

EDITORIAL

An overview of the once-weekly GLP-1 receptor agonists from the pharmacist's perspective

Traditionally, the pharmacist's role has focused on the supply of medicines and counselling patients. However, this role has evolved and pharmacists are now an integral part of the healthcare team. Although the majority of individuals with type 2 diabetes (T2D) are managed in a primary care setting, on average, a pharmacist will see a patient up to nine times more than their primary care physician.¹ This puts them in the unique position to educate people in the proper use of medication, and advise when it might be beneficial to consider other treatment options. Thus, it is essential that pharmacists have a comprehensive understanding of the burden of T2D and the treatment options available, and are able to guide individuals through the management of potential adverse events (AEs).

T2D is a chronic, progressive disease associated with a number of comorbidities, which include cardiovascular disease (eg stroke and myocardial infarction), diabetic retinopathy, neuropathy and nephropathy.² Such comorbidities may require additional drugs, which not only add to the clinical burden but also impose additional financial burdens on individuals and society. In 2019, the global healthcare expenditure on diabetes was estimated to reach 760 billion United States (US) dollars, of which 42.7% was spent in the North America and Caribbean region.² Furthermore, this global expenditure is predicted to increase to 845 billion dollars by 2045.² It is therefore important to prevent or delay complications associated with T2D where possible to avoid polypharmacy and its associated costs. Although the cost of treatment is often the basis for clinical decision-making, early intervention, even if this involves more expensive treatment, is a long-term, cost-effective strategy that can help prevent or delay future complications.

The number of therapeutic options available to treat T2D continues to expand.³ Preferred treatment options have been shifting from sulphonylureas and thiazolidinediones to the newer sodium-glucose cotransporter-2 inhibitors and incretin-based glucagon-like peptide-1 receptor agonists (GLP-1 RAs; Table 1), which come with a need for pharmacists and other healthcare professionals (HCPs) to expand on their knowledge base.

As with any intervention, non-adherence remains an issue for pharmacists and is particularly challenging due to the reduced health-related quality of life and depression associated with T2D.^{5,6} The problem is further compounded by polypharmacy as a result of

the frequent comorbidities that accompany T2D, which can arise due to poor long-term glycaemic control. Additional barriers to treatment adherence include age, AEs, weight gain, regimen complexity, ease of administration, fear of injections and drug costs.⁷ Although achieving long-term glycaemic control remains the main goal of T2D management, effective treatment and long-term management require a comprehensive patient-centred approach.³ The American Diabetes Association (ADA) guidelines stress the importance of individualizing treatment while accounting for comorbidities, AEs and patient preferences that may affect adherence.³ Adherence may potentially be improved by using treatments with less frequent dosing, such as once-weekly formulations, which the patient may find less burdensome than daily injections.

The GLP-1 RA class of drugs has grown in the last decade; several agents are available in the US, including once-daily, twice-daily and once-weekly injectable formulations. Of these, the GLP-1 RAs, including the once-weekly formulations, have emerged as important therapeutic options for people with T2D, as evidenced by their positioning in current diabetes treatment guidelines and recommendations.^{3,4,8,9} Currently, three once-weekly GLP-1 RAs are approved and marketed for the treatment of T2D in the US: dulaglutide, exenatide extended-release and semaglutide subcutaneous.¹⁰⁻¹² A fourth once-weekly GLP-1 RA, albiglutide, was withdrawn from the market in 2018 and is not considered in detail in this supplement.¹³ The first article in this supplement, which focuses on the burden that T2D carries as a complex, multifaceted disease, is intended to provide pharmacists and other HCPs with a clear understanding of the challenges facing individuals with T2D and the role of effective treatment using GLP-1 RAs in preventing or delaying associated complications.¹⁴

Structural differences among the once-weekly GLP-1 RAs mean they each have unique pharmacodynamic and pharmacokinetic properties; however, as a class, they are all effective in lowering glycaemic levels and show beneficial or neutral effects on weight.³ In order for pharmacists and HCPs to understand the clinical efficacy data and safety profiles of GLP-1 RAs, it is important to have an understanding of their mechanism of action, an overview of which is provided in the second article in this supplement.¹⁵ GLP-1 RAs are incretin-based therapies that improve glycaemic control with a low risk of hypoglycaemia and have the

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TABLE 1 Overview of the main medication classes available for improving glycaemic control in patients with T2D

	Biguanides	Sulphonylureas	TZDs	DPP4is	SGLT2is	GLP-1 RAs	Insulins
Administration route and frequency	Oral, daily ^a	Oral, daily ^a	Oral, daily	Oral, daily	Oral, daily	s.c., daily ^a or weekly; oral, daily	s.c. daily ^a (or by pump); inhaled daily ^a
Main physiological MoA ⁴	Decreases hepatic glucose production and other non-insulin-mediated mechanisms	Increases insulin secretion	Increases insulin sensitivity	Increases insulin secretion and decreases glucagon secretion in a glucose-dependent manner	Inhibits glucose reabsorption by the kidney	Increases insulin secretion and decreases glucagon secretion in a glucose-dependent manner; increases satiety	Activates insulin receptor
Efficacy ^{b,4}	High	High	High	Intermediate	Intermediate to high	Intermediate to very high	High to very high
Main safety concerns ^{3,4}	GI symptoms; Vitamin B ₁₂ deficiency	Hypoglycaemia; increased weight	Increased weight; oedema/heart failure	Rare angioedema; increased risk of hospitalization due to heart failure (saxagliptin)	Genital infections; polyuria	GI symptoms; modest increase in heart rate	Hypoglycaemia; increased weight
Examples ⁴	Metformin	Glipizide Glimepiride Glyburide	Pioglitazone	Sitagliptin Saxagliptin Linagliptin Alogliptin	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Dulaglutide ^c Exenatide ^d Exenatide ER ^c Liraglutide Lixisenatide Semaglutide oral Semaglutide s.c. ^c	Aspart (conventional and fast acting) Degludec (U100, U200) Glargine (U100, U300) Gulisine Lispro (U100, U200)

Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitor; ER, extended-release; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; MoA, mechanism of action; s.c., subcutaneous; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

^aAdministered at least once-daily, depending on formulation or patient requirements.

^bEfficacy classification from Davies et al where it was categorized by change in HbA_{1c}: >22 mmol/mol (2%) very high, 11-22 mmol/mol (1%-2%) high, 6-11 mmol/mol (0.5%-1.5%) intermediate, <6 mmol/mol (0.5%) low.⁴

^cAdministered once-weekly.

^dAdministered twice-daily.

potential to reduce body weight.¹⁶⁻¹⁹ Their beneficial effect on glycaemic control arises through various mechanisms, including increased pancreatic beta-cell-mediated glucose-dependent insulin secretion and suppressed glucagon release, delayed gastric emptying and increased feelings of satiety.²⁰⁻²³ Importantly, their beneficial effects may also extend to the cardiovascular and renal systems.^{24,25}

The efficacy, safety and tolerability of the three once-weekly GLP-1 RAs are discussed in the context of their relevant randomized clinical trials in the third and fourth articles in this supplement.^{26,27} They examine the clinical implications of the differences among the drugs in this class and recognize the importance of safety and tolerability profiles when selecting the appropriate treatment for an individual. The final article in this series looks at the GLP-1 RA cardiovascular outcomes trials and their contribution to the treatment landscape.²⁸

The once-weekly GLP-1 RAs are now incorporated into clinical guidelines,^{3,4,8,9} and thus their use is likely to increase. This timely supplement presents a comprehensive overview of the currently marketed once-weekly GLP-1 RAs by a panel of experts in the field of pharmacy, providing pharmacists and other HCPs with a clear understanding of their place in T2D management.

KEYWORDS

GLP-1 receptor agonist, once-weekly, pharmacotherapy, type 2 diabetes

ACKNOWLEDGEMENTS

The author is grateful to Aneela Majid, PhD, 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.

CONFLICTS OF INTEREST

D Patel is an advisory board member and/or consultant for AstraZeneca, Becton & Dickinson, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk and Sanofi; and is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Merck, Novo Nordisk and Valeritas.

FUNDING INFORMATION

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

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How to cite this article: Patel D. An overview of the once-weekly GLP-1 receptor agonists from the pharmacist's perspective. *J Clin Pharm Ther*. 2020;45(Suppl 1):3-6. <https://doi.org/10.1111/jcpt.13227>