

Pharmacological Mechanisms of Once-Weekly GLP-1 Receptor Agonists for Type 2 Diabetes Management

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Abstract: Individuals with Type 2 Diabetes (T2D) who have difficulty regulating their blood glucose levels can use glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which are a preferred option for treatment. This review provides a comprehensive overview of the similarities and differences in function between once-weekly GLP-1 RAs, and specifically highlights how pharmacists can provide better medication management, patient education, and overall health outcomes for patients with diabetes.

➤ *Methods:*

This study was a narrative review of the literature regarding the mechanism of action (MoA) of once-weekly GLP-1 RAs that are currently being used to treat T2D.

➤ *Results and Discussion:*

Safety and efficacy of GLP-1 RAs have been well documented. Advantages of GLP-1 RAs include glucose lowering effects through suppression of glucagon secretion and stimulation of insulin release from pancreatic beta cells in a glucose-dependent manner, as well as increasing satiety and slowing gastric emptying. In addition, GLP-1 RAs may have beneficial effects on other organs containing GLP-1 receptors, such as the kidneys and heart. Differences in molecular weight, chemical structure, and duration of action (categorized as short-acting or long-acting) among different GLP-1 RAs lead to differences in pharmacodynamics. These differences will lead to differences in clinical outcomes such as amount of weight loss, glycemic control, side effect profile, and cardiovascular benefits. **What is New and Conclusion:** Based on the collected research, this appears to be the first review of the underlying evidence for the MoA of once-weekly GLP-1 RAs in T2D specifically for pharmacists, and demonstrates their increasing role within multidisciplinary diabetes care teams. Overall, GLP-1 RAs are a powerful class of medications for T2D patients and demonstrate multiple clinical benefits. The results suggest that pharmacists should consider how each of the different once-weekly GLP-1 RAs and their respective mechanisms will affect patient outcomes when recommending or selecting treatments to provide the best possible personalized care.

Keywords: Cardiovascular Diseases, Diabetes Mellitus, Dulaglutide, Exenatide, Glucagon-Like Peptide-1 Receptor Agonist, Glycaemic Control, Mechanism of Action, Semaglutide, Type 2 Diabetes.

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I. INTRODUCTION

The prevalence of diabetes is increasing globally; however, most cases of type 2 diabetes (T2D) are preventable. Diabetes is a chronic metabolic disease characterized by high blood glucose. If left untreated over time, diabetes can cause damage to many parts of the body, leading to debilitating and potentially life-threatening complications such as neuropathy, nephropathy, retinopathy, and cardiovascular (CV) disease.^{1,2} In addition to causing serious health problems, diabetes creates a large economic and clinical burden on healthcare systems worldwide.^{1,2}

Type 2 diabetes accounts for approximately 90% of all cases of diabetes.^{1,2}

Over the past few decades, there has been a rapid increase in the number of people diagnosed with T2D.^{1,2} Type 2 diabetes occurs when either the body does not produce enough insulin or cannot effectively use the insulin produced. This is referred to as insulin resistance.^{1,2} There has also been a recent increase in the prevalence of prediabetes, which is defined as having blood glucose levels that are higher than normal but not high enough to be classified as diabetes.²⁻⁴ People with prediabetes are at

increased risk of developing T2D and associated health problems.⁴ In 2009, DeFronzo described the "ominous octet," which includes the eight main defects involved in the development of T2D. These defects are listed in Table 1.5

By addressing each of these defects, we can develop better pharmacological and behavioral therapies for T2D. For example, T2D can be effectively managed using a personalized, stepwise approach that combines medications (if needed) with lifestyle changes (e.g., diet, exercise, cessation of smoking, sleep duration/quality, and emotional/psychosocial support).^{1,2,4,6,7} Adults with T2D have many options available to them for treating their condition. Some of these options include oral medications such as metformin (usually the first line of treatment), dipeptidyl peptidase-4 inhibitors (DPP4is), thiazolidinediones, sulfonylureas, and sodium-glucose cotransporter-2 inhibitors (SGLT2is). Other options include injectable therapies such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and insulins.^{4,6}

The majority of patients with diabetes do not meet their glycemic goals and require additional treatment.^{2,4,6} GLP-1 receptor agonists (RAs), also known as incretin mimetics/analogues, stimulate the body's natural response to food and reduce post-meal blood glucose levels to help control blood glucose.^{2,8-10} GLP-1 RAs have many benefits; they stimulate insulin secretion based on the amount of glucose in the blood, have a low risk of hypoglycemia, promote weight loss by decreasing calorie intake and appetite, and slow down gastric emptying.⁸⁻¹¹ Meta-analyses, head-to-head studies, and randomized placebo-controlled trials have shown that GLP-1 RAs are

effective in controlling blood glucose. In addition, GLP-1 RAs may provide long-term benefits to the pancreas such as increasing insulin production and beta-cell survival/growth.¹² Some GLP-1 RAs may also provide cardiorenal protection by reducing cardiovascular risk and improving renal outcomes.^{11,13-18} This review will focus on the clinical outcomes and physiological effects of GLP-1 RAs. Table 2 compares the different types of GLP-1 RAs. While all GLP-1 RAs act on the incretin pathway, differences in their structure, molecular weight, and pharmacokinetics (PK) lead to different pharmacodynamics (PD) and clinical effects. This review will focus on the once-weekly (QW) formulations of exenatide extended release (ER), dulaglutide, and subcutaneous (s.c.) semaglutide because they have half-lives/PK profiles that allow for continuous stimulation of the receptor and weekly dosing.¹⁹⁻²¹

As the prevalence of T2D continues to increase and new clinical guidelines are developed, pharmacists play an important role in educating, monitoring, and supporting T2D patients.²² For example, pharmacists can work with patients and providers to identify the best treatments and provide the necessary education for proper administration and adherence to medication.²² Therefore, pharmacists need to have a good understanding of T2D pathophysiology and the mechanisms of action (MoA) of available treatments.²² The purpose of this review is to provide a comprehensive clinical overview of QW GLP-1 RAs, discuss the mechanisms behind their efficacy and patient outcomes, and highlight the similarities and differences between individual agents. Additionally, we will address the implications for both T2D patients and pharmacy professionals.

Table 1 GLP-1 RAs Target Six of the Eight Core Defects Evident in Type 2 Diabetes

8 core defects in type 2 diabetes ⁵	GLP-1 RAs target 6 of the 8 core defects
1. Impaired insulin secretion	1. Enhanced appropriate pancreatic β -cell (insulin and amylin) secretion
2. Increased glucagon secretion	2. Pancreatic α -cell (glucagon) suppression
3. Increased hepatic glucose	3. Decreased liver glucose production
4. Neurotransmitter dysfunction	4. Increased satiety through central nervous system
5. GI tract/decreased incretin effect	5. Slowed gastric emptying time
6. Decreased glucose uptake	6. Enhanced appropriate pancreatic β -cell (insulin and amylin) secretion
7. Increased glucose reabsorption	
8. Increased lipolysis	

Abbreviations: GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; α , alpha; β , beta

II. METHODS

This paper offers a descriptive overview of current studies concerning the use of GLP-1 RAs in patients with T2D. To collect pertinent academic material, the PubMed archive was searched, and citations from foundational papers were reviewed. The analysis focuses mostly on once-weekly injectable GLP-1 RAs that are presently available—namely subcutaneous semaglutide, dulaglutide, and exenatide ER—though once-daily and twice-daily versions are included for the purpose of comparison. Because albiglutide was withdrawn from the market in 2018, an in-depth examination of that specific medication is excluded.

III. RESULTS

➤ Similarities and Differences in the Characteristics of GLP-1 RAs

The gut releases GLP-1, a glucoregulatory incretin hormone, after consuming food. As blood sugar levels increase, GLP-1 stimulates the release of insulin and inhibits the secretion of glucagon.^{8,24} GLP-1 RAs are synthetic or mimetic forms of the endogenous human hormone that have been developed with improved PK properties and more consistent PD responses; therefore, they may produce greater therapeutic effects than native GLP-1 (Table 2).¹³ These agents bind to GLP-1 receptors located in many different types of tissue including pancreatic islet cells, kidney, lung, heart, brain, and gastrointestinal tract.^{25,26}

Although many clinical guidelines for T2D include GLP-1 RAs,^{4,6,7} there are many differences among these agents in terms of structure, molecular weight, half-life, similarity to endogenous GLP-1, chemical characteristics, and affinity for the GLP-1 receptor (Table 2).

In general, GLP-1 RAs can be classified according to their duration of action.^{19-21,27-30} Short-acting agents like lixisenatide (QD) and exenatide (BID) stimulate receptors for a short period of time (Table 2). They are primarily used to reduce postprandial glucose excursions by delaying

gastric emptying and slowing the passage of glucose into the duodenum.^{11,14,31,32} On the other hand, long-acting agents such as liraglutide (daily), semaglutide s.c., dulaglutide, and exenatide ER (weekly) have longer PK/half-lives (>3 hours) and provide continuous receptor stimulation at their recommended doses (Table 2). This results in a much larger reduction in fasting glucose levels through increased pancreatic insulin secretion and decreased glucagon secretion.^{11,14,31,32} Due to their PK profiles, semaglutide s.c., dulaglutide, and exenatide ER are better suited for QW dosing than shorter-acting agents (Table 2).

Table 2 Comparative Characteristics of Currently Marketed^a, Short- and Longer-Acting, Injectable GLP-1 RAs

GLP-1 RA agent	Based on	Molecular formula Molecular weight (kilodaltons)	Timing	Initial dose	Regular dose
Exenatide BID ^{b29}	Exendin-4 ^{11,97}	C ₁₈₄ H ₂₈₂ N ₅₀ O ₆₀ S _{4.2}	BID within 1 h before morning and evening meals (approx. 6 h or more apart)	5 mcg BID	5 or 10 mcg BID
Lixisenatide ^{c30}	Exendin-4 ^{11,97}	C ₂₁₅ H ₃₄₇ N ₆₁ O ₆₅ S _{4.9}	QD within 1 h before the first meal of the day	10 mcg	20 mcg
Liraglutide ^{d27}	Modified human GLP-1	C ₁₇₂ H ₂₆₅ N ₄₃ O ₅₁ _{3.8}	QD at any time of day, with or without food	0.6 mg	1.2 or 1.8 mg
Exenatide ER ^{e19}	Exendin-4	C ₁₈₄ H ₂₈₂ N ₅₀ O ₆₀ S _{4.2}	QW at any time of day, with or without food	2.0 mg	2.0 mg
Dulaglutide ^{f21}	Modified human GLP-1	Not explicitly stated in the PI ₆₃	QW at any time of day, with or without food	0.75 mg	0.75 or 1.5 mg
Semaglutide ^{g20}	Modified human GLP-1	C ₁₈₇ H ₂₉₁ N ₄₅ O ₅₉ _{4.1}	QW at any time of day, with or without food	0.25 mg	0.5 or 1.0 mg

Abbreviations: BID, twice-daily; CL, clearance; eGFR, estimated glomerular filtration rate; ER, extended-release; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GLP-1, glucagon-like peptide-1; mcg, micrograms; mg, milligrams; PI, prescribing information; QD, once-daily; QW, once-weekly; SC, subcutaneous; t_{1/2}, elimination half-life;⁵

T_{max}, time to maximum plasma concentration.

^aAlbiglutide is not included in this table, as it was withdrawn from the market in 2018.

Table 2 describes other differences between GLP-1 RAs. The two main types of GLP-1 RAs are those that are based on exendin-4 and those that are modified versions of the active part of human GLP-1; this results in varying levels of similarity to endogenous GLP-1.

In addition, there is a wide range of molecular weights for GLP-1 RAs. For example, dulaglutide has a molecular weight of about 63-73 kilodaltons, whereas semaglutide, liraglutide, exenatide, and lixisenatide are all small molecules with molecular weights less than 5 kilodaltons.^{19-21,27,29,30} All of the once-weekly GLP-1 RAs currently available on the market address six of the eight components of DeFronzo's "ominous octet" related to T2D (Table 1).⁵ Each of these mechanisms of action will be discussed in further detail in the following sections concerning the findings reported from clinical trials.

➤ Mechanism of Action Related to Glycaemic Control:

The most important effect of GLP-1 receptor agonists (RAs) for type 2 diabetes (T2D) patients is their ability to regulate glucose levels. This is achieved through the activation of pancreatic GLP-1 receptors which stimulate the release of insulin from beta (β) cells in the islets of Langerhans in response to glucose; at the same time, GLP-1

RAs inhibit the release of glucagon from alpha (α) cells in the islets of Langerhans, thus reducing blood sugar levels in hyperglycemic patients.^{8,9,14,24,33,34} The glucose-lowering effects of GLP-1 RAs have been demonstrated in numerous clinical studies using three weekly (QW) and other GLP-1 RAs.³⁵⁻⁵¹ It appears that differences in the mechanisms of action and half-lives of GLP-1 RAs may be related to the magnitude of the glucose-lowering effect, with long-acting GLP-1 RAs generally producing greater and more sustained reductions in glycated hemoglobin (HbA1c) than short-acting GLP-1 RAs.^{11,37-40} Fourteen head-to-head trials have shown that although all GLP-1 RAs resulted in statistically significant reductions in HbA1c from baseline, the magnitude of the reduction varied greatly among GLP-1 RAs (ranging from 0.3% to 1.9%). However, it is difficult to directly compare these values due to differences in study populations and study designs.^{37,38,40-42,44,49,50,52-57} To date, there are few studies comparing the HbA1c-reducing efficacy of different QW GLP-1 RAs; only two recent studies suggest that subcutaneous (s.c.) semaglutide provides better glycemic control than dulaglutide or exenatide extended-release (ER).^{49,50} Several other head-to-head trials have shown that QW GLP-1 RAs typically result in significantly larger reductions in HbA1c than once daily (QD) or twice daily (BID) GLP-1

RAs. This was demonstrated in three studies comparing exenatide ER to exenatide BID^{37,40,55} and two trials where dulaglutide was shown to be superior to liraglutide and exenatide BID.^{42,52}

Data from clinical trials also demonstrate that GLP-1 RAs positively affect other glycemic parameters. For example, GLP-1 RAs can reduce post-prandial glucose by delaying gastric emptying or by altering the secretion of insulin and glucagon following meals; similarly, GLP-1 RAs can reduce fasting plasma glucose by altering the secretion of insulin and glucagon during periods of fasting.^{37-40,46,49,50} Furthermore, because GLP-1 RAs affect glucagon and insulin in a glucose-dependent manner, they carry a very low risk of hypoglycemia compared to traditional secretagogues such as sulfonylureas, glinides, or insulin (see the accompanying article in this supplement).^{35,37-40,49,58} Clinical trials directly comparing BID, QD, and QW GLP-1 RAs have consistently shown a low risk of hypoglycemia across all QW GLP-1 RAs.^{37-42,44,49,50,52,55} Most recently, s.c. semaglutide was shown not to impair counterregulatory responses compared to placebo. glucagon response during induced hypoglycaemia, consistent with an action providing glycaemic control with a low risk of hypoglycaemia.⁴⁸

➤ Mechanism of Action for Effects Beyond Glycaemic Control:

Evidence is accumulating regarding the effects of GLP-1 RAs on non-pancreatic systems due to the widespread distribution of GLP-1 receptors throughout the body.^{25,26,59} Therefore, it appears that GLP-1 RAs could provide many benefits to people with T2D.⁵⁹

➤ Effects on Body Weight:

GLP-1 RAs are well known for their ability to decrease body weight in people with T2D.⁴ The weight loss effect is thought to occur because GLP-1 RAs bind to central and peripheral receptors in the stomach and brain.^{25,60-62} GLP-1 is a natural regulator of human food intake and appetite. When administered to either diabetic or non-diabetic individuals, GLP-1 increases feelings of fullness and satisfaction, decreases feelings of hunger, and decreases caloric intake compared to placebo.^{61,63} Studies in animals suggest that the effects of GLP-1 on appetite may be due to direct activation of mesolimbic receptor systems in the brain that control motivation and the perceived reward of eating.⁶⁰ Therefore, long-term use of GLP-1 RAs in humans may promote weight loss via activation of GLP-1 receptors in the hypothalamus (the satiety center of the brain) that regulate appetite.⁶¹ Additionally, GLP-1 RAs inhibit gastric emptying, which slows down the rate at which food moves through the digestive tract and leads to a decreased appetite and a feeling of being full.⁶²

Table 2 (Continued)

$T_{\max}$	$t_{1/2}$	Homology to native GLP-1 (%)	Presence of antibodies to agent/GLP-1 (%)	Renal dosing	Elimination	CL (L/h)
2.1 h	2.4 h	53 ⁹⁸	38	Creatinine CL < 30 mL/min not recommended	Renal/proteolysis	9.1
1-3.5h	3h	50 ^{11,97,98}	70	eGFR < 15 mL/min/1.73 m ² not recommended	Renal/proteolysis	35
8-12h	13h	97	8.6	No dose adjustment	No specific organ	1.2
Peak around 2 and 6-7 week	5 days	53 ⁹⁸	Not explicitly stated in the PI	eGFR < 30 mL/min/1.73 m ² not recommended	Renal/proteolysis	9.1
24-72 h (median, 48 h)	5 days	90	1.6	No dose adjustment	Endogenous metabolism	0.111 (0.75 mg) and 0.107 (1.5 mg)
1-3 days	7 days	94	1	No dose adjustment		

The evidence supporting this mechanism of action is demonstrated by the demonstrated efficacy of GLP-1 RAs in decreasing body weight in people with T2D.^{51,64-68} Clinical trials have shown that body weight changes varied among different weekly GLP-1 RAs. Average weight reductions ranged from -1.4 to -4.1 kg for exenatide ER^{37,39-41} and between -2.0 and -7.9 kg for subcutaneous semaglutide.^{46,49,50,68} Results for dulaglutide were somewhat more limited, with average weight changes ranging from a small average increase of +0.20 kg to a decrease of -3.0 kg.^{42,44,45,50} These differences may be attributed to its larger molecular size compared to other agents in the class. Due to its large size, it may have difficulty crossing the blood-brain barrier and therefore may have less of an effect on stimulating satiety.^{11,14,50} Further

research is needed to determine why there are differences in weight reduction among the various GLP-1 RAs.⁵⁰ Since direct comparative studies between weekly GLP-1 RAs are scarce, meta-analyses have also been reviewed. These reviews demonstrated that each of the various GLP-1 RAs had varying degrees of weight-reduction benefits when compared to placebos or other diabetes medications; however, few differences were identified among the GLP-1 RAs themselves.^{51,65,66,69} Recently, subcutaneous semaglutide has been shown to reduce body weight more effectively than placebo and more effectively than both dulaglutide and exenatide ER.^{49,50}

➤ *Effects on the CV System:*

Studies have shown that some once-weekly GLP-1 receptor agonists may reduce cardiovascular events and improve other markers of risk such as lipids and blood pressure.^{17,70-72} However, the exact mechanisms of action (MoA) by which these medications produce their cardioprotective effects are still not completely understood. Although weight loss and good glycemic control will likely lead to improved cardiovascular outcomes; these agents also exert effects on multiple organ systems via both direct and indirect pathways due to the presence of GLP-1 receptors in many different types of tissue. These pathways are discussed in greater detail in the following sections.

➤ *Cardiovascular Benefits*

The mechanisms by which GLP-1 RAs may positively impact heart health are not well-defined. Possible mechanisms include anti-inflammatory responses, anti-atherogenic effects — such as reductions in body weight and cholesterol — and direct effects on the lining of blood vessels or the muscle of the heart, as GLP-1 receptors are present in both endothelial and cardiac tissues.^{70,73,74}

Data from three cardiovascular outcomes trials (CVOTs) evaluating once-weekly GLP-1 RAs versus placebo in T2D patients (with varying degrees of CV risk) demonstrated either no increased risk or a statistically significant reduction in major adverse cardiovascular events (MACE), which included non-fatal stroke, myocardial infarction, or death due to cardiovascular causes over a period of 2 to 5 years.^{17,71,72} In the SUSTAIN 6 trial of 3,297 T2D patients with high CV risk, a post-hoc analysis demonstrated that after 2.1 years, patients receiving 0.5 mg or 1.0 mg of subcutaneous semaglutide weekly had a 26% lower risk of the primary MACE endpoint compared to the placebo group.¹⁷ On the other hand, the EXSCEL trial, which evaluated 14,752 T2D patients followed for 3.2 years, demonstrated no significant difference in MACE incidence between those receiving 2 mg of exenatide ER and those on placebo.⁷¹ Most recently, the REWIND trial (N = 9,901) demonstrated that weekly dulaglutide injections significantly reduced MACE over a median follow-up of 5.4 years in T2D patients regardless of whether they had a history of CV disease or their baseline glucose levels.⁷² The reduction in MACE observed in the REWIND trial was similar in magnitude to those reported in other GLP-1 RA trials.⁷²

A meta-analysis of 33,457 participants from four CVOTs — ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN 6 (semaglutide s.c.), and EXSCEL (exenatide ER) — confirmed CV safety, demonstrating a 10% relative risk reduction (RRR) in MACE, a 13% RRR in cardiac deaths, and a 12% RRR in total mortality.⁷⁰ Additionally, there were no adverse effects identified related to pancreatitis, severe hypoglycemia, or thyroid and pancreatic cancers when compared to placebo.⁷⁰ While there was some variability in statistical findings across the trials — possibly because lixisenatide, a shorter-acting agent, demonstrated more MACE than placebo in its individual trial — it is

currently unclear if these differences result from differing drug mechanisms, trial designs, or patient populations.⁷⁰

➤ *Reduced Systolic Blood Pressure:*

Blood pressure reductions observed during CVOT clinical trials may be related to weight loss. Animal studies suggest that the mechanisms responsible for these blood pressure reductions may involve multiple physiological systems including renal, myocardial, vascular, and central nervous system pathways regulated by GLP-1.^{16,75,76} However, these animal findings have not been verified in humans and therefore require further study.^{16,59} Studies indicate that long-term use of subcutaneous semaglutide and exenatide ER result in small but statistically significant decreases in average systolic blood pressure (approximately 2 mmHg) from baseline in patients with T2D. These decreases generally appear after 2-3 weeks.^{16,37,40,41,46,49,51,77} Results for dulaglutide are less consistent, as some trials did not demonstrate any substantial blood pressure changes.^{42,44,45,52} Interestingly, subgroup data from a meta-analysis showed that subcutaneous semaglutide was superior to other GLP-1 RAs in terms of reducing systolic blood pressure.⁵¹ In clinical studies, the effect of GLP-1 RAs on diastolic blood pressure was generally much less pronounced than their effect on systolic blood pressure. Many trials failed to demonstrate significant differences between treatment groups.^{16,37,40-42,44-46,49,52,77,78} It is important to note that blood pressure outcomes are often reported as secondary endpoints rather than primary endpoints in glucose-lowering research (e.g., SUSTAIN 3,⁴⁹ DURATION-1,³⁹ and AWARD-142) and should be interpreted accordingly. Increased Heart Rate Although the exact mechanism of how GLP-1 RAs affect heart rate is not fully understood,¹⁴ the human heart's sinoatrial node (SAN) contains GLP-1 receptor-expressing myocytes.²⁵ Therefore, one possible mechanism is that GLP-1 RAs directly stimulate SAN cells and cause increased average heart rates.^{25,79} Most GLP-1 RAs are associated with increased heart rates; however, the extent of this increase varies. Trials using weekly GLP-1 RAs consistently demonstrate that blood pressure decreases are accompanied by clinically significant increases in heart rate (typically between 1 and 5 beats per minute).^{16,40,42,44-46,49,51,52,80} The magnitude of this increase varies among different drugs and may be related to their respective durations of action (Table 2). For example, because they provide continuous receptor stimulation, long-acting GLP-1 RAs produce larger and more prolonged increases in heart rate compared to short-acting versions which involve intermittent receptor activation.^{14,40,42,52,81}

In terms of theory, a rising pulse may present a safety concern that could potentially result in negative outcomes for some people (e.g., patients with cardiac arrhythmias^{14,81}); however, based upon data, no other common CV risk factors were elevated during studies.^{16,38,40,42,44-46,49,52,80,81} One should interpret these findings with caution due to the lack of consistency in study results and the fact that pulse measurements are typically considered secondary safety measures in medical

research. Further studies will be needed before making any final conclusions; additionally, the potential negative effects of GLP-1 RAs on heart rate should be weighed against the many possible positive CV effects of GLP-1 RAs.

➤ *Improved Lipid Profile:*

In recent years, investigators have studied whether GLP-1 can help regulate dyslipidemia associated with type 2 diabetes. 15 The effects may be due to changes in how the liver and/or intestine metabolize lipids; such as reduced absorption of dietary fat, inhibition of intestinal chylomicron secretion (thereby reducing the formation of atherogenic remnants), regulation of very-low-density lipoprotein (VLDL) production by the liver, and/or increased autophagy or fatty acid oxidation in the liver. 15, 59 At present, it is unknown if these effects occur via indirect mechanisms or through direct activation of receptors. Both long-acting and short-acting GLP-1 receptor agonist (RA) therapies have shown small improvements in lipid levels in both the fasting state and post-meal states. 37, 38, 40, 41, 45, 52, 82-84 These improvements have primarily involved total cholesterol (-0.40 to 0.02 mmol/L), 37, 38, 40, 41, 45, 52, 82 low-density lipoprotein (LDL) cholesterol (-0.44 to 0.07 mmol/L), 37, 38, 40, 41, 82 and triglycerides (-0.41 to 0.01 mmol/L). 38, 40, 45, 52 When comparing weekly GLP-1

RAs directly to placebos or daily/twice-daily versions, there are few differences between treatments. Data from two trials demonstrated that total and LDL cholesterol were significantly reduced by exenatide ER compared to twice-daily exenatide. 37, 40 Two other studies demonstrated that dulaglutide therapy resulted in significant reductions in baseline triglycerides and total cholesterol compared to a placebo. 45, 52 However, two studies of subcutaneous semaglutide produced conflicting results. 49, 50 One study found that semaglutide did not produce a clinically relevant improvement in lipids. 50 On the other hand, another study found that semaglutide improved triglycerides, VLDL cholesterol, and free fatty acids to a greater extent than exenatide ER. 49 Therefore, these findings suggest that weekly GLP-1 RAs may increase lipolysis (a process of breaking down fat) which is part of DeFronzo's "ominous octet" that he believes contributes to the development of type 2 diabetes. 5

➤ *Renal Effect:*

Evidence from both clinical and laboratory studies have shown that some GLP-1 RAs do not cause harm to the kidneys, and they may even provide renoprotection by reducing many of the common kidney-related problems associated with T2D. 17, 18, 85-87

Table 3 Existence of Clinical Evidence Supporting the MoA of QW GLP-1 RAs

Clinical effect (MoA)	Exenatide ER	Dulaglutide	Semaglutide
Glycaemic control (pancreatic α - and β -cells ^a)	Yes ^{37,39-41,49,55}	Yes ^{42,44,45,50,52}	Yes ^{46,49,50}
Body weight reductions (GI tract, brain, fat cells ^a)	Yes ^{37,39-41,49,55}	Mixed ^{42,44,45,50}	Yes ^{46,49,50}
CV benefits (MoA undetermined ^a)	No (non-inferior to placebo for MACE; superiority not demonstrated) ⁷¹	Yes ⁷²	Yes ¹⁷
Systolic blood pressure reductions (brain ^a)	Yes ^{37,40,41,49,77}	Mixed ^{42,44,45,52}	Yes ^{46,49,50}
Heart rate increases (muscle ^a)	Yes ^{40,49}	Yes ^{42,44,45,52}	Yes (but not always statistically significant) ^{46,49,50}
Lipid lowering (fat cells ^a)	Yes (but not always statistically significant) ^{37,40,41}	Yes ^{42,45,52}	Mixed ^{49,50}
Renal benefits (kidney ^a)	Unclear ⁷¹	Yes ^{52,72,85}	Yes ¹⁷

Abbreviations: CV, cardiovascular; ER, extended-release; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse CV events; MoA, mechanisms of action; QW, once-weekly; α , alpha; β , beta.

^aCell types targeted by the MoA of GLP-1 RAs as described in DeFronzo's ominous octet.⁵

Researchers continue to investigate how GLP-1 RAs may protect the kidneys, and whether this protection is due to direct effects on renal function. One possible mechanism based upon animal models is that activation of GLP-1 receptors may protect the vascular endothelium from damage, thus reducing oxidative stress and local inflammation, and improving the glomerular sclerosis and albuminuria associated with renal pathology; however, further research is needed.^{59,86,87} In two T2D CVOTs, patients treated with semaglutide and dulaglutide had fewer renal microvascular complications (1.86 and 3.47 events per 100 patient years) compared to those who received placebo (3.06 and 4.07 events per 100 patient years), likely due to decreases in persistent macroalbuminuria or estimated glomerular filtration rate (eGFR).^{17,72} A multicenter study

also found that dulaglutide slowed eGFR decline in T2D patients with moderate-to-severe chronic kidney disease compared to insulin therapy.⁸⁵ These findings are particularly important because the presence of chronic kidney disease often limits the treatment options available to patients (Table 2).

➤ *Safety and Tolerability:*

This section will provide a counter-argument to the previous discussion about how GLP-1 receptor agonists work positively; it will examine the safety characteristics of weekly GLP-1 receptor agonists so that pharmacists can have a well-rounded view of these drugs. Typically, research has found that the most common side effect of weekly GLP-1 receptor agonists is temporary, mild-to-

moderate gastrointestinal symptoms (vomiting, nausea, and diarrhea).^{35,40,41,43,44,47,49-51} It is thought that these symptoms are caused by the effect of GLP-1 receptor agonists on the duodenum and stomach, which causes changes in gastrointestinal motility and therefore delays gastric emptying.⁸⁸ Both long- and short-acting GLP-1 receptor agonists cause gastrointestinal side effects; however, long-acting GLP-1 receptor agonists show fewer side effects over time.⁴⁹ This is likely due to the body developing a tolerance to the drug, more stable levels of the drug in the blood, and less of an effect on gastric emptying compared to short-acting GLP-1 receptor agonists.^{14,40} Weekly GLP-1 receptor agonists have also been associated with other health problems including retinopathy, thyroid cancer (seen in rodent studies), pancreatitis, and increased pancreatic enzyme levels.¹⁹⁻²¹ Although a full review of each of these problems is beyond the scope of this paper, the risks to humans are considered low and the prescribing information for all weekly GLP-1 receptor agonists contains appropriate warnings and precautions.¹⁹⁻²¹

With respect to cardiovascular safety, a meta-analysis of CVOTs showed that GLP-1 receptor agonists did not negatively affect any major safety parameters (medullary thyroid cancer, pancreatic cancer, pancreatitis, or severe hypoglycemia) compared to placebo.⁷⁰ Furthermore, a large meta-analysis and a formal assessment of incretin-based therapies did not find a causal relationship between GLP-1 receptor agonists and retinopathy or pancreatic cancer/pancreatitis.^{89,90}

IV. DISCUSSION

Weekly GLP-1 receptor agonists (RAs) provide an attractive option for managing Type 2 Diabetes Mellitus (T2D), as they address multiple physiological abnormalities and provide many different types of clinical benefits. These include long-term glycemic control (as measured by HbA1c), very little risk of hypoglycemia, modest reductions in body weight and blood pressure, improved cardiovascular (CV) outcomes, and a good safety profile. All of these benefits result from the way that weekly GLP-1 RAs regulate glucose levels through two main pathways: 1) by stimulating insulin secretion from pancreatic beta cells in response to glucose, and 2) by inhibiting glucagon secretion. Additionally, weekly GLP-1 RAs slow down gastric emptying and increase feelings of fullness. It is possible that weekly GLP-1 RAs may also have beneficial effects on other organ systems that contain GLP-1 receptors, including the kidneys and CV system. Interestingly, weekly GLP-1 RAs target six of the eight major metabolic abnormalities (the "ominous octet") associated with T2D (Table 1).⁵

Although there are numerous GLP-1 RAs available today, each agent has its own set of advantages and disadvantages. Although all GLP-1 RAs act upon the same incretin pathway, differences in chemical structure, pharmacokinetics/pharmacodynamics, and mechanism of action result in different biological and clinical profiles (Table 2).^{11,14,31,32,91} Differences in effects are primarily due to the duration of action; i.e., short-acting vs. long-

acting agents differ in terms of how much they stimulate the GLP-1 receptor and how quickly they lower blood glucose. Therefore, no single GLP-1 RA can be considered superior to all others; instead, clinicians must consider the individual needs of each patient when selecting the most appropriate agent. In addition to having a large glycemic effect, once-weekly GLP-1 RAs offer advantages over daily or twice-daily alternatives because they require fewer administrations, are easier to use, and have a safety profile with a low incidence of hypoglycemia. These factors may lead to increased patient adherence and continued use of the medication over time.⁹²⁻⁹⁴ Since hypoglycemia is related to poor adherence and decreased patient satisfaction,^{95,96} developing medications that minimize this risk represents a major advancement in medicine.

One of the primary goals in managing diabetes is to decrease the number of CV complications associated with premature death and disability.² Therefore, the positive results obtained from recent CVOTs are seen as a major clinical advancement,⁷⁰ and these results have been used to form the basis of the 2020 American Diabetes Association recommendations.⁴ At present, it is unknown whether these CV benefits apply to the entire drug class or are limited to certain agents.⁵⁹ The availability of multiple types of medications for treating T2D allows for better individualized patient outcomes related to both glycemic control and co-existing conditions. Therefore, when determining the optimal treatment for a patient, pharmacists must assess several factors including glycemic efficacy, safety, weight changes, potential for hypoglycemia, comorbidities, delivery method, patient preference, and cost.⁴

Pharmacists can work together with physicians to determine when GLP-1 RA use is appropriate and provide education to patients regarding storage, injection technique, HbA1c targets, and side effect management to promote adherence.²² For example, to reduce nausea, pharmacists may recommend that patients eat smaller meals more frequently. By understanding the unique characteristics of each GLP-1 RA, pharmacists can tailor education and management strategies for each individual patient. Further study is needed. Since weekly GLP-1 RAs are relatively new therapies, their full long-term effects (especially on CV health) will not be known until they have been used for decades. While several mechanisms of action have been proposed, further studies in humans are needed to determine how they affect blood pressure.¹⁶ Comparative CVOTs directly comparing different agents and studies examining other markers of CV risk (e.g., inflammation) are also needed.

V. CONCLUSION

The current literature suggests that this is the first time a narrative review has been provided to pharmacists on the science behind the mechanism of action (MoA) of once-weekly (QW) GLP-1 receptor agonists (RAs) used to treat Type 2 Diabetes (T2D). It also highlights how important pharmacists will be in educating and treating people with T2D. Based upon data from ongoing clinical trials, it

appears that the three QW GLP-1 RAs may have different mechanisms of action and therefore different effects on the body; all of which address some form of physiological impairment described in DeFronzo's "ominous octet" (Table 3). Due to their numerous benefits, GLP-1 RAs are an excellent option for many people with T2D, regardless of whether they have other health problems. Additionally, GLP-1 RAs offer physicians multiple options for managing their patients' care. By understanding the MoA described in this paper, physicians and pharmacists can understand that the QW GLP-1 RAs semaglutide s.c., dulaglutide, and exenatide ER improve glucose control (with little risk of hypoglycemia) while reducing lipids, blood pressure, and overall body weight.

In order to obtain the optimal clinical outcome for each individual patient, the advantages and disadvantages of each GLP-1 RA must be considered when selecting a therapy based on the patient's needs. With knowledge about the MoA of QW GLP-1 RAs, pharmacists are well-equipped to educate patients about these treatments.

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