Association of GLP-1 Receptor Agonists and Risk of Pancreatitis: A Pharmacovigilance Study Based on FAERS Database

By

Adwiza Chakraborty Bishakha
19146074

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

School of Pharmacy
Brac University
March 2023

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:

Adwiza Chakraborty Bishakha
Student ID: 19146074

Approval

The thesis/project titled “Association of GLP-1 Receptor Agonists and Risk of Pancreatitis: A Pharmacovigilance Study Based on FAERS Database” submitted by Adwiza Chakraborty Bishakha (19146074) of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 9th March, 2023.

Examining Committee:

Supervisor:
(Member)

_____

Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
Brac University

Assistant Dean and
Program Director:
(Member)

_____

Dr. Hasina Yasmin
Professor, Assistant Dean and Program Director, School of Pharmacy
Brac University

Dean:

_____

Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
Brac University

Ethics Statement

The project does not involve any kind of animal trial or clinical trial on humans.

Abstract

GLP-1 Receptor Agonists (GLP-1 RAs) are a choice of antidiabetic drugs in the management of Type-2 Diabetes Mellitus (T2DM). Currently, there are five classes of GLP-1 RA drugs available in the market, all of which are widely prescribed among T2DM patients worldwide. Despite their efficacy in managing the symptoms of T2DM, there are some unusual side effects like pancreatitis that may occur according to FAERS database while using the drugs. Although, different studies have suggested otherwise. The study that is conducted is based on the post surveillance data retrieved from FAERS database. This study has established that there is a significant association of pancreatitis and GLP-1 RAs for which signal detection was used by using reporting odds ratio (ROR).

Keywords: Type-2 Diabetes Mellitus; GLP-1 Receptor Agonists; pancreatitis; FAERS; pharmacovigilance

Dedication

Dedicated to my mother and respected faculty members.

Acknowledgement

I would like to express my heartiest gratitude towards my supervisor, Dr. Eva Rahman Kabir (Professor and Dean, School of Pharmacy, Brac University), who has given her constant guidance and support so I could complete my project. I thank her for teaching me from the very scratch and for spending so much time to proofread and correct my mistakes. I would also like to thank Dr. Mesbah Talukder (Professor, School of Pharmacy, Brac University) for his valuable suggestions in this project.

Table of Contents

Declaration.....**ii**

Approval ..... **iii**

Ethics Statement.....**iv**

Abstract.....**v**

Dedication .....**vi**

Acknowledgement.....**vii**

Table of Contents ..... **viii**

List of Tables .....**x**

List of Figures.....**xi**

List of Acronyms.....**xii**

Chapter 1 Introduction.....**1**

1.1 Diabetes and its Management 1

1.2 Aim and Objectives.....5

Chapter 2 Methodology.....**6**

Chapter 3 General Characteristics of GLP-1 Agonists.....**10**

3.1 Structural Activity Relationship and Chemical Structure of GLP-1 agonists 10

3.2 Mechanism of Action.....10

3.3 FDA Approved GLP-1 Agonist Drugs 12

3.4 Adverse Drug Reactions 18

Chapter 4 Results and Discussion **21**

.....24

Chapter 5 Conclusion 27

References.....28

List of Tables

Table 1: Characteristics of GLP-1 RA Drugs 17

Table 2: Adverse Effects of FDA Approved GLP-1RA Drugs 19

Table 3: Reporting of Odds Ratio (ROR) and CI for GLP-1 Agonist drugs using whole database as reference from 2017-2022 21

Table 4: Reporting Odds Ratio (ROR) and CI for GLP-1 Agonist drugs using insulin as reference from 2017-2022 23

List of Figures

Figure 1: Research Methodology and Workflow.....7

Figure 2: Mechanism of Action of GLP-1 Receptor Agonists 11

Figure 3: Chemical Structure of Exenatide.....12

Figure 4: Chemical Structure of Liraglutide.....13

Figure 5: Chemical Structure of Dulaglutide.....14

Figure 6: Chemical Structure of Lixisenatide.....15

Figure 7: Chemical Structure of Semaglutide.....16

Figure 8: Graph comparing GLP-1 Agonist drugs with other drugs in the database in terms of ROR 21

Figure 9: Forest Plot for whole database as reference for GLP-1 receptor agonist drugs.....22

Figure 10: Graph comparing GLP-1 Agonist drugs with insulin in terms of ROR.....23

Figure 11: Forest plot for insulin as reference for GLP-1 receptor agonist drugs.....24

List of Acronyms

DM	Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization
OAD	Oral Anti-diabetic Drug
TZD	Thiazolidinediones
SGLT-2	Sodium-Glucose Cotransporter Type 2
AGI	Alpha Glucosidase Inhibitor
GLP-1	Glucagon Like Peptide-1
GLP-1 RA	Glucagon Like Peptide-1 Receptor Agonist
ASCVD	Atherosclerotic Cardiovascular Disease
ADR	Adverse Drug Reaction
ROR	Reporting Odds Ratio
CI	Confidence Interval
MeSH	Medical Subject Heading
FAERS	FDA Adverse Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
GPCR	G-Protein Coupled Receptor

CNS	Central Nervous System
DPP-4	Dipeptidyl Peptidase-4
IgG4	Immunoglobulin D4
CADRMP	Canadian Adverse Drug Reaction Monitoring Program
CARM	The Centre for Adverse Drug Reactions Monitoring
UMC	Upsala Monitoring Center

Chapter 1

Introduction

1.1 Diabetes and its Management

In the history of diseases, Diabetes Mellitus (DM) might be the oldest one known to human kind. It is a chronic condition where the body is unable to produce sufficient insulin leading to reduced metabolism of proteins, carbohydrates and lipids (Baynest, 2015). DM can be classified into three types- Type 1 DM (T1DM), Type 2 DM (T2DM) and gestational diabetes. T1DM is characterized by the inability of the body to produce insulin at all due to death of the beta cells, often caused by autoimmune diseases. T2DM occurs when cells are resistant to insulin or when production of insulin is not enough. Gestational diabetes is the elevated blood sugar level during pregnancy (Paliika, 2002).

According to WHO, diabetes is termed as a disease when high levels of blood sugars lead to severe damages to organs like heart, kidney, eyes, blood vessels and nerves with T2DM being the most common. Genetic predisposition, relation between environment and gene, epigenetics, sluggish lifestyle, unhealthy diet that includes a large number of foods that are very high in calorie which subsequently leads to obesity and increased body weight, unhealthy consumption of alcohol, smoking, are the potential risk factors behind this disease (Zheng et al., 2018). It occurs when the β cells of the pancreas is dysfunctional and unable to secret sufficient insulin, when the tissues are resistant to insulin and when there is a deficiency in compensatory insulin secretion by the body. As the disease progresses, body becomes unable to continue the homeostasis of glucose through secretion of insulin which follows to hyperglycemia. Patients who have an increased percentage of fat in their body, insulin resistance is enhanced by the adipose tissue through multiple inflammatory actions, for example, deregulation of adipokine and release of free fatty acid in a high amount (Galicia-Garcia et al., 2020).

Type 2 diabetes has been reported as a global pandemic with the patient numbers constantly increasing with each passing year. By the year 2035, there will be more than 590 million patients who will be suffering from this disease (Reed et al., 2021). Although there is no complete cure for T2DM yet, it can be managed by lowering cardiovascular risk and by achieving target blood glucose level. In can include two strategies where one is maintaining a healthy lifestyle for which physical activity, healthy diet and controlling smoking and alcohol consumption is necessary (van den Arend et al., 2000). Another strategy is the use of therapeutic products. There are several drugs that aid in the management of this disease, especially oral antidiabetic drugs (OAD) which is the first line of treatment (Deb et al., 2017). While hundreds of drugs are in still in the clinical trial phase, there are almost 60 FDA approved drugs that falls under these classes- sulfonylureas, biguanides, thiazolidinediones (TZD), sodium-glucose cotransporter type 2 (SGLT2) inhibitors, alpha glucosidase inhibitors (AGIs), incretin-dependent therapies (GLP-1 agonists), different types of insulin and combinations of these drugs (Dahlén et al., 2022). Along with managing symptoms such as blurred vision, excess urination, increased thirst, lethargy that are associated with T2DM, reducing the risk of long-term complications is the goal of the glucose lowering medications. Thus, drugs must be chosen according to the patient's condition. For instance, patients who have the risk of developing ASCVD, which is one of the main causes of death among T2DM patients, are recommended to take SGLT2 inhibitors and GLP-1 agonists (Davies et al., 2018).

However, one of the factors that needs to considered while prescribing a drug is the adverse drug reaction (ADR). Each class of antidiabetic drugs is responsible for having multiple adverse effects. Pharmacovigilance activity can be of great importance in case of detecting and managing these adverse drug reactions of the antidiabetic drugs (Deb et al., 2017). It may be termed as the assessment, monitoring, understanding and prevention of ADRs vis multiple mechanisms such as spontaneous reporting by the patients themselves (Inácio et al., 2017).

Pharmacovigilance is done in the post-marketing stage so that the new drug can be monitored when it is in the market and by doing so, an evaluation of risk-benefit ratio can be done. A pharmacovigilance system is considered to be successful when it includes pharmacists and physicians in the detection and reporting of the ADRs by the patients as the ADR reporting data makes up the backbone of a pharmacovigilance system (Hussain et al., 2020).

Databases of adverse events that are collected by means of spontaneous reporting is an essential of information that is required for ensuring drug safety among the public. It can be done by both the regulatory authorities and pharmaceutical organizations. To conduct the signal detection, spontaneous reports are taken into consideration in the initial phase. Thorough investigation is carried out after a signal has been detected (Rothman et al., 2004). Disproportionality study of the spontaneous reports can produce pharmacovigilance signals that can aware the population about unpredictable or unusual adverse drug reactions in the early stage of post marketing phase. In this regard, if a drug generates a large number of adverse reactions which is not anticipated, it gives a signal and the rate of reporting is thus "disproportionate" in comparison to the other adverse reactions which were previously recorded in the database of pharmacovigilance. Furthermore, in order to investigate pharmacovigilance reports, case and non-case studies are conducted which is a branch of disproportionality studies. Here, "cases" are the reports that include the information about the adverse reaction that is to be studied and "non-cases" are the other reports which do not include the same. Moreover, to estimate the strength of the disproportionality in the studies, Reporting Odds Ratio (ROR) is calculated (Faillie, 2019). Odds ratio is used to find whether there is a connection between the risk factor and the result mentioned in the clinical trials. The value of ROR and Confidence Interval (CI) range is important in determining whether there is any signal at all. If the signal is more than 1 at 95%CI, the number of reported adverse reactions of the drug in the study is high and more disproportionality is indicated with a larger value of

ROR. On the other hand, the adverse reaction is not often reported if ROR is less than 1 and it implies that there is no signal (Meurer & Tolles, 2017). CI is another crucial term that is related to odds ratio. When the inaccuracy of true effect size is estimated in the population of interest in the study population, it is referred to as Confidence Interval (CI). Study sample is used to calculate the true effect size among source population while CI is needed to specify the extent of inaccuracy around the effect size which is measured. CI of the study and its effect size indicate reasonable values for the source population. Furthermore, errors while account sampling is also considered in case of CI calculation. A narrow CI represents that the data is reliable and true effect size in case of source population is represented (Patino & Ferreira, 2015).

1.2 Aim and Objectives

Aim

The aim of the study was to explore the incidence of pancreatitis in patients taking GLP-1 agonist drugs.

Objective

The objectives of the study are-

1. To identify whether there is a relationship between taking GLP-1 agonist drugs and pancreatitis
2. To create awareness among clinicians and patients regarding any uncommon side effect of drugs prescribed for T2DM patients

Chapter 2

Methodology

Using PubMed and Google Scholar, a systematic literature search was carried out. Medical subject headings (MeSH) and texts used for the search included : “GLP-1 associated pancreatitis” , “ adverse drug reactions of GLP-1 agonists” , “ patient reports for GLP-1 agonists” , “adverse drug reactions of exenatide”, “adverse drug reactions of liraglutide”, “adverse drug reactions of dulaglutide”, “adverse drug reactions of lixesenatide”, “adverse drug reactions of semaglutide”, “pancreatitis associated with exenatide”, “pancreatitis associated with liraglutide” , “pancreatitis associated with dulaglutide”, “pancreatitis associated with lixesenatide” , “pancreatitis associated with semaglutide” , “pharmacovigilance” etc. Publication date was limited to 2017. Language was restricted to English.

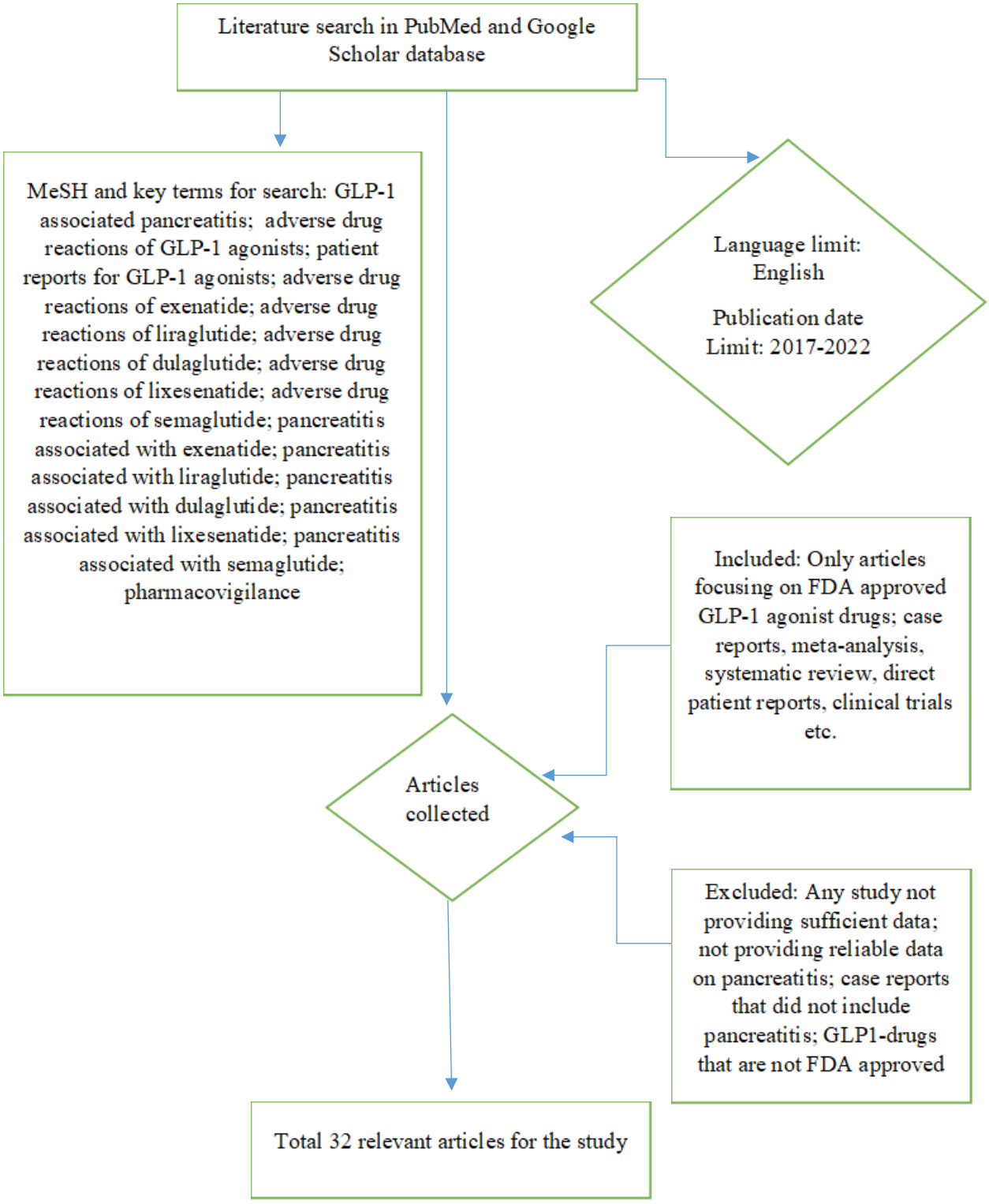

Figure 1: Research Methodology and Workflow

FDA Adverse Event Reporting System (FAERS) database was used to retrieve data based on case reports. It is the database where individual case safety reports forms containing standardized data that are submitted via electronic or physical means, are collected and mining is done to get safety signals. This helps to produce the hypothesis which is needed for further investigation. FAERS data has provided more than half of the label changes that were related to postmarket safety of drugs (Lavertu et al., 2021). By using "search by product" option in the FAERS database, "Exenatide", "Liraglutide", "Semaglutide", "Lixisenatide", "Dulaglutide" and different types of insulin (Insulin Aspart, Insulin Lispro, Insulin Glulisine, Insulin Human, Insulin Degludec, Insulin Glargine and Insulin Detemir) were searched. The search was limited to year 2017 to 2022. Data where the drug of interest was present was included and data where drugs are suspected to cause the adverse reaction were excluded. With the use of case number and matching their event date, age and sex, duplicated reports were also excluded. Pancreatitis was the endpoint of this study. Standardized terminologies of the MedDRA were used to identify the end point of the adverse effect. Furthermore, we retrieved listing of cases of adverse reaction from the dashboard for each drug by selecting the "reaction" option and put all the data in an excel sheet.

The retrieval and analysis of the data were done in January 2023 by using the FAERS database. A disproportionality analysis was conducted in this study by using ROR and its 95% CIs. In order to investigate the reporting association of the suspected drugs (GLP-1 RAs) with the adverse event (pancreatitis), the calculation of ROR and its 95% CI was done at first. The whole database was taken as the reference (control) (Salem et al.,2019). After that, the ROR and its CI was estimated to find the association of pancreatitis and the suspected drugs (GLP-1 RAs) among its class by choosing the GLP-1 RAs as the reference, which was done to find the drug with the highest relation to the adverse event among its class. Finally, the ROR and CI was calculated using insulin class as the reference. In this study, the ROR confirmed the odds of

the association of pancreatitis and the suspected drug (GLP-1 RAs) against odds of the same adverse event being associated with all other drugs. All the data analyses were conducted using R, version 4.2.1.

Chapter 3

General Characteristics of GLP-1 Agonists

GLP-1 RAs are recommended by physicians for multiple benefits like lowering blood glucose level, reducing blood pressure and weight loss etc. (Zhao et al., 2021). Following are the general characteristics of GLP-1 agonists.

3.1 Structural Activity Relationship and Chemical Structure of GLP-1 agonists

Secretin receptors belong to a broader class of peptide hormone binding family that is made up of seven transmembrane extensions which are heterotrimeric G-protein coupled receptors (GPCRs). The glucagon-like peptide-1 (GLP-1) receptor belongs to the class B1 which are similar to secretin receptors (Willard et al., 2012). It is a 463-amino-acid transmembrane-spanning protein. It has a long extracellular N-terminus containing a region of α-helical, two β-sheets which are unparallel and is made up of five β-strands and disulfide bonds which are formed with six cysteine residues in their conserved state (Koole et al., 2013).

3.2 Mechanism of Action

Whenever blood sugar increases, insulin is released by the pancreas which acts as a key to allow it to enter the body's cells for use as energy. In case of diabetes, the body does not make enough insulin or cannot use it as it should for normal body function. GLP-1RAs aid in insulin release and synthesis of insulin, thereby increasing the level of insulin in the body (Baggio & Drucker, 2007). Furthermore, it directly affects the α cells to become oversensitive towards glucose which results in less release of glucagon. This decreased secretion of glucagon in turn suppresses the amount of glucose from liver and reduces the need of insulin. In addition to that,

GLP1-Ras present in the CNS helps in metabolism of glucose peripherally (Shaefer et al., 2015). Moreover, the GLP-1RAs by binding to the GLP-1 receptors in the CNS, mediate an inhibitory response with the help of vagus nerve by suppressing gastric acid that is stimulated upon food intake as well as pentagastrin. This inhibitor effect results in delayed gastric emptying time which leads to a lesser absorption of after-meal glucose level. GLP-RAs also exhibit cardioprotective effects and aids in glucose uptake in muscle tissues (Baggio & Drucker, 2007).

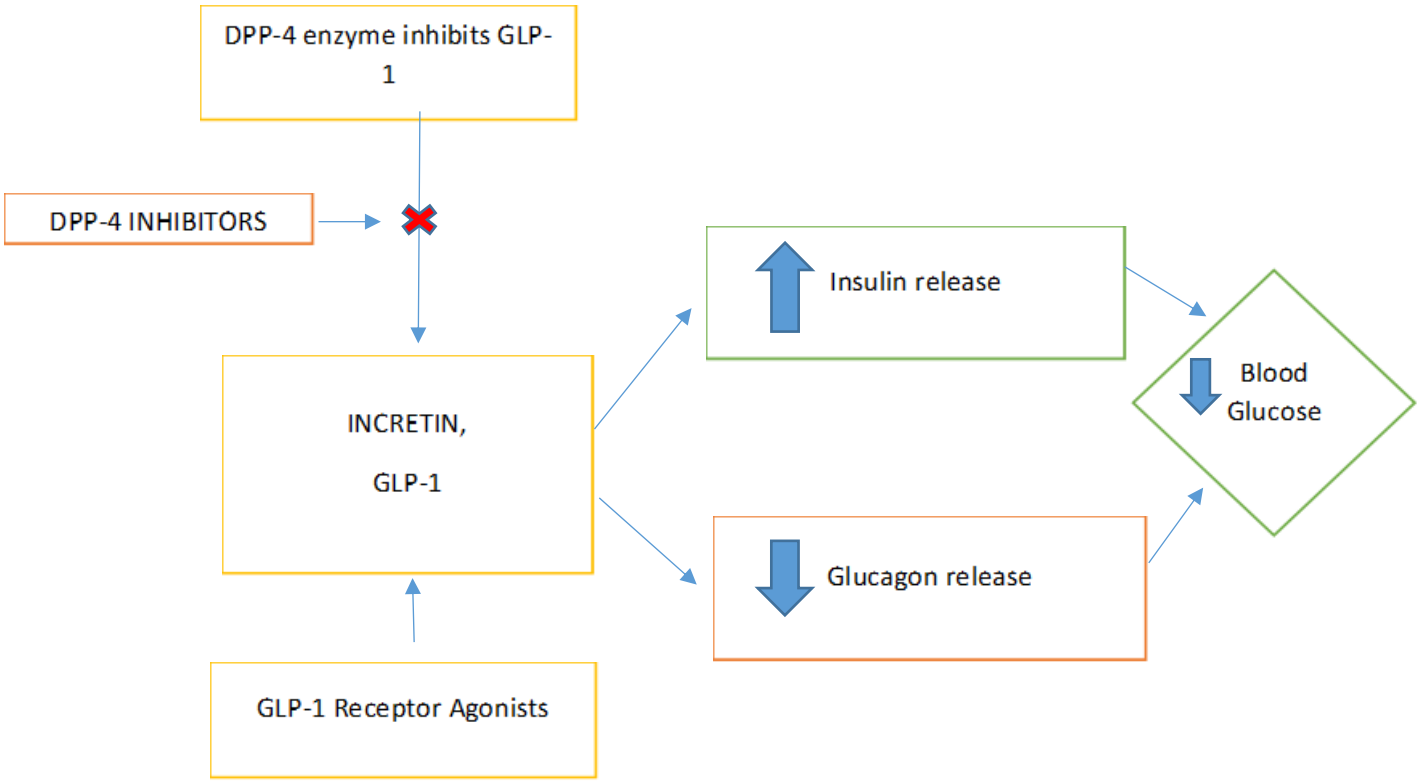

Figure 2: Mechanism of Action of GLP-1 Receptor Agonists. Adapted from (García-Compeán et al., 2015).

3.3 FDA Approved GLP-1 Agonist Drugs

There are currently six classes of FDA approved GLP1- agonist drugs- Semaglutide, Albiglutide, Dulaglutide, Liraglutide which are long-acting drugs and Exenatide and Lixisenatide are short acting drugs (Nauck et al., 2021). Among these, Albiglutide was discontinued in 2017 (Vaduganathan et al., 2019). Thus, albiglutide is not discussed in this study.

Exenatide

Exenatide has binding ability to GLP-1 and works as a GLP-1 analogue, that lowers the level of glucose by reducing concentrations of glucagon, decelerating gastric emptying, raising stimulation of insulin release that is glucose dependent and thereby increasing sufficiency to enhance glycemic control in T2DM patients. Exendin-4 is 39-amino acid peptide which is bigger than human GLP-1 and has 53% similarity with the human GLP-1 in case of structure and physiology. It is resistant to deactivation that is caused by DPP-4. Exenatide has binding capacity to GLP-1 receptor being a synthetic form of exendin-4 peptide which is why it resists degradation by DPP-4 to a greater extent (Aroda, 2018). It is eliminated through kidney by glomerular filtration which is accompanied by deactivation by proteolytic enzymes (Neumiller, 2009).

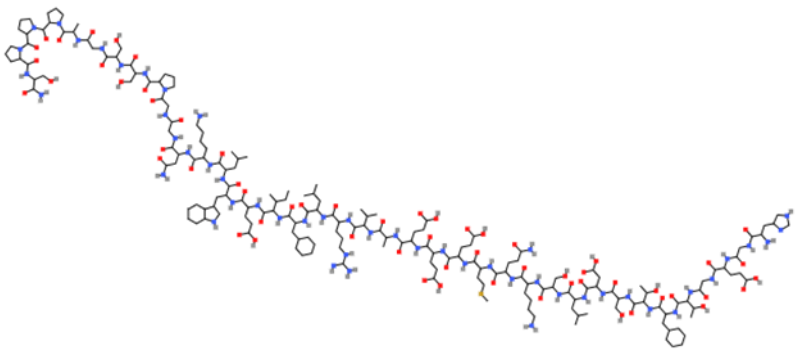

Figure 3: Chemical Structure of Exenatide

Liraglutide

Liraglutide has an additional use in reducing body weight in patients along with controlling glycemic index and the role of the arcuate nucleus situated in the hypothalamus is very critical in this case. It suppresses food intake and by such means, reduces body weight. The mechanism is dependent on consumption of energy and gastric emptying impact by GLP-1 (Ladenheim, 2015). Liraglutide is different from the natural GLP-1 because it has lysine residue which is acylated at position 26 along with side chain of a hexadecanoyl-glutamyl including substitution with single lysine-to-arginine amino acid at position 34(Jacobsen et al., 2016). Liraglutide is less prone to DPP-4 degradation, resulting to lengthier duration of albumin binding, metabolic stability along with lesser absorption than native GLP-1 (Neumiller, 2009).

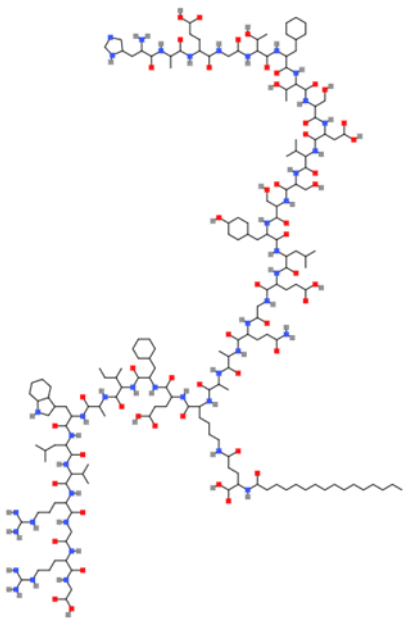

Figure 4: Chemical Structure of Liraglutide

Dulaglutide

Dulaglutide works as a GLP-1 agonist and by binding and activating the GLP-1 receptor to decrease secretion of glucagon and increase secretion of insulin whenever there is a rise in glucose level in the blood along with slowing up gastric emptying process with the aim to reduce the level of glucose after a meal. The GLP-1 agonist part of dulaglutide is 90% similar in structure and physiology to endogenous human GLP-1. It is consisted of a disulfide-linked chains that are identical in nature and each of the chain include sequence of human GLP-1 agonist and with the help of a miniature peptide linker, it is bound covalently to a mutated human immunoglobulin G4 (IgG4) heavy chain. Furthermore, amino acids are substituted in such a way that they enhance its solubility, avoids degradation by DPP-4 enzyme leading to less immunogenicity and a very long half-life. Renal clearance is restrained due to the fusion of GLP-1 part of the molecule with the Fc domain situated in an IgG4 which aids in extending the duration of its activity (Kuritzky et al., 2014). The drug is broken into amino acids it's made up of when administered. Bioavailability is 65% upon 0.75 mg administration which can reduce to 47% when the dose if increased to 1.5mg (Garber, 2011).

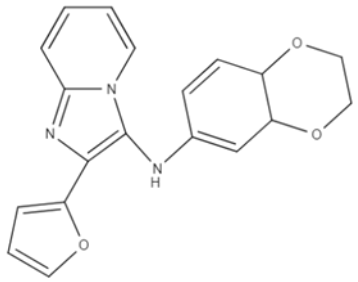

Figure 5: Chemical Structure of Dulaglutide

Lixisenatide

The mechanism of action of this class involves reduction of gastric emptying time by decreasing secretion of glucagon from the α cells of the pancreas. Additionally, it increases secretion of insulin which is dependent on glucose by stimulating βcells of pancreas. The main goal of this drug administration is to achieve desirable glycemic index (Anderson & Trujillo, 2016).

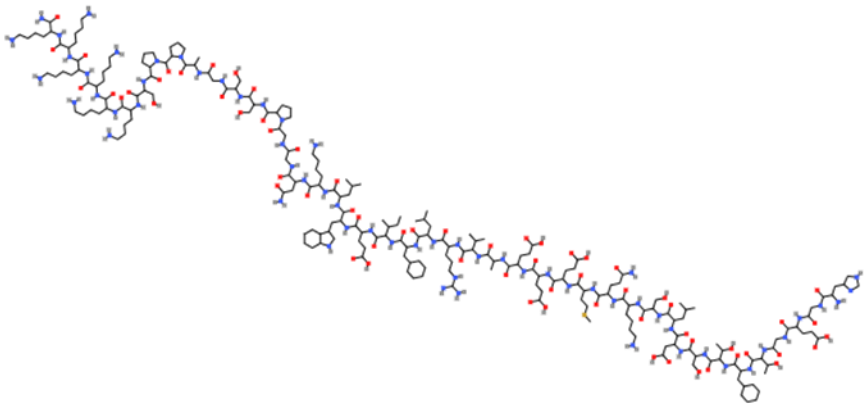

Figure 6: Chemical Structure of Lixisenatide

Semaglutide

Like other GLP-1 agonist drugs, semaglutide has the same mechanism for delaying the gastric emptying process and lowering of glucose level in blood in T2DM patients. However, it has a significant use in weight loss as well. It does so by reducing total intake of energy during all the meals followed by breakfast. It also lowers craving for foods containing fat and reduces hunger as well which is associated with control of appetite (Blundell et al., 2017). Semaglutide is 94% homologues to endogenous human GLP-1-(7–37) (Tan et al., 2017).

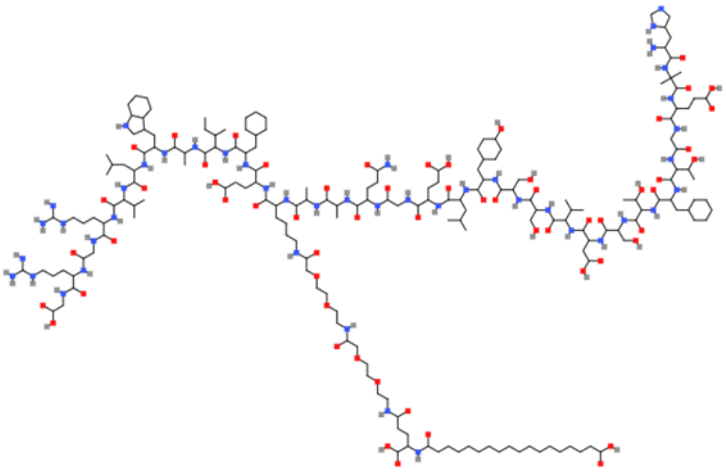

Figure 7: Chemical Structure of Semaglutide

Table 1: Characteristics of GLP-1 RA Drugs

Name of the Drug	**Approval Date**	**Type of action**	**Administration time and route**	**Pharmacokinetic Characteristics**
Exenatide (Brand names: Bydureon, Byetta)	June 2005	Short acting	Immediate-release (IR) preparation via subcutaneous route twice daily or as extended-release (ER) formulation, once in a week (Cirincione & Mager, 2017)	$t_{1/2}$= 2.4 h C_{max}= 211 pg/mL (twice daily) 300 pg/mL (once weekly) T_{max}= 2h (twice daily) 7 - 8 weeks (once weekly) (Neumiller, 2009)
Liraglutide (Brand names: Saxenda, Victoza)	December 2014	Long acting	Once daily by subcutaneous injection (Peterson & Pollom, 2010)	$t_{1/2}$= 13 h C_{max}=9.4 nmol/L T_{max}= 9 -12h (Neumiller, 2009)
Dulaglutide (Brand name: Trulicity)	September 2014	Long acting	Once a week via subcutaneous route (Garber, 2011)	$t_{1/2}$= 120 h C_{max}= 114 ng/mL T_{max}=12-72 h (Garber, 2011)
Lixesenatide (Brand name: Adlyxin)	July 2016	Short acting	Once in a day via subcutaneous route (Anderson & Trujillo, 2016)	$t_{1/2}$= 3 h C_{max}= 84 pg/ml T_{max}= 2 h (Anderson & Trujillo, 2016)
Semaglutide (Brand names: Ozempic, Rybelsus, Wegovy	December 2017	Long acting	Once in a week via subcutaneous route (Wilding et al., 2021)	$t_{1/2}$= 165-184 h C_{max}=10.3 nmol/L T_{max}= 24h (Tan et al., 2017)

3.4 Adverse Drug Reactions

Adverse drug reaction (ADR) may be termed as a significantly harmful reaction that results from administration of a medicinal product. Understanding adverse effects might help in predetermining future risks and thus can help in prevention of those risks by changing dosing schedule, changing the treatment or discontinuation of the product (Coleman & Pontefract, 2016). Spontaneous reporting of the ADRs by healthcare professionals is crucial in managing ADRs and this leads to an efficient post-marketing surveillance and safety of the drug. There are multiple ADR reporting systems present in different countries. For instance, the United Kingdom uses “Yellow Card Scheme”, Canada uses “Canadian Adverse Drug Reaction Monitoring Program (CADRMP)”, New Zealand uses “The Centre for Adverse Drug Reactions Monitoring (CARM) programme”, USA uses “MedWatch” and “FDA Adverse Event Reporting System (FAERS)”, etc. However, the global database of ADR is managed by the Uppsala Monitoring Centre (UMC), which is the executive authority of the drug monitoring programme run by the World Health Organization (WHO) (Rabbur & Emmerton, 2010). For this study, FAERS database was used for documentation of the adverse effects of GLP-1 agonist drugs.

A number of adverse effects were found upon literature search such as nausea, constipation, diarrhea, vomiting with hypoglycemia being the most common ones. However, some unusual side effects, for instance, thyroid cancer and pancreatitis were noticed as well (Shaefer et al., 2015). All the adverse effects found in this study are summarized in Table 2.

Table 2: Adverse Effects of FDA Approved GLP-1RA Drugs

Adverse effects	FDA Approved Drugs				
	Dulaglutide-September ,2014	Liraglutide-December ,2014	Exenatide-June, 2005	Semaglutide-December,2017	Lixisenatide-July 27,2016
Nausea	5,552	1,477	1,203	2,708	12
Diarrhea	3,142	683	543	1,353	2
Vomiting	2,760	842	606	1,573	6
Delayed gastric emptying	176(impaired)	37(impaired)	64(impaired)	53(impaired)	-
Alterations in intestinal motility and transit time	15 (motility disorder)	4(motility disorder)	2(motility disorder)	7(motility disorder)	-
Alterations in intestinal transit time (decreased)	2	-	-	-	-
Constipation	810	355	226	754	1
Hypoglycemia	283	143	101	96	11
Nonfatal myocardial infarction	182	64	107	49	1
Nonfatal stroke (total)	15	14	3	3	-
Heat Stroke	3	-	-	-	-
Ischaemic Stroke	5	2	1	1	-
Haemorrhagic Stroke	3	11	-	2	-
Brain Stem Stroke	2	-	-	-	-
Embolic Stroke	1	-	1	-	-
Thrombotic Stroke	1	1	1	-	-
Injection site reaction	176	40	153	55	-
Pancreatitis	1,050	554	216	428	3
Nasopharyngitis	179	58	99	92	-
Influenza	146	50	55	71	-
Upper respiratory tract infections	19	11	7	39	-
Acute kidney injury	249	200	94	178	1
Dizziness	956	341	380	483	9
Mild tachycardia	56(just tachycardia)	35(just tachycardia)	13(just tachycardia)	38(just tachycardia)	-

Infections	64	28	40	18	10 (no term for just infection, total number of infection cases stated)
Headaches	809	402	367	639	3
Dyspepsia	688	213	180	282	-
Injection-site pruritus	812	86	861	9	1
Erythema	88	42	101	33	1
Anaphylaxis (anaphylactic reaction)	27	17	21	13	-
Might induce unwanted cell proliferation and increase the risk of cancer	924 (total number of cancer cases)	860	629	288	8
Gastric emptying undergoes rapid tachyphylaxis	no exact term found -	1	no exact term found	no exact term found	no exact term found
Therapeutic Response Shortened	48	-	2	2	-
Therapeutic Response Decreased	24	12	2	5	-
Therapeutic Response Unexpected	3	14	32	2	-

As shown in the Table 2, it can be seen that cases of pancreatitis reported is quite high and can be a major concern associated with these drugs. Pancreatitis is the inflammation of pancreas and is divided into two classes- acute and chronic. Acute pancreatitis occurs if any inflammatory disease is present in the pancreas and is characterized by high level of pancreatic enzymes and abdominal pain. Chronic pancreatitis happens due to long term inflammatory disease in pancreas and the physical damage is not reversible. Due to chronic pancreatitis, function of the pancreas may be lost forever and is often associated with pain (Sarner & Cotton, 1984). Thus, from all these mentioned side effects, pancreatitis was chosen to be the primary concern for this study.

Chapter 4

Results and Discussion

During the period of 2017-2022, the number of total cases for pancreatitis induced by the GLP-1 agonist drugs in FAERS was 2241 (Dulaglutide 1040, Liraglutide 554, Exenatide 216, Semaglutide 428 and Lixisenatide 3) (Table 2). Signal Detection was done using two approaches. First approach used the whole database as the reference and in the second approach, insulin was used as the reference drug to remove disease biases.

Table 3: Reporting of Odds Ratio (ROR) and CI for GLP-1 Agonist drugs using whole database as reference from 2017-2022

Name of the Drugs	Reporting Odds Ratio (ROR)	Confidence Interval (Range)
Dulaglutide	17.58	16.45 - 18.78
Liraglutide	47.31	43.04 - 51.99
Exenatide	10.16	8.75 - 11.81
Semaglutide	26.87	24.40 - 29.60
Lixisenatide	37.86	11.89 - 120.50

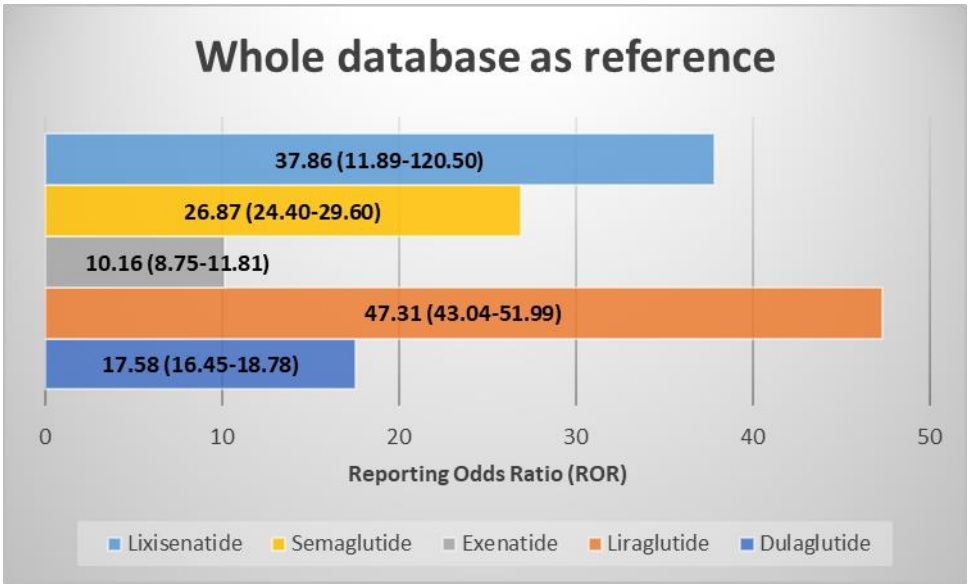

Figure 8: Graph comparing GLP-1 Agonist drugs with other drugs in the database in terms of ROR

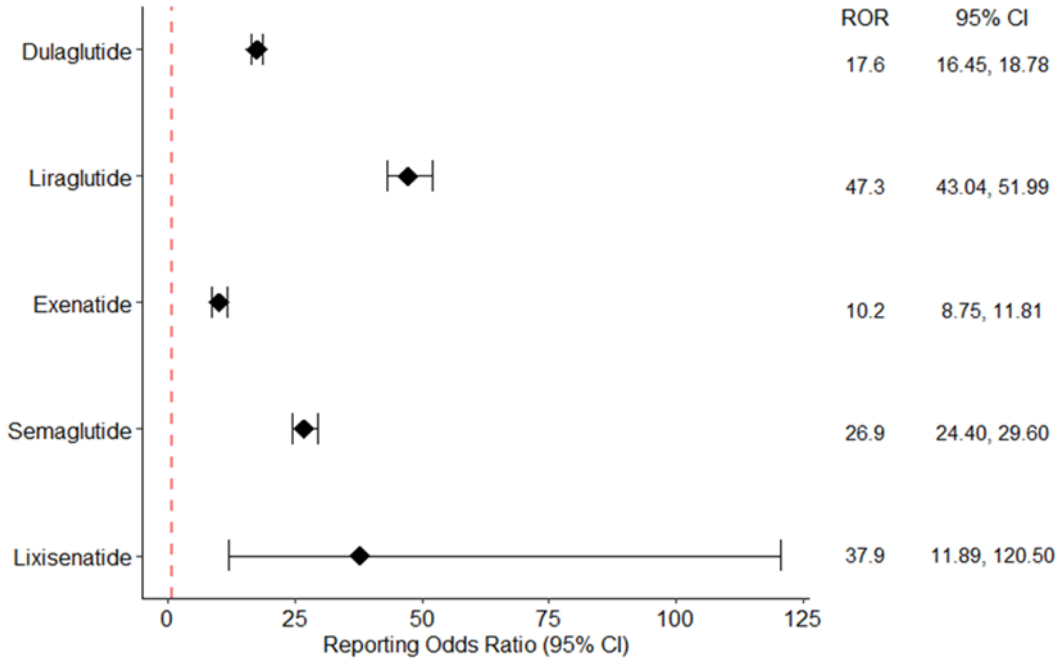

Figure 9: Forest Plot for whole database as reference for GLP-1 receptor agonist drugs

According to Table 3, all the five drugs showed strong signals in the first approach. Liraglutide showed the strongest signal (ROR 47.31, 95% CI 43.04 - 51.99). Lixisenatide showed second highest signal (ROR 37.86, 95% CI 11.89 - 120.50) and semaglutide showed the third highest signal (ROR 26.87, 95% CI 24.40 - 29.60). Dulaglutide showed a lesser signal than that of semaglutide and lixisenatide (ROR 17.58, 95% CI 16.45 - 18.78). Exenatide showed the least signal (ROR 10.16, 95% CI 8.75 - 11.81). A clear comparison of GLP-1 RAs from the other drugs in the database can be seen from the graph chart (Figure 8).

Furthermore, a forest plot is given for a graphical representation of the results when the whole database is used as a reference (Figure 9). The middle points of the diamonds indicate pooled effect size of the analysis and pooled 95% CI is shown by the two sides of the diamonds and the horizontal lines are indicative of the confidence interval range. A smaller line would mean a more precise study. Another important feature of forest plot is the line of no effect, which indicates the point where there is no difference present between two experimental groups of the study. It is usually 0 or 1 and in case of odds ratio, it passes through 1. The result is

considered to be significant when the 95% CI crosses the line of no effect (Chang et al., 2022). When comparing the length of the line of CIs (figure 9), it can be observed that lixisenatide has the widest line which implies a less precise result. Dulaglutide, exenatide and semaglutide produce more accurate results. When compared, liraglutide produces a less accurate result than dulaglutide, exenatide and semaglutide but more precise than lixisenatide.

Table 4: Reporting Odds Ratio (ROR) and CI for GLP-1 Agonist drugs using insulin as reference from 2017-2022

Name of the Drugs	Reporting Odds Ratio (ROR)	Confidence Interval (Range)
Dulaglutide	11.1	8.00 - 15.40
Liraglutide	36.27	25.56 - 51.47
Exenatide	6.31	4.28 - 9.30
Semaglutide	19.9	13.93 - 28.44
Lixisenatide	37.49	4.91 - 286.31

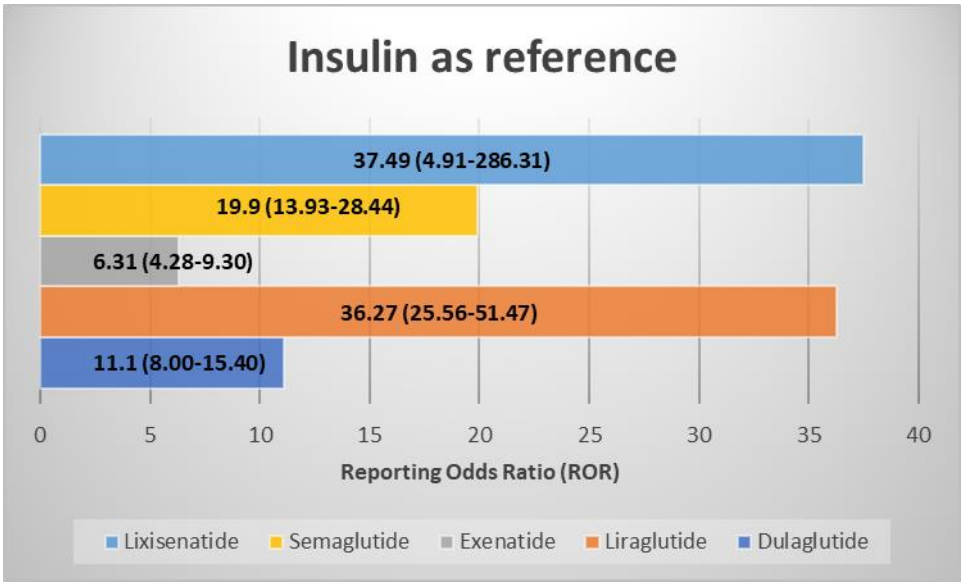

Figure 10: Graph comparing GLP-1 Agonist drugs with insulin in terms of ROR

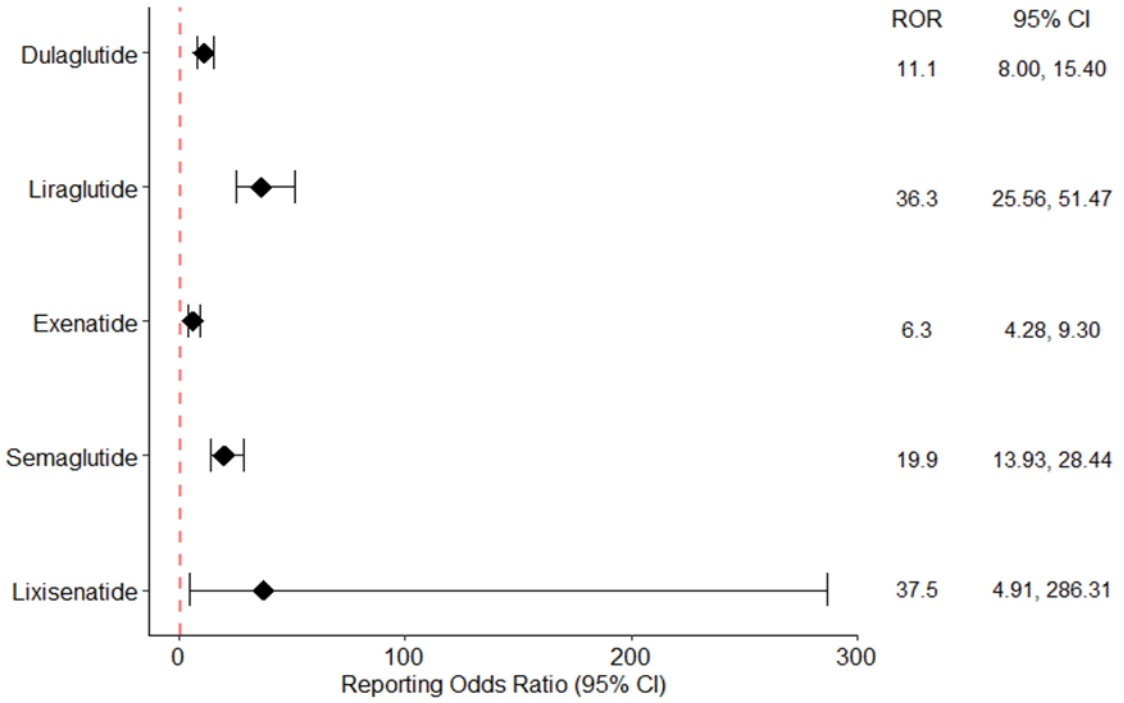

Figure 11: Forest plot for insulin as reference for GLP-1 receptor agonist drugs

As shown in table 4, in the second approach where insulin was used as the reference drug, signals became lower compared to the signals of first approach although all five drugs showed signals. Lixisenatide showed the strongest signal here (ROR 37.49, 95% CI 4.91 - 286.31) which was similar to the signal that was received from the first approach for the same drug. The second highest signal was seen in case of liraglutide (ROR 36.27, 95% CI 25.56 - 51.47) that was lesser than that of the first approach. Semaglutide (ROR 19.9, 95% CI 13.93 - 28.44) showed a signal stronger than dulaglutide (ROR 11.1, 95% CI 8.00 - 15.40). Both of them showed weaker signal than that was seen in the previous approach. Weakest signal was shown by exenatide (ROR 6.31, 95% CI 4.28 - 9.30). Comparison of the five drugs when insulin is used as a reference is given the column chart shown here (Figure 10). In the given forest plot (Figure 11), it is seen that lixisenatide produces a wider line of CI which means it gives a less precise result. Liraglutide and semaglutide produces more accurate results respectively when the lines of CIs are compared. However, in this regard, exenatide and dulaglutide generate most precise results.

Based on the study done, it can be established that there is an association of pancreatitis and GLP-1RA dugs. As shown in the results in the first approach, each of the drug shows strong signals and it proves that there is a clear correlation present between pancreatitis and these drugs. In the second approach, insulin was used as the reference drug because it is considered the choice of treatment when OADs fail even after the treatment period of 2-3 months and A1C is more than 7% (Swinnen et al., 2009). It was done to remove the disease bias which means to inspect whether the adverse effect was actually caused by the disease itself or the drug. In this study, the signals detected from this approach was much weaker than that of the first approach, except lixisenatide. This implies that the disease bias is not present in the study. There would not have been any signal if disease was associated with the adverse effect. Since the data were taken from FAERS database, it was assumed that the cases were reported by the clinicians and therefore, patient history has been taken into account.

Multiple studies have been conducted in the past years to find the association of pancreatitis and GLP-1 RA drugs. Few of the studies suggested that there is a relation of pancreatitis to the GLP-1 RA drugs. Multiple animal studies were done where chronic pancreatitis was seen in 30% of the male rats after exenatide was administered for 10 weeks. Another study where 1,269 control subjects were included who had same age, pattern of inclusion, sex, and T2DM complications along 1,269 hospitalized cases that included acute pancreatitis implied that there is an association of GLP-1 RAs and pancreatitis (Filippatos et al., 2014). Again, there are studies which concluded that the risk of pancreatitis is associated with the use of GLP-1 RA drugs (Cao et al., 2020). However, the pharmacovigilance analysis that is conducted in this study concludes that there is a significant risk of pancreatitis involved with the use of GLP-1 RA drugs.

The possible explanation of the association of the GLP-1 receptor agonist drugs and pancreatitis can be the fact that the exocrine cells of the pancreas have proliferative ability

where the GLP-1 receptor is present. Thus, there might be a possibility that due to this capacity of proliferation, cell linings in the smaller ducts may be subjected to overgrowth which might lead to partial damage in the ducts. For this reason, the back pressure in the pancreatic acini will rise and inflammation might occur. Although rare, due to this reason, acute pancreatitis may occur when GLP-1 RA drugs are administered (Consoli & Formoso, 2015).

Chapter 5

Conclusion

GLP-1 RA drugs are extremely effective in managing the symptoms of T2DM. Even so, there are certain risks like pancreatitis associated with the administration of these drugs (Filippatos et al., 2014). A number of recent studies have suggested that there is no risk of developing pancreatitis with the use of these drugs but the number of cases retrieved from FAERS database and this study establishes the opposite. Thus, we need to be concerned and aware of this adverse reaction. Further studies are much needed in this area where patient histories are taken into account and credibility of the case reports of are properly analyzed.

References

Anderson, S. L., & Trujillo, J. M. (2016). Lixisenatide in type 2 diabetes: Latest evidence and clinical usefulness. In *Therapeutic Advances in Chronic Disease* (Vol. 7, Issue 1, pp. 4–17). https://doi.org/10.1177/2040622315609312

Aroda, V. R. (2018). A review of GLP-1 receptor agonists: Evolution and advancement, through the lens of randomised controlled trials. In *Diabetes, Obesity and Metabolism* (Vol. 20, pp. 22–33). Blackwell Publishing Ltd. https://doi.org/10.1111/dom.13162

Baggio, L. L., & Drucker, D. J. (2007). Biology of Incretins: GLP-1 and GIP. *Gastroenterology*, *132*(6), 2131–2157. https://doi.org/10.1053/j.gastro.2007.03.054

Baynest, H. W. (2015). Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. *Journal of Diabetes & Metabolism*, *06*(05). https://doi.org/10.4172/2155-6156.1000541

Blundell, J., Finlayson, G., Axelsen, M., Flint, A., Gibbons, C., Kvist, T., & Hjerpsted, J. B. (2017). Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes, Obesity and Metabolism*, *19*(9), 1242–1251. https://doi.org/10.1111/dom.12932

Cao, C., Yang, S., & Zhou, Z. (2020). GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials. *Endocrine*, *68*(3), 518–525. https://doi.org/10.1007/s12020-020-02223-6

Chang, Y., Phillips, M. R., Guymer, R. H., Thabane, L., Bhandari, M., Chaudhary, V., Wykoff, C. C., Sivaprasad, S., Kaiser, P., Sarraf, D., Bakri, S., Garg, S. J., Singh, R. P., Holz, F. G., & Wong, T. Y. (2022). The 5 min meta-analysis: understanding how to read and interpret a forest

plot. In *Eye (Basingstoke)* (Vol. 36, Issue 4, pp. 673–675). Springer Nature. https://doi.org/10.1038/s41433-021-01867-6

Cirincione, B., & Mager, D. E. (2017). Population pharmacokinetics of exenatide. *British Journal of Clinical Pharmacology*, *83*(3), 517–526. https://doi.org/10.1111/bcp.13135

Coleman, J. J., & Pontefract, S. K. (2016). CMJv16n5-CME_Coleman.indd. In *CME CLINICAL PHARMACOLOGY* (Vol. 16).

Consoli, A., & Formoso, G. (2015). Potential side effects to GLP-1 agonists: Understanding their safety and tolerability. In *Expert Opinion on Drug Safety* (Vol. 14, Issue 2, pp. 207–218). Informa Healthcare. https://doi.org/10.1517/14740338.2015.987122

Dahlén, A. D., Dashi, G., Maslov, I., Attwood, M. M., Jonsson, J., Trukhan, V., & Schiöth, H. B. (2022). Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. In *Frontiers in Pharmacology* (Vol. 12). Frontiers Media S.A. https://doi.org/10.3389/fphar.2021.807548

Davies, M. J., D'Alessio, D. A., Fradkin, J., Kernan, W. N., Mathieu, C., Mingrone, G., Rossing, P., Tsapas, A., Wexler, D. J., & Buse, J. B. (2018). Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the european association for the study of diabetes (EASD). In *Diabetes Care* (Vol. 41, Issue 12, pp. 2669–2701). American Diabetes Association Inc. https://doi.org/10.2337/dci18-0033

Deb, T., Chakrabarty, A., & Ghosh, A. (2017). Adverse drug reactions in Type 2 diabetes mellitus patients on oral antidiabetic drugs in a diabetes outpatient department of a tertiary care teaching hospital in the Eastern India. *International Journal of Medical Science and Public Health*, *6*(3), 1. https://doi.org/10.5455/ijmsph.2017.0423203102016

Faillie, J. L. (2019). Case–non-case studies: Principle, methods, bias and interpretation. *Therapie*, *74*(2), 225–232. https://doi.org/10.1016/j.therap.2019.01.006

Filippatos, T. D., Panagiotopoulou, T. v., & Elisaf, M. S. (2014). Adverse Effects of GLP-1 Receptor Agonists. In *The review of diabetic studies : RDS* (Vol. 11, Issues 3–4, pp. 202–230). https://doi.org/10.1900/RDS.2014.11.202

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of type 2 diabetes mellitus. In *International Journal of Molecular Sciences* (Vol. 21, Issue 17, pp. 1–34). MDPI AG. https://doi.org/10.3390/ijms21176275

Garber, A. J. (2011). Long-acting glucagon-like peptide 1 receptor agonists: A review of their efficacy and tolerability. In *Diabetes Care* (Vol. 34, Issue SUPPL. 2). https://doi.org/10.2337/dc11-s231

García-Compeán, D., González-González, J. A., Lavalle-González, F. J., González-Moreno, E. I., Maldonado-Garza, H. J., & Villarreal-Pérez, J. Z. (2015). The treatment of diabetes mellitus of patients with chronic liver disease. In *Annals of Hepatology* (Vol. 14, Issue 6, pp. 780–788). Fundacion Clinica Medica Sur. https://doi.org/10.5604/16652681.1171746

Hussain, R., Hassali, M. A., Ur Rehman, A., Muneswarao, J., & Hashmi, F. (2020). Physicians' understanding and practices of pharmacovigilance: Qualitative experience from a lower middle-income country. *International Journal of Environmental Research and Public Health*, *17*(7). https://doi.org/10.3390/ijerph17072209

Inácio, P., Cavaco, A., & Airaksinen, M. (2017). The value of patient reporting to the pharmacovigilance system: a systematic review. *British Journal of Clinical Pharmacology*, *83*(2), 227–246. https://doi.org/10.1111/bcp.13098

Jacobsen, L. v., Flint, A., Olsen, A. K., & Ingwersen, S. H. (2016). Liraglutide in Type 2 Diabetes Mellitus: Clinical Pharmacokinetics and Pharmacodynamics. *Clinical Pharmacokinetics*, *55*(6), 657–672. https://doi.org/10.1007/s40262-015-0343-6

Koole, C., Pabreja, K., Savage, E. E., Wootten, D., Furness, S. G. B., Miller, L. J., Christopoulos, A., & Sexton, P. M. (2013). Recent advances in understanding GLP-1R (glucagon-like peptide-1 receptor) function. *Biochemical Society Transactions*, *41*(1), 172–179. https://doi.org/10.1042/BST20120236

Kuritzky, L., Umpierrez, G., Ekoé, J. M., Mancillas-Adame, L., & Landó, L. F. (2014). Safety and efficacy of dulaglutide, a once weekly GLP-1 receptor agonist, for the management of type 2 diabetes. *Postgraduate Medicine*, *126*(6), 60–71. https://doi.org/10.3810/pgm.2014.10.2821

Ladenheim, E. E. (2015). Liraglutide and obesity: A review of the data so far. In *Drug Design, Development and Therapy* (Vol. 9, pp. 1867–1875). Dove Medical Press Ltd. https://doi.org/10.2147/DDDT.S58459

Lavertu, A., Vora, B., Giacomini, K. M., Altman, R., & Rensi, S. (2021). A New Era in Pharmacovigilance: Toward Real-World Data and Digital Monitoring. In *Clinical Pharmacology and Therapeutics* (Vol. 109, Issue 5, pp. 1197–1202). John Wiley and Sons Inc. https://doi.org/10.1002/cpt.2172

Meurer, W. J., & Tolles, J. (2017). Logistic regression diagnostics understanding how well a model predicts outcomes. In *JAMA - Journal of the American Medical Association* (Vol. 317, Issue 10, pp. 1068–1069). American Medical Association. https://doi.org/10.1001/jama.2016.20441

Nauck, M. A., Quast, D. R., Wefers, J., & Meier, J. J. (2021). GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art. In *Molecular Metabolism* (Vol. 46). Elsevier GmbH. https://doi.org/10.1016/j.molmet.2020.101102

Neumiller, J. J. (2009). Differential chemistry (structure), mechanism of action, and pharmacology of GLP-1 receptor agonists and DPP-4 inhibitors. In *Journal of the American Pharmacists Association : JAPhA: Vol. 49 Suppl 1*. https://doi.org/10.1331/JAPhA.2009.09078

Paliika, V. (2002). *PATHOPHYSIOLOGY OF DIABETES MELLITUS*.

Patino, C. M., & Ferreira, J. C. (2015). Intervalos de confiança: Uma ferramenta útil para estimar o tamanho do efeito no mundo real. In *Jornal Brasileiro de Pneumologia* (Vol. 41, Issue 6, pp. 565–566). Sociedade Brasileira de Pneumologia e Tisiologia. https://doi.org/10.1590/S1806-37562015000000314

Peterson, G. E., & Pollom, R. D. (2010). Liraglutide in clinical practice: Dosing, safety and efficacy. In *International Journal of Clinical Practice* (Vol. 64, Issue SUPPL. 167, pp. 35–43). https://doi.org/10.1111/j.1742-1241.2010.02498.x

Rabbur, R. S. M., & Emmerton, L. (2010). An introduction to adverse drug reaction reporting systems in different countries. *International Journal of Pharmacy Practice*, *13*(1), 91–100. https://doi.org/10.1211/0022357055821

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. In *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* (Vol. 14, pp. 3567–3602). Dove Medical Press Ltd. https://doi.org/10.2147/DMSO.S319895

Rothman, K. J., Lanes, S., & Sacks, S. T. (2004). The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiology and Drug Safety*, *13*(8), 519–523. https://doi.org/10.1002/pds.1001

Sarner, M., & Cotton, P. B. (1984). Classification of pancreatitis. *Gut*, *25*(7), 756–759. https://doi.org/10.1136/gut.25.7.756

Shaefer, C. F., Kushner, P., & Aguilar, R. (2015). User's guide to mechanism of action and clinical use of GLP-1 receptor agonists. *Postgraduate Medicine*, *127*(8), 818–826. https://doi.org/10.1080/00325481.2015.1090295

Swinnen, S. G., Hoekstra, J. B., & DeVries, J. H. (2009). Insulin therapy for type 2 diabetes. In *Diabetes care: Vol. 32 Suppl 2*. https://doi.org/10.2337/dc09-s318

Tan, X., Cao, X., Zhou, M., Zou, P., & Hu, J. (2017). Efficacy and safety of once-weekly semaglutide for the treatment of type 2 diabetes. *Expert Opinion on Investigational Drugs*, *26*(9), 1083–1089. https://doi.org/10.1080/13543784.2017.1360274

Vaduganathan, M., Patel, R. B., Singh, A., McCarthy, C. P., Qamar, A., Januzzi, J. L., Scirica, B. M., Butler, J., Cannon, C. P., & Bhatt, D. L. (2019). Prescription of Glucagon-Like Peptide-1 Receptor Agonists by Cardiologists. In *Journal of the American College of Cardiology* (Vol. 73, Issue 12, pp. 1596–1598). Elsevier USA. https://doi.org/10.1016/j.jacc.2019.01.029

van den Arend, I. J. M., Stolk, R. P., Krans, H. M. J., Grobbee, D. E., & Schrijvers, A. J. P. (2000). Management of type 2 diabetes: a challenge for patient and physician. In *Patient Education and Counseling* (Vol. 40). www.elsevier.com/locate/pateducou

Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., van Gaal, L. F., Lingvay, I., McGowan, B. M., Rosenstock, J., Tran, M. T. D., Wadden, T. A., Wharton, S., Yokote, K., Zeuthen, N., & Kushner, R. F. (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. *New England Journal of Medicine*, *384*(11), 989–1002. https://doi.org/10.1056/nejmoa2032183

Willard, F. S., Bueno, A. B., & Sloop, K. W. (2012). Small molecule drug discovery at the glucagon-like peptide-1 receptor. In *Experimental Diabetes Research* (Vol. 2012). https://doi.org/10.1155/2012/709893

Zhao, X., Wang, M., Wen, Z., Lu, Z., Cui, L., Fu, C., Xue, H., Liu, Y., & Zhang, Y. (2021). GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects. In *Frontiers in Endocrinology* (Vol. 12). Frontiers Media S.A. https://doi.org/10.3389/fendo.2021.721135

Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. In *Nature Reviews Endocrinology* (Vol. 14, Issue 2, pp. 88–98). Nature Publishing Group. https://doi.org/10.1038/nrendo.2017.151

Salem, J. E., Manouchehri, A., Bretagne, M., Lebrun-Vignes, B., Groarke, J. D., Johnson, D. B., Yang, T., Reddy, N. M., Funck-Brentano, C., Brown, J. R., Roden, D. M., & Moslehi, J. J. (2019). Cardiovascular Toxicities Associated With Ibrutinib. *J Am Coll Cardiol*, 74(13), 1667-1678. https://doi.org/10.1016/j.jacc.2019.07.056