Received: 5 February 2020 | Revised: 24 April 2020 | Accepted: 10 May 2020

DOI: 10.1111/jcpt.13230

REVIEW ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

A review of GLP-1 receptor agonists in type 2 diabetes: A focus on the mechanism of action of once-weekly agents

Susan Cornell BS, PharmD, CDE, FAPhA, FAADE

Chicago College of Pharmacy, Midwestern University, Downers Grove, IL, USA

Correspondence
Susan Cornell, Chicago College of Pharmacy, Midwestern University, 555 W. 31 Street, Alumni Hall 355, Downers Grove, IL 60515.
Email: scorne@midwestern.edu

Funding information
Novo Nordisk Inc., Plainsboro, New Jersey, USA, funded the medical writing support for this review.

Abstract

What is known and objective: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are one of the preferred approved treatment options for people with type 2 diabetes (T2D) and inadequate glycaemic control. The objective of this review is to provide a general clinical overview of the similarities and differences in the mechanisms of action (MoA) of the once-weekly GLP-1 RA class of medications, highlighting the role of pharmacists in providing optimal medication management, education and care for people with diabetes.

Methods: This is a narrative review of the published literature regarding the MoA of the currently available once-weekly GLP-1 RAs in T2D.

Results and discussion: GLP-1 RAs have an established efficacy and safety profile. Their benefits derive from their blood glucose-lowering effects, which include pancreatic beta-cell-mediated glucose-dependent insulin secretion and suppressed glucagon release, and their ability to slow gastric emptying and promote satiety. GLP-1 RAs may also exert beneficial effects on multiple organ systems in which GLP-1 receptors are present, including the cardiovascular and renal systems. Differences between individual GLP-1 RAs with regard to their molecular size, structure and duration of action (short or longer acting) have led to differing pharmacodynamics and clinical effects such as degree of glycaemic control, weight loss abilities, cardiovascular effects and tolerability profiles.

What is new and conclusion: From the literature, this appears to be the first review of the evidence base supporting the MoA of once-weekly GLP-1 RAs in T2D aimed at pharmacists, with a particular emphasis on the expanding role of pharmacists in team-based diabetes management. As a class, GLP-1 RAs are an effective treatment option for people with T2D, shown to achieve multi-factorial clinical benefits. The results suggest that when selecting or advising about treatments, pharmacists should consider how the different once-weekly GLP-1 RAs and their MoA affect clinical outcomes in order to ensure optimal treatment for individuals.

KEYWORDS
cardiovascular diseases, diabetes mellitus, dulaglutide, exenatide, glucagon-like peptide-1 receptor agonist, glycaemic control, mechanism of action, semaglutide, type 2 diabetes

1 | WHAT IS KNOWN AND OBJECTIVE

Diabetes mellitus is a chronic and progressive metabolic disease characterized by raised levels of glucose in the blood, which, if left untreated over time, can damage various body organs leading to disabling and life-threatening complications such as cardiovascular (CV) disease, neuropathy, nephropathy and retinopathy.[1,2] Diabetes also imposes a substantial clinical and economic burden on the global healthcare system.[1,2]

Even though it is largely preventable, type 2 diabetes (T2D) accounts for around 90% of diabetes cases.[1,2] Furthermore, the prevalence of T2D has risen dramatically over the past few decades.[1,2] T2D occurs when the body cannot produce enough of the hormone insulin or effectively use the insulin it produces, defined as insulin resistance.[1,2] Prediabetes, a term used to describe elevated glucose levels that are too high to be considered normal but that do not meet the criteria for diabetes, has also increased in recent years.[2-4] People with prediabetes are at an increased risk of developing T2D and its associated complications.[4] In 2009, DeFronzo described the 'ominous octet': the eight key defects that contribute to the pathophysiology of T2D, as outlined in Table 1.[5]

Targeting the various defects of this octet can help in optimizing medication and lifestyle therapies. This is evident as T2D can be effectively managed by combining lifestyle changes (including diet, physical activity, smoking cessation, psychosocial/emotional care and sleep quantity and quality) with medication when required, using an individual, progressive approach.[1,2,4,6,7] There are a number of pharmacotherapy options for adults with T2D, including oral medications such as metformin (commonly the first medication prescribed for T2D), sodium-glucose cotransporter-2 inhibitors (SGLT2is), dipeptidyl peptidase-4 inhibitors (DPP4is), thiazolidinediones and sulphonylureas, and injectable medications such as insulins and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).[4,6] Over time, due to the progression of the disease and the decline in beta (β)-cell function, intensification of lifestyle and/or pharmacotherapy is often required for individuals who have not met their treatment goals.[2,4,6]

GLP-1 RAs (also known as incretin analogues or mimetics) act to enhance the body's natural response to food and reduce glucose levels after eating, to achieve glycaemic control.[2,8-10] They have multiple specific desirable effects such as regulating insulin secretion in proportion to environmental glucose levels, a low risk of hypoglycaemia, facilitating weight loss via reduced appetite and energy intake, and delayed gastric emptying.[8-11] A wealth of data, including randomized placebo-controlled trials and head-to-head trials, as well as several meta-analyses, have shown that GLP-1 RAs are effective agents for normalizing plasma glucose concentrations.[8-11] As well as improving glycaemic control, GLP-1 RAs are thought to mediate other effects that assist in regulating glycaemia and provide long-term pancreatic effects, such as enhancing insulin synthesis and β-cell proliferation and survival.[12] Furthermore, some GLP-1 RAs may have beneficial effects on the cardiorenal system including reducing CV risk and improving renal outcomes.[11,13-18] These effects and clinical results of GLP-1 RAs form the basis of this review.

A comparison of GLP-1 RAs can be found in Table 2. Despite all GLP-1 RAs impacting the incretin hormone system, differences in their molecular size, structure and pharmacokinetics (PK) have led to differing pharmacodynamics (PD) and clinical effects, which will be detailed in this review. This review focuses on the once-weekly (QW) GLP-1 RAs exenatide extended-release (ER), dulaglutide and semaglutide subcutaneous (s.c.), which have half-lives or PK that provide ongoing receptor activation and support QW administration.[19-21]

As a consequence of the increasing prevalence of T2D and changes to treatment guidelines, pharmacists play an important role in the education, management and care of people with T2D.[22] For example, pharmacists can work with prescribers and people with T2D to identify the most suitable treatment options available and provide the essential education for proper medication use and adherence.[22] Thus, it is important for pharmacists to fully understand the disease process and the mechanisms of action (MoA) of the available treatment options.[22]

The objective of this review is to provide a general clinical overview of the QW GLP-1 RAs regarding the mechanisms underlying their effects and treatment outcomes, and with a focus on the commonalities and differences among individual agents. The implications for pharmacists and people with T2D will also be discussed.

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. Increased insulin uptake in peripheral tissue via weight loss
7. Increased glucose reabsorption	
8. Increased lipolysis	

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

2 | METHODS

This is a narrative review of the published literature concerning the use of GLP-1 RAs in people with T2D. Articles were identified through searches of PubMed and bibliographies of key publications. The review focuses on the currently available QW GLP-1 RA injectable class of medications, that is exenatide ER, dulaglutide and semaglutide s.c., while also considering once-daily (QD) and twice-daily (BID) GLP-1 RAs for comparison purposes only. Albiglutide is not considered in detail, as it was withdrawn from the market in 2018.[23]

3 | RESULTS AND DISCUSSION

3.1 | Similarities and differences in the characteristics of GLP-1 RAs

GLP-1 is an incretin glucoregulatory hormone released from the gut in response to food ingestion, which stimulates insulin release and decreases glucagon secretion when plasma glucose levels are elevated.[8,24] GLP-1 RAs are synthetic analogues or mimetics of the native human GLP-1 with improved PK properties and more stable PD profiles, thereby providing pharmacological effects greater than endogenous GLP-1 (Table 2).[13] GLP-1 RAs bind to GLP-1 receptors that are widely expressed in a number of tissues throughout the body, for example in pancreatic islet cells, as well as cells in the kidney, lung, heart, brain and gastrointestinal tract.[25,26] GLP-1 RAs are included in various clinical practice guidelines for T2D[4,6,7]; however, they differ substantially in their duration of action, molecular size and structure, homology to endogenous GLP-1, chemical and physiological properties and affinity for the GLP-1 receptor (Table 2).

As a general rule, GLP-1 RAs can be divided according to their duration of action.[19-21,27-30] Short-acting GLP-1 RAs (exenatide [BID] and lixisenatide [QD]) deliver short-lived receptor activation (Table 2) and are more strongly associated with reductions in post-prandial glucose levels by delaying gastric emptying and facilitating slower delivery of glucose to the duodenum.[11,14,31,32] The longer-acting QD (liraglutide) and QW (exenatide ER, dulaglutide, semaglutide s.c.) agents have longer half-lives/PK (>3 hours) and deliver continuous receptor activation at their recommended doses (Table 2), which produce greater reductions in fasting blood glucose by stimulating insulin secretion and inhibition of glucagon release from the pancreas.[11,14,31,32] The PK of the long-acting exenatide ER, dulaglutide and semaglutide s.c. agents, in comparison with the shorter-acting agents, makes them ideal for QW dosing (Table 2).

Other differences in the characteristics of the GLP-1 RAs are highlighted in Table 2. For example, GLP-1 RAs can be derivatives of exendin-4 or modified from the active fragment of the human GLP-1, which is reflected in their varying homology to native GLP-1. Furthermore, GLP-1 RAs can be large (~63-73 kilodaltons: dulaglutide) or small (<5 kilodaltons: exenatide, liraglutide, lixisenatide, semaglutide) in molecular weight.[19-21,27,29,30]

The currently available QW GLP-1 RAs target six (Table 1) of DeFronzo's ominous octet evident in T2D.[5] These MoA are discussed more fully in the following sections, under reported clinical trial outcomes.

3.2 | Mechanism of action related to glycaemic control

The core effect of GLP-1 RAs in T2D is good glycaemic control, which is achieved through effects on GLP-1 receptors in the pancreas, essentially stimulating insulin release from pancreatic islet β-cells in a glucose-dependent manner and suppressing glucagon secretion from pancreatic islet alpha (α)-cells, which contributes to the reduction in blood glucose levels in people with hyperglycaemia.[8,9,14,24,33,34]

This glycaemic control has been shown consistently across clinical trials with the three QW and other GLP-1 RAs.[35-51] The differing half-lives and MoA appear to influence the degree of the glycaemic control. Greater and more consistent reductions in glycated haemoglobin (HbA_{1c}) levels were seen with longer-acting GLP-1 RAs compared with short-acting agents.[11,37-40]

In 14 head-to-head comparisons, all GLP-1 RAs led to notable reductions in HbA_{1c} levels from baseline, but these were highly variable, ranging from 0.3% to 1.9% in the different studies, although they are not directly comparable due to differences in study design and participant cohorts.[37,38,40-42,44,49,50,52-57] There is a lack of studies comparing the different QW GLP-1 RAs regarding their HbA_{1c}-lowering effects, with just two recent studies suggesting semaglutide s.c. has superior efficacy for improving glycaemic control compared with exenatide ER and dulaglutide.[49,50] In the other head-to-head comparisons, participants given QW GLP-1 RAs generally had significantly greater reductions in HbA_{1c} than those given QD or BID agents, as shown in three studies with exenatide ER versus exenatide BID[37,40,55] and in two studies with dulaglutide versus exenatide BID and liraglutide, respectively.[42,52]

In clinical trials, GLP-1 RAs have also shown beneficial effects on other measures of glycaemic control, for example in their ability to lower both post-prandial glucose (via enhanced gastric emptying or post-prandial insulin secretion and inhibited glucagon secretion) and fasting plasma glucose (via enhanced insulin secretion/reduced glucagon secretion in the fasting state).[37-40,46,49,50]

Furthermore, because the action of GLP-1 RAs on insulin and glucagon secretion is dependent upon glucose levels, they are also associated with a low risk of hypoglycaemia compared with conventional, secretagogue agents (eg, insulin, glinides or sulphonylureas; see sister article in this supplement for details).[35,37-40,49,58] In head-to-head clinical studies of GLP-1 RAs delivered QW, QD or BID, the risk of hypoglycaemia was similarly low across all QW GLP-1 RAs.[37-42,44,49,50,52,55] More recently, compared with placebo, semaglutide s.c. did not impair the counterregulatory

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)	SC dosing		
			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**

Note: Long-acting GLP-1 RAs indicated as bold text.

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.

[a]Albiglutide is not included in this table, as it was withdrawn from the market in summer 2018.

[b]Byetta®; Amylin Pharmaceuticals; approved in 2005.

[c]Adlyxin®; Sanofi-Aventis; approved in 2016. Lixisenatide is also available in combination with insulin glargine under the name Soliqua®/Suliqua®.

[d]Victoza®; Novo Nordisk; approved in 2010. Liraglutide is also available in combination with insulin degludec under the name Xultophy®.

[e]Bydureon®; AstraZeneca; approved in 2012.

[f]Trulicity®; Eli Lilly and Company; approved in 2014.

[g]Ozempic®; Novo Nordisk; approved in 2017.

glucagon response during induced hypoglycaemia, consistent with an action providing glycaemic control with a low risk of hypoglycaemia.[48]

3.3 | Mechanism of action for effects beyond glycaemic control

A large body of data is accumulating regarding the effects of GLP-1 RAs beyond glycaemic control, with effects due to the widespread expression of GLP-1 receptors beyond the pancreas.[25,26,59] These extra-pancreatic effects suggest GLP-1 RAs have the potential to provide multiple benefits to people with T2D.[59]

3.3.1 | Effects on body weight

GLP-1 RAs are recognized for their ability to reduce body weight in people with T2D.[4] The weight loss effect is thought to be linked to GLP-1 RA MoA on central and peripheral receptors in the brain and stomach.[25,60-62] Native GLP-1 is a physiological regulator of appetite and energy intake in humans, as it enhances satiety and fullness, reduces hunger and suppresses energy intake compared with placebo in both healthy people and those with T2D.[61,63] Animal studies suggest this may be due to direct actions on mesolimbic brain receptor pathways affecting perceptions of food reward and motivation.[60] In humans, therefore, the continued use of GLP-1 RAs could encourage weight loss via stimulation of GLP-1 receptors in hypothalamic satiety centres in the brain that regulate appetite.[61] GLP-1 RAs also inhibit gastric emptying, thereby slowing gastrointestinal motility and leading to feelings of satiety and diminished appetite.[62]

This aspect of their MoA is evident through proven efficacy for reducing body weight in people with T2D.[51,64-68] Clinical studies showed changes in body weight that varied among the QW GLP-1 RAs, whereby average body weight reductions ranged from −1.4 to −4.1 kg in studies with exenatide ER[37,39-41] and −2.0 to −7.9 kg in studies with semaglutide s.c.[46,49,50,68] Dulaglutide has shown slightly more modest effects (ranging from an mean increase of +0.20 kg to reductions of −3.0 kg),[42,44,45,50] which could perhaps be due to its larger molecular size compared with other GLP-1 RAs. Its large size could hinder its ability to cross the blood-brain barrier and therefore have less of an effect on stimulating satiety.[11,14,50] Further research is required to understand the causes of the differences in body weight.[50]

Due to the small number of head-to-head comparisons between the QW GLP-1 RAs, meta-analyses were also reviewed. They showed the varying weight loss benefits of the different GLP-1 RAs

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
1-3.5 h	3 h	50[11,97,98]	70	eGFR < 15 mL/min/1.73 m^2 not recommended	Renal/proteolysis	35
8-12 h	**13 h**	**97**	**8.6**	**No dose adjustment**	**No specific organ**	**1.2**
Peaks around 2 and 6-7 weeks	**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**	**Urine and faeces**	**0.05**

compared with placebo and other anti-diabetic agents, with few differences between the GLP-1 RAs.[51,65,66,69] Recently, semaglutide s.c. has been shown to reduce body weight versus placebo and to a greater extent than exenatide ER and dulaglutide.[49,50]

3.3.2 | Effects on the CV system

Some QW GLP-1 RAs have been reported to reduce the incidence of CV events and improve CV risk factors such as blood pressure and serum lipid concentrations.[17,70-72] The MoA involved in the CV effects of GLP-1 RAs have not yet been fully established. Weight loss and good glycaemic control may help to improve CV outcomes, but GLP-1 RAs also exert a range of direct and indirect effects on other organ systems in which GLP-1 receptors are present, which are discussed further in the following sections.

Improved CV outcomes

The MoA for GLP-1 RAs impacting CV outcomes are unclear, but could be due to anti-atherogenic mechanisms (such as beneficial effects on common CV risk factors such as weight and lipid profiles), anti-inflammatory pathways, and direct actions on the myocardium and/or vascular endothelium (as GLP-1 receptors are present in the heart and endothelial tissue).[70,73,74]

Three CV outcomes trials (CVOTs) have shown either no increased risk or significantly reduced risk (over 2-5 years) of major adverse CV events (MACE; eg, CV death, non-fatal myocardial infarction, non-fatal stroke) for the QW GLP-1 RAs versus placebo in people with T2D and with or without high CV risk.[17,71,72] Following a median observation period of 2.1 years, the SUSTAIN 6 trial in 3297 people with T2D at high risk of or with established CV disease found that those treated with semaglutide s.c. (at doses of 0.5 mg or 1.0 mg QW) showed a significant 26% lower risk of the primary composite MACE outcome compared with those receiving placebo (post hoc analysis).[17] In the large EXSCEL trial, in 14 752 people with T2D with or without previous CV disease and a median follow-up of 3.2 years, the incidence of MACE did not differ significantly between those who received injections of exenatide ER (2 mg) or a matching placebo.[71] In the more recently published REWIND study, during a median follow-up of 5.4 years, weekly injections with dulaglutide reduced MACE compared with placebo in people with T2D (N = 9901) with or without previous CV disease and a wide range of glycaemic control.[72] Moreover, the effect size was similar to that observed in other GLP-1 RA CVOTs.[72]

A meta-analysis of four CVOTs including lixisenatide (ELIXA), liraglutide (LEADER), semaglutide s.c. (SUSTAIN 6) and exenatide ER (EXSCEL) (N = 33 457) concluded CV safety across all trials (with a 10% relative risk reduction [RRR] in the MACE primary outcome,

13% RRR in CV mortality and 12% RRR in all-cause mortality).[70] There were also no detrimental effects on other safety variables such as severe hypoglycaemia, pancreatitis, pancreatic cancer or medullary thyroid cancer compared with placebo.[70] A degree of statistical heterogeneity was seen between the trials, thought to be due to the larger number of MACE in the active (shorter-acting lixisenatide) versus placebo treatment group in one of the studies.[70] However, it is yet to be determined whether differences can be explained by differences in MoA among the agents or if they are due to differences in study design or populations.

Reduced systolic blood pressure

The CVOT clinical results may be related to the effects on blood pressure, which may in turn be due to weight loss effects. Animal studies have suggested that the MoA related to blood pressure effects could involve numerous body systems, including GLP-1-regulated vascular, myocardial, renal and central nervous system pathways.[16,75,76] However, such findings in animals have not yet been replicated in humans, and further studies are needed.[16,59]

Studies have shown that the chronic use of exenatide ER and semaglutide s.c. is associated with modest but statistically significant reductions in mean systolic blood pressure (~2 mmHg) compared with baseline in people with T2D, with an effect usually within 2-3 weeks.[16,37,40,41,46,49,51,77] Results for dulaglutide have been more mixed, with some studies showing no meaningful blood pressure changes.[42,44,45,52] Of note, subgroup analyses from a meta-analysis suggested semaglutide s.c. was more efficacious than other GLP-1 RAs in reducing systolic blood pressure.[51] In clinical trials, the GLP-1 RA effect on diastolic blood pressure was generally much smaller, with many studies showing no statistically significant between-treatment changes.[16,37,40-42,44-46,49,52,77,78] Of note, blood pressure effects are usually described as part of the secondary rather than primary outcomes in glycaemia-lowering studies (including AWARD-1,[42] DURATION-1[39] and SUSTAIN 3[49]) and should therefore be interpreted with a degree of caution.

Increased heart rate

Although the MoA of GLP-1 RAs affecting heart rate have yet to be fully clarified,[14] the GLP-1 receptor is expressed on myocytes in the sinoatrial node (SAN) of the human heart.[25] Therefore, a leading hypothesis is that GLP-1 RAs may directly stimulate the cells of the SAN, leading to mean increases in heart rate.[25,79]

Most GLP-1 RAs have been associated with increases in heart rate, but to varying degrees. In studies with QW GLP-1 RAs, these medications have consistently shown that reductions in blood pressure are associated with clinically relevant increases in heart rate (in the range of 1-5 beats per minute).[16,40,42,44-46,49,51,52,80] The extent of the increase varies among the different agents, which could be related to their individual durations of action (Table 2), for example due to their continuous receptor activation, longer-acting GLP-1 RAs are associated with more pronounced and sustained increases compared with short-acting agents, which show more intermittent receptor activation.[14,40,42,52,81]

An increased heart rate is theoretically a safety concern, which could be associated with adverse events in certain people, such as those with cardiac arrhythmias[14,81]; however, it is evident that other common CV risks were not increased in trials.[16,38,40,42,44-46,49,52,80,81] These findings should be interpreted cautiously as results have been inconsistent among studies and heart rate is usually included as a secondary safety endpoint in clinical trials. Further research is needed before any firm conclusions can be made; moreover, any potentially detrimental effects on heart rate need to be weighed against the other, potentially beneficial CV effects of GLP-1 RAs.

3.3.3 | Improved lipid profiles

In recent years, GLP-1 has been investigated for its ability to regulate the dyslipidaemia associated with T2D.[15] The observed effects may be due to changes in intestinal and/or hepatic lipid handling, due to reduced absorption of dietary lipids, inhibition of intestinal chylomicron output (thereby reducing formation of atherogenic remnants), regulation of hepatic very-low-density lipoprotein (VLDL) production, and enhanced hepatic fatty acid oxidation or autophagy.[15,59] Whether these effects occur via direct receptor activation or through indirect pathways has yet to be established.

Modest improvements in fasting and post-prandial lipid profiles have been found following GLP-1 RA treatment with both short- and longer-acting agents,[37,38,40,41,45,52,82-84] mostly regarding 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] Considering head-to-head studies comparing QW GLP-1 RAs with placebo and QD or BID GLP-1 RAs, there are a few between-treatment differences. Evidence from two studies has shown that exenatide ER significantly reduced total and LDL cholesterol compared with exenatide BID.[37,40] Treatment with dulaglutide resulted in significant reductions in serum total cholesterol and triglycerides from baseline compared with placebo in two studies.[45,52] However, two trials with semaglutide s.c. had different results.[49,50] In the first, treatment with semaglutide had no clinically relevant impact on lipid levels,[50] but in a second, semaglutide improved free fatty acid, VLDL cholesterol and triglyceride levels compared with exenatide ER.[49] These results suggest the QW GLP-1 RAs may therefore impact the accelerated lipolysis, one of DeFronzo's ominous octet thought to contribute to the pathophysiology of T2D.[5]

3.3.4 | Renal effects

Recent animal and human data suggest that some GLP-1 RAs do not have adverse effects on the kidney and could in fact be renoprotective, providing beneficial effects by reducing the renal complications commonly associated with T2D.[17,18,85-87] The possible kidney-protecting mechanisms of GLP-1 RAs are uncertain, and it is unclear if

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.

[a]Cell types targeted by the MoA of GLP-1 RAs as described in DeFronzo's ominous octet.[5]

these findings relate to direct effects on kidney function. One theory from animal studies is that GLP-1 receptor activation can protect the vascular endothelium from injury, reducing oxidative stress and the local inflammatory response, ameliorating the albuminuria and glomerular sclerosis evident in kidney disease; this however needs further research.[59,86,87]

In two T2D CVOTs, semaglutide and dulaglutide were associated with lower rates of renal microvascular events (1.86 and 3.47 events/100 patient years, respectively) versus placebo (3.06 and 4.07 events/100 patient years, respectively, in the two trials), thought to be driven by a reduction in estimated glomerular filtration rate (eGFR) or persistent macroalbuminuria.[17,72] In a further multicentre study, it was shown that dulaglutide attenuated a decline in eGFR compared with insulin in people with T2D and moderate-to-severe chronic kidney disease.[85] These findings are of particular importance because the presence of chronic kidney disease can affect the treatment options available (Table 2).

3.4 | Safety and tolerability

For balance with the positive MoA detailed so far, this review must also mention the safety profile of QW GLP-1 RAs to ensure pharmacists have a complete understanding of these treatments. The most common adverse effects in GLP-1 RAs studies are generally transient, mild-to-moderate gastrointestinal events, particularly nausea, vomiting and diarrhoea.[35,40,41,43,44,47,49-51] Gastrointestinal events are thought to be due to GLP-1 RA effects on the stomach and duodenum, with gastrointestinal motility disturbances related to delayed gastric emptying.[88] Gastrointestinal events are reported with both short- and long-acting GLP-1 RAs[19-21,27,29,30]; however, long-acting formulations are associated with diminished effects over time,[49] probably due to the development of tolerance and because of reduced fluctuation in plasma drug levels and less of an effect on gastric emptying compared with short-acting agents.[14,40]

QW GLP-1 RAs have also been associated with other safety concerns, including increased pancreatic enzymes and pancreatitis, retinopathy and thyroid cancer (in rodent studies).[19-21] An in-depth discussion of these effects is beyond the scope of this review; however, risks are considered low in humans and all QW GLP-1 RAs carry warnings and precautions regarding these effects in their prescribing information.[19-21] As well as CV safety, a meta-analysis of CVOTs concluded there were no detrimental effects on other significant safety variables such as severe hypoglycaemia, pancreatitis, pancreatic cancer or medullary thyroid cancer for GLP-1 RAs versus placebo.[70] Furthermore, a large meta-analysis and an official assessment of incretin-based drugs were unable to find causal relationships between GLP-1 RAs and retinopathy and pancreatitis/pancreatic cancer, respectively.[89,90]

4 | DISCUSSION

As a class, QW GLP-1 RAs appear to be an attractive treatment option for people with T2D, targeting a number of pathophysiological defects and achieving multi-factorial clinical benefits, including sustained reductions in HbA_{1c}, low hypoglycaemic risk, moderate reductions in body weight and blood pressure and improved CV outcomes, with a generally acceptable safety and tolerability profile. These benefits derive from their blood glucose-lowering effects, such as pancreatic β-cell-mediated glucose-dependent insulin secretion and suppressed glucagon release, as well as other effects including slowing of gastric emptying time, promotion of satiety signals and suppression of appetite. QW GLP-1 RAs may also exert beneficial effects on multiple organ systems that express GLP-1 receptors, including the CV and renal systems. Importantly, as shown throughout this review, the actions of GLP-1 RAs are thought to impact six of the eight core defects (ominous octet) evident in T2D (Table 1).[5]

Although there are several GLP-1 RAs available, each has its own advantages and disadvantages. Although all GLP-1 RAs impact

the incretin system, there are differences in their chemical and physiological properties and MoA, which affect their biological profiles and clinical outcomes (Table 2).[11,14,31,32,91] It is thought that duration of action may explain most of the variation in effects, that is short- and longer-acting agents differ in levels of GLP-1 receptor activation, duration of action and glucose effects. Consequently, there is no one preferred GLP-1 RA for patients with T2D, and individual needs should be considered when selecting the most appropriate agent.

In addition to their robust glycaemic effects, QW GLP-1 RAs are an appealing treatment option versus QD and BID agents, owing to their reduced dosing frequency (reduced injection burden), ease of use and safety profile, which includes a low risk of hypoglycaemia. All are factors that might help improve treatment adherence and persistence.[92-94] As hypoglycaemia may be linked to poor adherence and decreased treatment satisfaction,[95,96] the development of blood glucose-lowering drugs that mitigate hypoglycaemic risk has been an important development in recent years.

Reducing the CV complications of T2D linked to premature morbidity and mortality[2] is considered a priority in diabetes care.[91] The improvements seen in recent CVOTs should therefore be seen as a major therapeutic advance,[70] and indeed, the results have informed the 2020 American Diabetes Association guidelines.[4] At this stage, it is not clear if the CV benefits are a class effect or if they are limited to individual agents.[59]

The availability of various pharmacotherapeutic options for T2D can help to improve individualized patient outcomes, not only in terms of glycaemic control, but also for other coexisting conditions. As such, pharmacists should consider a range of factors when selecting the most appropriate therapy for individual patients, including the glycaemic effect of the agent, as well as safety and tolerability risks, weight effects, hypoglycaemia risk, comorbid conditions, dosing frequency/method, individual preference and cost.[4]

Pharmacists can work with prescribers to identify in which situations GLP-1 RA therapy would be appropriate and educate people on practical details such as how to store the medication, proper preparation and injection technique, individual HbA_{1c} targets, and how to manage or minimize any adverse events, all of which can help to improve adherence.[22] For example, specific advice on minimizing gastrointestinal adverse events may include recommendations to eat smaller, more frequent meals to minimize nausea. Consideration of the different characteristics of each available GLP-1 RA can help the pharmacist to tailor treatment management and education to individual needs.

Further research in the area is still needed. As QW GLP-1 RAs are relatively new treatments, their long-term effects will not be fully understood until they have been in use for decades. This is particularly evident regarding CV outcomes. Although a number of MoA have been suggested, further mechanistic studies on the effects on blood pressure are required in humans.[16] Head-to-head CVOTs and studies of other CV risk factors, such as inflammation, are needed.

5 | WHAT IS NEW AND CONCLUSION

From the literature, this appears to be the first narrative review of the published evidence base supporting the MoA of QW GLP-1 RAs in T2D for pharmacists, with an emphasis on their expanding role in the education, management and care of people with T2D. Findings from the available clinical trial evidence suggest that each of the three QW GLP-1 RAs may have different underlying MoAs and therefore clinical effects, targeting a wide range of defects, as outlined in DeFronzo's ominous octet (Table 3). Due to their multifactorial benefits, GLP-1 RAs are a potentially appealing option for a variety of people with T2D (with or without additional health complications) and offer options to healthcare providers in their clinical decision-making.

Due to their specific MoA detailed in this review, pharmacists and healthcare providers will understand that the QW GLP-1 RAs exenatide ER, dulaglutide and semaglutide s.c. increase glycaemic control (with a low risk of hypoglyacemia) and reduce body weight, blood pressure and cholesterol levels. The advantages and limitations of each GLP-1 RA should be considered when selecting treatment options on an individual-need basis, in order to ensure optimal therapeutic outcomes for patients. Equipped with the information on MoA of QW GLP-1 RAs, pharmacists should be ready to advise and educate patients on these matters as needed.

ACKNOWLEDGEMENTS

The author is grateful to Nancy Milligan, MSc, on behalf of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc, for writing assistance in the development of this manuscript. This assistance was funded by Novo Nordisk Inc., which also had a role in reviewing it for medical accuracy.

CONFLICT OF INTEREST

S Cornell serves on the advanced practitioner advisory board for Novo Nordisk and Becton Dickinson.

ORCID

Susan Cornell https://orcid.org/0000-0002-9934-035X

REFERENCES

1. World Health Organization. *Global report on diabetes*. World Health Organization; 2016.
2. International Diabetes Federation. IDF Diabetes Atlas, Ninth edition; 2019. https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/159-idf-diabetes-atlas-ninth-edition-2019.html. Accessed April 21, 2020
3. Mainous AG 3rd, Tanner RJ, Jo A, Anton SD. Prevalence of prediabetes and abdominal obesity among healthy-weight adults: 18-year trend. *Ann Fam Med*. 2016;14:304-310.
4. American Diabetes Association. Standards of medical care in diabetes – 2020. *Diabetes Care*. 2020;43:S1-S224.
5. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2

diabetes management algorithm – 2019 executive summary. *Endocr Pract*. 2019;25:69-100.
6. Buse JB, Wexler DJ, Tsapas A, et al. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;2020(43):487-493.
7. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36:741-744.
8. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab*. 2002;87:1239-1246.
9. Singh S, Wright EE, Kwan AYM, et al. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2017;19:228-238.
10. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. *Diabetes Obes Metab*. 2016;18:317-332.
11. Doyle ME, Egan JM. Mechanisms of action of GLP-1 in the pancreas. *Pharmacol Ther*. 2007;113:546-593.
12. Thrasher J. Pharmacologic management of type 2 diabetes mellitus: available therapies. *Am J Cardiol*. 2017;120:S4-s16.
13. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8:728-742.
14. Farr S, Taher J, Adeli K. Glucagon-like peptide-1 as a key regulator of lipid and lipoprotein metabolism in fasting and postprandial states. *Cardiovasc Hematol Disord Drug Targets*. 2014;14:126-136.
15. Goud A, Zhong J, Peters M, Brook RD, Rajagopalan S. GLP-1 agonists and blood pressure: a review of the evidence. *Curr Hypertens Rep*. 2016;18:16.
16. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834-1844.
17. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322.
18. Amylin Pharmaceuticals. Bydureon® (exenatide extended-release) for injectable suspension, for subcutaneous use prescribing information; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022200s026lbl.pdf. Accessed May 17, 2019
19. Novo Nordisk A/S. Ozempic (semaglutide) injection, for subcutaneous use; prescribing information; 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209637s003lbl.pdf. Accessed January 28, 2020
20. Eli Lilly and Company. Trulicity (dulaglutide) injection for subcutaneous use; prescribing information; 2020. https://pi.lilly.com/us/trulicity-uspi.pdf. Accessed April 17, 2020
21. Meece J. The role of the pharmacist in managing type 2 diabetes with glucagon-like peptide-1 receptor agonists as add-on therapy. *Adv Ther*. 2017;34:638-657.
22. GlaxoSmithKline. Tanzeum (albiglutide) discontinuation; 2017. https://www.tanzeum.com/pdfs/consumer-faq.pdf. Accessed February 28, 2018
23. Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 7-36: a physiological incretin in man. *Lancet*. 1987;2:1300-1304.
24. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014;155:1280-1290.
25. Wei Y, Mojsov S. Tissue-specific expression of the human receptor for glucagon-like peptide-I: brain, heart and pancreatic forms have the same deduced amino acid sequences. *FEBS Lett*. 1995;358:219-224.
26. Novo Nordisk A/S. Victoza® (liraglutide), prescribing information; 2019. https://www.novo-pi.com/victoza.pdf. Accessed July 27, 2019
27. GlaxoSmithKline LLC. Tanzeum® (albiglutide) for injection, for subcutaneous use prescribing information; 2017. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/. Accessed May 17, 2019
28. Amylin Pharmaceuticals. Byetta® (exenatide) injection, prescribing information; 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s25lbl.pdf. Accessed February 28, 2018
29. Sanofi-Aventis US. Adlyxin (lixisenatide), prescribing information; 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208471Orig1s000lbl.pdf. Accessed February 28, 2018
30. Fineman MS, Cirincione BB, Maggs D, Diamant M. GLP-1 based therapies: differential effects on fasting and postprandial glucose. *Diabetes Obes Metab*. 2012;14:675-688.
31. Guo XH. The value of short- and long-acting glucagon-like peptide-1 agonists in the management of type 2 diabetes mellitus: experience with exenatide. *Curr Med Res Opin*. 2016;32:61-76.
32. Banting DRA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773-795.
33. Kirk RK, Pyke C, von Herrath MG, et al. Immunohistochemical assessment of glucagon-like peptide 1 receptor (GLP-1R) expression in the pancreas of patients with type 2 diabetes. *Diabetes Obes Metab*. 2017;19:705-712.
34. Theodorakis MJ, Carlson O, Michopoulos S, et al. Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. *Am J Physiol Endocrinol Metab*. 2006;290:E550-E559.
35. Jendle J, Grunberger G, Blevins T, Giorgino F, Hietpas RT, Botros FT. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. *Diabetes Metab Res Rev*. 2016;32:776-790.
36. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab*. 2017;19:524-536.
37. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240-1250.
38. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374:39-47.
39. Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care*. 2010;33:1255-1261.
40. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96:1301-1310.
41. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381:117-124.
42. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care*. 2014;37:2159-2167.
43. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin

after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;37:2149-2158.
44. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384:1349-1357.
45. Miyagawa J, Odawara M, Takamura T, Iwamoto N, Takita Y, Imaoka T. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. *Diabetes Obes Metab*. 2015;17:974-983.
46. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care*. 2016;39:231-241.
47. Kapitza C, Dahl K, Jacobsen JB, Axelsen MB, Flint A. Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial. *Diabetologia*. 2017;60:1390-1399.
48. Korsatko S, Jensen L, Brunner M, et al. Effect of once-weekly semaglutide on the counterregulatory response to hypoglycaemia in people with type 2 diabetes: a randomized, placebo-controlled, double-blind, crossover trial. *Diabetes Obes Metab*. 2018;20:2565-2573.
49. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care*. 2018;41:258-266.
50. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol*. 2018;6:275-286.
51. Andreadis P, Karagiannis T, Malandris K, et al. Semaglutide for type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2018;20:2255-2263.
52. Odawara M, Miyagawa J, Iwamoto N, Takita Y, Imaoka T, Takamura T. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in Japanese patients with type 2 diabetes: 52 weeks of treatment in a randomized phase III study. *Diabetes Obes Metab*. 2016;18:249-257.
53. Rosenstock J, Raccah D, Koranyi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care*. 2013;36:2945-2951.
54. Rosenstock J, Balas B, Charbonnel B, et al. The fate of taspoglutide, a weekly GLP-1 receptor agonist, versus twice-daily exenatide for type 2 diabetes: the T-emerge 2 trial. *Diabetes Care*. 2013;36:498-504.
55. Ji L, Onishi Y, Ahn CW, et al. Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2013;4:53-61.
56. Kapitza C, Forst T, Coester HV, Poitiers F, Ruus P, Hincelin-Mery A. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. *Diabetes Obes Metab*. 2013;15:642-649.
57. Pratley RE, Nauck MA, Barnett AH, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol*. 2014;2:289-297.
58. Trujillo JM. Safety and tolerability of once-weekly GLP-1 RAs in type 2 diabetes. *J Clin Pharm Ther*. 2020;45(Suppl. 1):43–60.
59. Sarafidis P, Ferro CJ, Morales E, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrol Dial Transplant*. 2019;34:208-230.
60. Dickson SL, Shirazi RH, Hansson C, Bergquist F, Nissbrandt H, Skibicka KP. The glucagon-like peptide 1 (GLP-1) analogue, exendin-4, decreases the rewarding value of food: a new role for mesolimbic GLP-1 receptors. *J Neurosci*. 2012;32:4812-4820.
61. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest*. 1998;101:515-520.
62. Nauck MA, Kemmeries G, Holst JJ, Meier JJ. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. *Diabetes*. 2011;60:1561-1565.
63. Gutzwiller J-P, Drewe J, Göke B, et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. *Am J Physiol*. 1999;276:R1541-R1544.
64. Unni S, Wittbrodt E, Ma J, et al. Comparative effectiveness of once-weekly glucagon-like peptide-1 receptor agonists with regard to 6-month glycaemic control and weight outcomes in patients with type 2 diabetes. *Diabetes Obes Metab*. 2018;20:468-473.
65. Sun F, Chai S, Li L, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss in patients with type 2 diabetes: a systematic review and network meta-analysis. *J Diabetes Res*. 2015;2015:157201.
66. Potts JE, Gray LJ, Brady EM, Khunti K, Davies MJ, Bodicoat DH. The effect of glucagon-like peptide 1 receptor agonists on weight loss in type 2 diabetes: a systematic review and mixed treatment comparison meta-analysis. *PLoS One*. 2015;10:e0126769.
67. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2012;344:d7771.
68. Ahrén BO, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes Obes Metab*. 2018;20:2210-2219.
69. Zaccardi F, Htike ZZ, Webb DR, Khunti K, Davies MJ. Benefits and harms of once-weekly glucagon-like peptide-1 receptor agonist treatments: a systematic review and network meta-analysis. *Ann Intern Med*. 2016;164:102-113.
70. Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6:105-113.
71. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228-1239.
72. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121-130.
73. Baggio LL, Yusta B, Mulvihill EE, et al. GLP-1 receptor expression within the human heart. *Endocrinology*. 2018;159:1570-1584.
74. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation*. 2008;117:2340-2350.
75. Kim M, Platt MJ, Shibasaki T, et al. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. *Nat Med*. 2013;19:567-575.
76. Yamamoto H, Kishi T, Lee CE, et al. Glucagon-like peptide-1-responsive catecholamine neurons in the area postrema link peripheral glucagon-like peptide-1 with central autonomic control sites. *J Neurosci*. 2003;23:2939-2946.

77. Robinson LE, Holt TA, Rees K, Randeva HS, O'Hare JP. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. *BMJ Open*. 2013;3:e001986.
78. Katout M, Zhu H, Rutsky J, et al. Effect of GLP-1 mimetics on blood pressure and relationship to weight loss and glycemia lowering: results of a systematic meta-analysis and meta-regression. *Am J Hypertens*. 2014;27:130-139.
79. Smits MM, Tonneijck L, Muskiet MHA, et al. Heart rate acceleration with GLP-1 receptor agonists in type 2 diabetes patients: an acute and 12-week randomised, double-blind, placebo-controlled trial. *Eur J Endocrinol*. 2017;176:77-86.
80. Sun F, Wu S, Guo S, et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Res Clin Pract*. 2015;110:26-37.
81. Lorenz M, Lawson F, Owens D, et al. Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. *Cardiovasc Diabetol*. 2017;16:6.
82. Sun F, Wu S, Wang J, et al. Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. *Clin Ther*. 2015;37(1):225-241.e8.
83. Hasegawa Y, Hori M, Nakagami T, Harada-Shiba M, Uchigata Y. Glucagon-like peptide-1 receptor agonists reduced the low-density lipoprotein cholesterol in Japanese patients with type 2 diabetes mellitus treated with statins. *J Clin Lipidol*. 2018;12(1):62-69.e1.
84. Hjerpsted JB, Flint A, Brooks A, Axelsen MB, Kvist T, Blundell J. Semaglutide improves postprandial glucose and lipid metabolism, and delays first-hour gastric emptying in subjects with obesity. *Diabetes Obes Metab*. 2018;20:610-619.
85. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. 2018;6:605-617.
86. Tanaka T, Higashijima Y, Wada T, Nangaku M. The potential for renoprotection with incretin-based drugs. *Kidney Int*. 2014;86:701-711.
87. Kodera R, Shikata K, Kataoka HU, et al. Glucagon-like peptide-1 receptor agonist ameliorates renal injury through its anti-inflammatory action without lowering blood glucose level in a rat model of type 1 diabetes. *Diabetologia*. 2011;54:965-978.
88. Tella SH, Rendell MS. Glucagon-like polypeptide agonists in type 2 diabetes mellitus: efficacy and tolerability, a balance. *Ther Adv Endocrinol Metab*. 2015;6:109-134.
89. Dicembrini I, Nreu B, Scatena A, et al. Microvascular effects of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized controlled trials. *Acta Diabetol*. 2017;54:933-941.
90. European Medicines Agency. Assessment report for GLP-1 based therapies: Review under Article 5(3) of Regulation (EC) No 726/2004; 2013. https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-glp-1-based-therapies_en.pdf2013. Accessed July 27, 2019
91. Lovshin JA. Glucagon-like peptide-1 receptor agonists: a class update for treating type 2 diabetes. *Can J Diabetes*. 2017;41:524-535.
92. Garcia-Perez LE, Alvarez M, Dilla T, Gil-Guillen V, Orozco-Beltran D. Adherence to therapies in patients with type 2 diabetes. *Diabetes Ther*. 2013;4:175-194.
93. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307.
94. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med*. 2008;31:213-224.
95. Lopez JM, Annunziata K, Bailey RA, Rupnow MF, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes mellitus and their quality of life, work productivity, and medication adherence. *Patient Prefer Adherence*. 2014;8:683-692.
96. Walz L, Pettersson B, Rosenqvist U, Deleskog A, Journath G, Wandell P. Impact of symptomatic hypoglycemia on medication adherence, patient satisfaction with treatment, and glycemic control in patients with type 2 diabetes. *Patient Prefer Adherence*. 2014;8:593-601.
97. DeYoung MB, MacConell L, Sarin V, Trautmann M, Herbert P. Encapsulation of exenatide in poly-(D, L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. *Diabetes Technol Ther*. 2011;13:1145-1154.
98. Goke R, Fehmann HC, Linn T, et al. Exendin-4 is a high potency agonist and truncated exendin-(9–39)-amide an antagonist at the glucagon-like peptide 1-(7–36)-amide receptor of insulin-secreting beta-cells. *J Biol Chem*. 1993;268:19650-19655.

How to cite this article: Cornell S. A review of GLP-1 receptor agonists in type 2 diabetes: A focus on the mechanism of action of once-weekly agents. *J Clin Pharm Ther*. 2020;45(Suppl 1):17–27. https://doi.org/10.1111/jcpt.13230