for sex, report source, and GLP-1RA class.

[b] Result from the Wilcoxon rank sum test for age, and the Pearson's Chi-Squared test for sex, report source, and GLP-1RA class.

Table 4. Results from the multinomial logistic regression model examined the association between SAE outcomes and sample characteristics.[a]

Characteristic	SAE outcome					
	HO/RI		DS/CA		OT	
	Adjusted ROR (95% CI)	P value[b]	Adjusted ROR (95% CI)	P value[b]	Adjusted ROR (95% CI)	P value[b]
Age (years)	0.988 (0.985 - 0.992)[c]	< 0.001	0.977 (0.971 - 0.983)[c]	< 0.001	0.986 (0.982 - 0.989)[c]	< 0.001
Sex						
Male	[Reference]	NA	[Reference]	NA	[Reference]	NA
Female	1.399 (1.271 -1.541)[c]	< 0.001	1.480 (1.236 - 1.773)[c]	< 0.001	1.691 (1.537 - 1.861)[c]	< 0.001
Report type						
Healthcare professionals	[Reference]	NA	[Reference]	NA	[Reference]	NA
Consumer	1.308 (1.179 - 1.451)[c]	< 0.001	2.878 (2.352 - 3.522)[c]	< 0.001	1.842 (1.661 - 2.042)[c]	< 0.001
Other	0.167 (0.129 - 0.216)[c]	< 0.001	0.336 (0.161 - 0.700)[d]	0.0036	0.115 (0.086 - 0.154)[c]	< 0.001
GLP-1RA class						
Semaglutide	[Reference]	NA	[Reference]	NA	[Reference]	NA
Liraglutide	0.959 (0.836 - 1.099)	0.5481	0.399 (0.312 - 0.509)[c]	< 0.001	0.987 (0.862 - 1.130)	0.8493
Dulaglutide	0.835 (0.725 - 0.962)[d]	0.013	0.363 (0.284 - 0.463)[c]	< 0.001	0.637 (0.553 - 0.733)[c]	< 0.001
Exenatide	0.779 (0.667 - 0.909)[d]	0.0016	0.345 (0.258 - 0.461)[c]	<.0001	0.819 (0.703 - 0.955)[d]	0.0106
Tirzepatide	0.728 (0.564 - 0.941)[d]	0.0152	0.391 (0.254 - 0.603)[c]	<.0001	0.505 (0.391 - 0.652)[c]	<.0001
Misuse						
No	[Reference]	NA	[Reference]	NA	[Reference]	NA
Yes	1.419 (1.266 - 1.589)[c]	< 0.001	0.913 (0.742 - 1.122)	0.3864	1.957 (1.750 - 2.188)[c]	< 0.001

Abbreviations: DE/LT, Death/Life-threatening; HO/RI, Hospitalization/required Immediate Intervention; DS/CA, Disability/Congenital anomaly; OT, Other Serious Medical Events; ROR, Reporting Odds Ratio; GLP-1RA, GLP-1 Receptor Agonist.

[a]Analysis of reports from the FDA Adverse Event Reporting System using a multinomial logistic regression model. The reference category is DE/LT

[b] Result from the Wald Chi-Square test; [c] $p < 0.001$; [d] $p < 0.05$

Table 5. Results from the logistic regression model examined the association between the misuse of GLP-1RAs and sample characteristics.

Characteristic	Misuse vs Non-Misuse	
	Adjusted ROR (95% CI)	**P value[b]**
Age	0.995 (0.993 - 0.997)[a]	< 0.001
Sex		
Male	[Reference]	NA
Female	1.341 (1.262 - 1.425)[a]	< 0.001
Report type		
Healthcare professionals	[Reference]	NA
Consumer	1.468 (1.377 - 1.566)[a]	< 0.001
Other	0.143 (0.085 - 0.240)[b]	0.0036
GLP-1RA class		
Semaglutide	[Reference]	NA
Liraglutide	0.578 (0.534 - 0.626)[a]	< 0.001
Dulaglutide	0.838 (0.773 - 0.910)[a]	< 0.001
Exenatide	0.498 (0.451 - 0.549)[a]	< 0.001
Tirzepatide	1.007 (0.867 - 1.168)	0.932

[a] Result from the Wald Chi-Square test

[b] $p < 0.001$

[c] $p < 0.05$

7. FIGURES

Figure 1. Multinomial Logistic Regression Analysis of GLP-1RA-Associated Serious Adverse Events

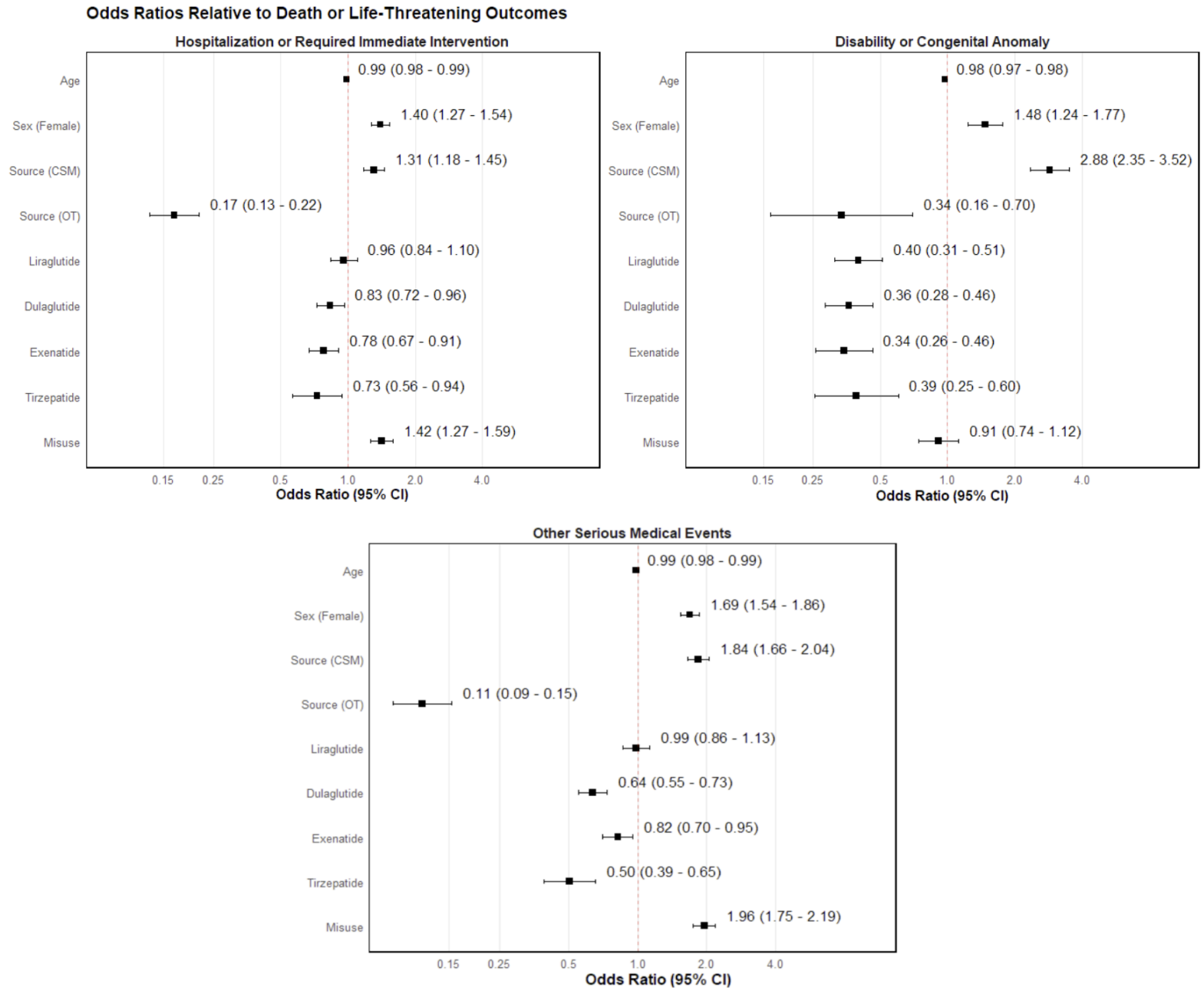
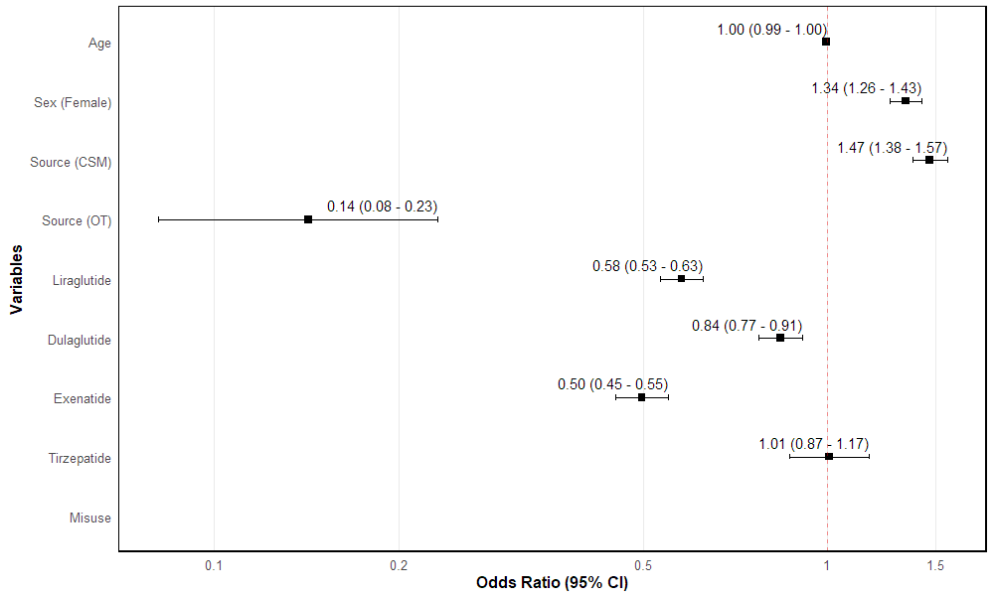


Figure 2. Logistic Regression Analysis of the Misuse of GLP-1RA



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