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REVIEW ARTICLE

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Managing the multifaceted nature of type 2 diabetes using once-weekly injectable GLP-1 receptor agonist therapy

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Abstract

What is known and objective: As a highly prevalent chronic condition associated with complications and high mortality rates, it is important for pharmacists to have a comprehensive understanding of the impact of type 2 diabetes (T2D) and available treatment options. The use of injectable glucagon-like peptide 1 receptor agonists (GLP-1 RAs) is recommended as an effective and convenient treatment regimen for improving glycaemic control in individuals with T2D, with a good safety profile; however, the wider extent of its potential benefits often are unknown to clinical pharmacists. The objective of this article is to provide an overview of the impact of T2D on individuals and to discuss the multifaceted role of once-weekly (QW) GLP-1 RAs in addressing these challenges.

Methods: This is a narrative review of the published literature regarding the use of injectable GLP-1 RAs in managing health complications in people with T2D.

Results and discussion: Recent findings reveal additional benefits of GLP-1 RAs in managing T2D complications, including atherosclerotic cardiovascular (CV) disease, retinopathy, neuropathy, and nephropathy. Dulaglutide and semaglutide have been shown to provide additional CV benefit in patients at high risk of CV events compared with standard of care/placebo and may offer renal protection in patients with chronic kidney disease. Cost-effectiveness studies, taking into consideration these different complications, have shown that QW GLP-1 RAs were cost-effective compared with other therapies. GLP-1 RAs may also help to improve overall health-related quality of life, reducing the risk of depression and 'diabetes distress', and limiting the risk of hypoglycaemia.

What is new and conclusion: From the literature, this appears to be the first review of the evidence supporting the multifaceted role of QW GLP-1 RAs in T2D, with particular emphasis on their use in comorbid conditions, as well as associated potential financial and well-being benefits. The results suggest that QW GLP-1 RAs may be an attractive treatment option for improving glycaemic control in T2D, especially in individuals with (or at risk of) additional comorbidities or health complications.

KEYWORDS
comorbidities, dulaglutide, economic impact, exenatide, glucagon-like peptide-1 receptor agonist, glycaemic control, management, semaglutide, treatment burden, type 2 diabetes mellitus

1 | WHAT IS KNOWN AND OBJECTIVES

Globally, 463 million adults (9.3%) were living with diabetes in 2019, the majority of whom had type 2 diabetes (T2D), which correlated with a global spending of USD 760 billion for the treatment of diabetes and related complications.[1] Without intervention, the number of adults with diabetes is forecast to rise by 51% to 700 million (10.9%) by 2045.[1] The United States (US) has one of the highest prevalence rates of diabetes globally, comprising 10.8% of the population aged 20-79 years.[1] Diabetes is cited as the seventh leading cause of death in the US in 2015[2]; co-reported causes of death are most likely to include hypertension and hypertensive renal disease. This overall high prevalence of T2D and the associated economic costs put pressure on all healthcare professionals (HCPs), including pharmacists, to help people living with T2D optimally manage their diabetes in the context of their daily routine and other health conditions.[3]

Type 2 diabetes is the most prevalent form of diabetes, accounting for approximately 91% of all diagnosed cases in the US.[4] The estimated prevalence of diagnosed T2D corresponds to approximately 21 million adults.[4] New cases in the US, however, appear to be plateauing, with no overall increase in incidence since 2008.[5] Despite this, prevalence remains especially high in the 'diabetes belt', an area identified by the Centers for Disease Control and Prevention (CDC) in the southern portion of the US, consisting of 644 counties in 15 states.[6] High rates in this region may also partly reflect the increased prevalence of T2D in rural regions, compared to urban counterparts.[7] Diabetes disproportionately impacts some races/ethnic groups, with 15.1% of Native Americans/Alaskans being diagnosed with T2D compared with 7.4% of non-Hispanic whites in the US.[2] Other races known to have an increased risk are non-Hispanic blacks (12.7%) and Hispanics (12.1%) (particularly Mexican Americans, 13.8%).[2] To ensure best treatment outcomes, HCPs need to be aware of the impact of T2D and the potential complexity of a treatment regimen. In practice, they should be mindful of avoiding one that is overly complicated or burdensome, as well as leveraging the most cost-effective treatment strategies from the perspectives of the patient (eg patient out-of-pocket costs) and the broader healthcare system (eg hospitalizations, surgical procedures).

The American Diabetes Association (ADA) recommends a patient-centred approach when choosing between pharmacologic agents for attaining glycaemic goals.[8] HCPs, including pharmacists, should consider a wide range of factors, including the individual's concurrent conditions (ie atherosclerotic cardiovascular disease [ASCVD], heart failure and chronic kidney disease), hypoglycaemia risk, impact on weight, out-of-pocket costs, risk of side effects and patient preferences, when making such choices.[8] The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) also recommend a similar approach to selecting pharmacologic agents, with an emphasis on identifying comorbidities and overall risk/benefit profile of each medication.[9]

In most adults with T2D, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are one of the preferred options after metformin and comprehensive lifestyle modifications, as outlined in the ADA Standards of Care, except for people with heart failure, chronic kidney disease, or high out-of-pocket costs.[8] Furthermore, GLP-1 RAs are preferred over insulin for most individuals who require additional glucose lowering to that which can be obtained using an oral agent to manage their diabetes.[8,9] Similar to other medications, GLP-1 RAs have associated side effects, the most common of which are gastrointestinal symptoms, mainly nausea[10-12] (for further details, see the sister article in this supplement[13]). Fortunately, these issues affect a relatively small percentage of patients and are often transient, resolving within a few weeks after treatment initiation or dose increases.[14] Other common adverse effects include injection-site reactions, headache, and constipation for some GLP-1 RAs.[10-12] The once-weekly (QW) formulation of the injectable GLP-1 RAs are the focus of this review, as they provide a convenient and effective treatment option for many patients. Currently, four QW injectable GLP-1 RAs are approved: albiglutide,[15] dulaglutide,[12] exenatide extended-release (ER)[11] and recently semaglutide subcutaneous (s.c.)[10]; however, albiglutide was withdrawn from the market in 2018[16] and will not be addressed here further. Also, most recently, an oral version of once-daily semaglutide was approved in the US[17]; it is not going to be reviewed here.

The objective of this article is to provide an overview of the multifaceted impact that T2D can have on individual patients, including condition- and treatment-related factors, and discuss the role of QW GLP-1 RAs in helping to address these challenges within this population. This should provide HCPs, including pharmacists, with a clearer understanding of the challenges facing patients with T2D and how to help them optimally manage this condition, when balancing the short-term effect of managing glucose levels and the long-term delay of complications.

2 | METHODS

This is a narrative review of the published literature concerning the use of GLP-1 RAs in managing health complications in people with T2D. Articles were identified through searches of PubMed using

TABLE 1 Impact of CVD on patients with T2D

Factor	Prevalence	Risk factors	Economic impact	HRQoL
CVD (including CHD, cerebrovascular disease, peripheral arterial disease, or heart failure)	~70 per 1000 patients with diabetes (hospitalization discharge data)[2]	Age, obesity, tobacco use, dyslipidaemia, hypertension[23]	Increases annual treatment costs per patient by 112% (compared with patients with T2D and without CVD)[80]	-
CHD	~18 per 1000 patients with diabetes (hospitalization discharge data)[2]	As above	Increases annual treatment costs per patient by 107% (compared with patients with T2D and without CHD)[80]	Presence of angina reduced this from 0.82 to 0.17; presence of other CHD from 0.82 to 0.78[91]
Stroke	~12 per 1000 patients with diabetes (hospitalization discharge data)[2]	As above	Increases annual treatment costs per patient by 322% (compared with patients with T2D and without a stroke)[80]	Presence of hemiplegia stroke reduced this from 0.82 to 0.68[91]; transient ischaemic attack reduced this to 0.75; a cerebral vascular accident reduced this to 0.73[91]
HF	~12 per 1000 patients with diabetes[92]	As above	Increases annual treatment costs per patient by 59% (compared with patients with T2D and without HF)[80]	Presence of HF reduced this from 0.82 to 0.72[91]

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; HRQoL, health-related quality of life; T2D, type 2 diabetes

terms related to diabetes, T2D, impact, comorbidities, complications and bibliographies of key publications (up to May 2019). The review focuses on the currently available literature related to the burden of diabetes (including data on morbidity, mortality, economic costs and related health complications), while also considering the role of the QW GLP-1 RA injectable class of medications as a suitable treatment option for managing these challenges.

This article focuses on the common comorbidities associated with T2D, including macrovascular and microvascular complications, first detailing the impact of each comorbidity before discussing the different roles of GLP-1 RAs in their management. It also considers treatment-related and lifestyle factors, including hypoglycaemia, quality of life (QoL) and cost implications.

3 | RESULTS AND DISCUSSION

Beyond its implications for managing glucose levels, T2D is associated with a number of comorbidities that can significantly impact a patient's treatment options and/or ability to effectively manage their treatment regimens.[18] Notably, a longer duration of diabetes is associated with an increased risk of developing further complications,[19] and adjustments to treatment regimens may be required over time.

Importantly, reductions in glycated haemoglobin (HbA_{1c}) may reduce the likelihood of developing microvascular complications in T2D; however, this is not necessarily the case with macrovascular complications that may develop regardless of well-managed glucose levels.[20] Even if complications and/or comorbidities are not present and glycaemic targets can be attained, maintaining these glycaemic goals can be very difficult for patients, potentially resulting in 'diabetes distress'.[21] There is, however, increasing evidence that the role of GLP-1 RAs extends beyond improving attainment of glucose goals in T2D (glycaemic efficacy of QW GLP-1 RAs is detailed in another article within this supplement[22]) and may have beneficial implications for individuals with additional comorbid conditions or complications.[8] These are considered in more detail throughout this review.

3.1 | Macrovascular complications

3.1.1 | ASCVD

Atherosclerotic cardiovascular disease is a multifaceted condition that can impact patients' lives (Table 1), encompassing three cardiovascular (CV) territories: coronary heart disease (CHD), stroke/cerebrovascular disease and peripheral arterial disease (PAD).[23] When ASCVD is present in people with diabetes, it has a more aggressive course and a worse prognosis.[24] People with diabetes and a history of stroke also have more severe neurological deficits and disability, a poorer long-term prognosis and a higher incidence of stroke recurrence than people without diabetes.[25,26] PAD can be a significant barrier to exercise or physical activity as a result of the intermittent claudications in the lower extremities.[27] PAD is also associated with substantial

morbidity, including functional impairment, amputation and higher risk of death.[28,29] The combination of hyperglycaemia, insulin resistance, dyslipidaemia, hypertension and chronic inflammation can injure the vascular endothelium, significantly contributing to the higher level of ASCVD risk in people with T2D.[30] ASCVD is the leading cause of death in people with T2D.[23] Data from the US National Health Interview Surveys in 2000-2009 show that men with diabetes are 1.67 times more likely to die from ASCVD than men without T2D, with similar results observed in females.[31]

3.1.2 | QW GLP-1 RAs and macrovascular complications

Large randomized cardiovascular outcomes trials (CVOTs) have been conducted in patients with T2D at high risk of CV events[32-34] to evaluate the CV safety of the three QW GLP-1 RAs currently available on the market: semaglutide s.c.,[10] exenatide ER[11] and dulaglutide.[12] No increased CV risk was reported for any of the QW GLP-1 RAs within these respective trials[32-34] (discussed in detail in the sister article within this supplement[35]). The outcomes trials for exenatide ER and dulaglutide were designed to show superiority for the endpoint of composite major adverse CV events (MACE) compared with standard of care (SoC)/placebo,[32,33] with only the dulaglutide trial demonstrating superiority.[32] The semaglutide CVOT also demonstrated superiority over SoC/placebo, but this association was only revealed in the post hoc analysis, since the trial was pre-approval and non-inferiority in design.[34] Since all CVOTs recruited patients with high risk of CV events and were designed to evaluate MACE for the entire population as randomized, none were powered or predefined to show statistical results in just one subpopulation (ie established CV disease [CVD] vs high CV risk).[32-34] These data significantly contributed to the recommendation from the 2020 ADA Standards of Care to utilize GLP-1 RAs with demonstrated CVD benefit in combination with metformin and comprehensive lifestyle management for people living with T2D and established ASCVD,[8] demonstrating one of the ways the QW GLP-1 RAs can aid comprehensive T2D management.

3.2 | Microvascular complications

3.2.1 | Overview of microvascular complications

Retinopathy

Diabetic retinopathy (DR) is a microvascular complication that can affect the peripheral retina, the macula, or both, and is a leading cause of visual disability and blindness in people with diabetes.[1,18] A large cohort study of 7.7 million patients between 2004 and 2014 estimated the prevalence of DR among people living with diabetes to be 28.3%.[36] The prevalence of DR increases with prolonged duration of diabetes.[18]

Diabetic neuropathy

Diabetic neuropathy (DN) refers to a collection of clinically diverse disorders affecting the nervous system, with differing anatomic features, clinical courses and phenotypes.[37] Patients with DN have sensory loss or pain, but the symptoms differ depending on the nerves involved.[18,38] Diabetic polyneuropathy, which has a lifetime prevalence of approximately 50% in people with diabetes, is the most common complication from diabetes.[39] In the long run, severe DN may be a major contributing factor can that lead to amputations of extremities.[18] Characteristic traits of peripheral neuropathy include axonal thickening with progression to axonal loss, basement membrane thickening, pericyte loss, neuronal filament loss and decreased capillary blood flow, leading to decreased nerve perfusion and abnormal mitochondrial activity.[38] Up to half of patients with peripheral DN may present without any reportable symptoms.[39,40] If diagnosis of peripheral neuropathy in lower extremities has not been regularly undertaken by HCPs, these neuropathies will often go unrecognized, and when preventive foot care is not implemented, patients are at risk of injury to their insensate feet. People with T2D may also develop autonomic neuropathy, including cardiac autonomic dysfunction, which is manifested as abnormal heart rate and vascular control.[18]

Nephropathy

Approximately 20%-40% of people with diabetes have persistent albuminuria, low estimated glomerular filtration rate (eGFR) or other manifestations of diabetic nephropathy.[18,41] Initial symptoms experienced by patients with T2D and nephropathy may include high blood pressure, cloudy urine (increased albumin levels in the urine) or an increased need to urinate. Diabetic kidney disease is the leading cause of end-stage renal disease and may eventually lead to renal failure.[18]

3.2.2 | QW GLP-1 RAs and microvascular complications

The known risk factors for these microvascular complications include persistently elevated glucose levels, age, duration of diabetes, tobacco use, dyslipidaemia, hypertension and obesity.[18,42] To aid patients, pharmacists and other HCPs should be prepared to provide guidance on mitigating these risk factors through comprehensive lifestyle management and appropriate pharmacologic agents (if indicated) from the very outset of T2D. Unlike macrovascular outcomes, no studies have looked at the impact of QW GLP-1 RAs on microvascular outcomes as their primary outcomes, although some newer trials have looked at these as secondary outcomes.[32,34,43,44] Useful, relevant data have been obtained from the DCCT and UKPDS trials, wherein intensive glycaemic management (mainly through insulin and sulphonylurea-insulin use, respectively) was shown to reduce the risk of microvascular outcomes over a 10-year period vs other glycaemia-management methods.[45,46] Therefore, the impact of QW GLP-1 RAs on preventing microvascular complications likely results

largely from their ability to help patients better manage their glucose levels, with a high overall level of efficacy in doing so.[8]

QW GLP-1 RAs and retinopathy

The SUSTAIN 1-5 trials, which investigated QW semaglutide s.c., revealed no imbalance in DR adverse events in patients using semaglutide vs their comparator arms.[14,47-51] However, in SUSTAIN 6, semaglutide was associated with a significant risk in DR complications (endpoint defined as the need for retinal treatment [photocoagulation or intravitreal injection] or the occurrence of vitreous haemorrhage or the onset of diabetes-related blindness) vs placebo (hazard ratio (HR) 1.76; 95% confidence interval (CI): 1.11-2.78).[34] This effect, however, may be attributed to the rate and magnitude of HbA_{1c} reduction in patients who had pre-existing DR and markedly elevated glucose levels at baseline, and who were treated with insulin.[51] DR complications were not one of the predefined endpoints in other QW GLP-1 RA clinical trials, and a meta-analysis of DR across GLP-1 RA trials demonstrated no increased risk of DR for this class.[52] Similar to initiating treatment with insulin, it is recommended that patients with a history of DR should be monitored when initiating semaglutide.[10] Due to the risk of DR in all people living with T2D, the ADA recommends regular retinal screening, at least every 1-2 years if there is no history of DR, and at least annually if any level of DR is present.[18]

QW GLP-1 RAs and neuropathy

Diabetic neuropathy is a difficult complication to manage, as it may interfere with a patient's ability to engage in physical activity,[38] and also affects routine tasks related to managing diabetes, such as checking blood glucose, due to an exaggerated pain response.[53] This may further exacerbate feelings of depression due to chronic pain that is difficult to treat.[54] Although no direct impact from QW GLP-1 RAs has been measured on DN, some added benefits of their use in this patient population include a relatively infrequent injection (compared to once daily or multiple times per day injections) and a medication that does not inherently require frequent self-monitored blood glucose checks due to its mechanism of action and pharmacokinetic profile.

QW GLP-1 RAs and nephropathy

Advanced stages of nephropathy and chronic kidney disease can limit treatment options for patients,[8] and the ADA Standards of Care recommend that HCPs be alert to any changes in urinary albumin excretion or eGFR.[18] Many anti-diabetes treatments are contraindicated for patients with severe renal impairment, which specifically includes exenatide ER in patients with creatinine clearance <30 mL/min or end-stage renal disease.[11] Fortunately, the other two QW GLP-1 RAs (dulaglutide and semaglutide s.c.) can continue to be used in patients with advanced chronic kidney disease, even when other medications are contraindicated or require dose adjustments.[10,12] Furthermore, emerging data suggest that some QW GLP-1 RAs may actually slow the progression of nephropathy. In SUSTAIN 6, semaglutide was associated with a lower incidence of new or worsening nephropathy (defined as persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance <45 mL/1.73 m^2 or the need for continuous renal-replacement therapy) compared with placebo (HR 0.64; 95% CI: 0.46-0.88).[34] In REWIND, dulaglutide was also associated with a lower incidence of a renal outcome (defined as new macroalbuminuria, a sustained decline in eGFR of ≥ 30% from baseline or chronic renal-replacement therapy) compared with placebo (HR 0.85; 95% CI: 0.77-0.93).[32] The EXSCEL trial did not investigate a similar outcome when evaluating exenatide ER, so its impact on renal outcomes is unclear.[33] However, renal function should continue to be monitored in patients with renal impairment, and a dose decrease or discontinuation may be warranted for patients experiencing severe adverse gastrointestinal reactions. Additionally, to ensure early treatment of any renal conditions, annual screening of urinary albumin excretion and eGFR is recommended by the ADA in all individuals with T2D.[18]

3.3 | The impact of T2D on social and economic factors

3.3.1 | Hypoglycaemia

Hypoglycaemia is another problem associated with T2D treatment regimens that may have significant health implications for those affected.[20,55] Unsteadiness and weakness are common symptoms of hypoglycaemia, but severe hypoglycaemic episodes require assistance from someone else, as the patient may be unconscious or have a seizure.[20] Hypoglycaemia may cause serious morbidity, inducing major vascular events such as stroke, myocardial infarction, acute cardiac failure and ventricular arrhythmias.[55] In a 7-year review of 102 cases of hypoglycaemic coma secondary to either insulin or glyburide (glibenclamide), 92 patients had T2D, seven sustained physical injury, five died, two suffered myocardial ischaemia and one patient had a stroke as a consequence of severe hypoglycaemia.[56] Hypoglycaemia severity also appears to be correlated with reduced health-related QoL (HRQoL) and productivity.[57]

3.3.2 | QW GLP-1 RAs and hypoglycaemia

GLP-1 RAs are less likely to cause hypoglycaemia due to their glucose-dependent mechanism of glucose lowering, unless used jointly with sulphonylureas or insulin (see also the two sister articles in this supplement about the mode of action of GLP-1 RAs[58] and their safety profiles[13]). This characteristic makes QW GLP-1 RAs an attractive first-line option to add to metformin and comprehensive lifestyle management for patients who have a compelling need to minimize hypoglycaemia, which arguably is anybody with T2D taking pharmacologic therapy.[8] Furthermore, the low hypoglycaemia risk is another reason why the addition of a GLP-1 RA is preferred prior to adding a basal or bolus insulin for most patients with T2D according to the 2020 ADA Standards of Care.[8]

TABLE 2 Monthly costs of currently marketed QW GLP-1 RAs

GLP-1 RA	Maximum approved dose[a]	Median AWP (as of November 2019)[8b]	Median NADAC (as of November 2019)[8b]	Typical dosing schedule	Titration schedule
Dulaglutide[12]	1.5 mg	USD 911	USD 730	Subcutaneous injection, QW	Initiate at 0.75 mg subcutaneously QW. Dose can be increased to 1.5 mg QW for additional glycaemic control
Exenatide ER[11]	2 mg	USD 840	USD 672	Subcutaneous injection, QW	2 mg QW only
Semaglutide s.c.[10]	1 mg	USD 927	USD 745	Subcutaneous injection, QW	Start at 0.25 mg QW. After 4 wk, increase the dose to 0.5 mg QW. If after at least 4 wk additional glycaemic control is needed, increase to 1 mg QW

Note: Pricing data adapted from ADA Standards of Care 2020.[8]

Abbreviations: ADA, American Diabetes Association; AWP, average wholesale price; ER, extended-release; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NADAC, National Average Drug Acquisition Cost; QW, once weekly; s.c., subcutaneous; wk, weeks.

[a]Utilized to calculate median AWP and NADAC; generic prices used, if available commercially.

[b]Calculated for 30-d supply (AWP or NADAC unit price × number of doses required to provide maximum approved daily dose × 30 d); median AWP or NADAC listed alone when only one product and/or price.

3.3.3 | QoL

People with or at high risk of T2D report an overall decreased HRQoL.[59,60] In a cross-sectional study conducted in the US, 'Quality of Well-Being' index scores in people living with T2D were lower in women and people with a concurrent diagnosis of obesity, kidney disease or arterial hypertension, compared with men and people without obesity or other comorbidities.[61]

Depression

Depression is a common comorbidity in patients with T2D, with its prevalence twice as high in patients with T2D vs those without.[62] The mechanisms underlying the association between diabetes and depression, however, remain poorly understood.[63] A systematic review of people with diabetes and depression revealed a significant relationship between depression and treatment non-adherence.[64] Depression in diabetes can also adversely affect self-care and exercise regimens.[63] Comorbid diabetes and depression are also associated with increased odds of disability,[65] significant deterioration in QoL[63] and increased mortality risk[66] compared with people with diabetes who do not have depression.

Diabetes distress

It is important to distinguish between depression found in people with T2D and 'diabetes distress'. While depression is chronic and affects many aspects of a person's life, diabetes distress refers to specific (and often transient) feelings of frustration or stress a person may feel about their experience of living with diabetes, including the emotional burden, as well as physician- and regimen-related, and interpersonal factors.[21] Although diabetes distress may be a temporary or intermittent issue for many, it can lead to other serious problems such as depression or burnout if not managed appropriately, resulting in a patient no longer managing their health sufficiently.[67,68] A concurrent diagnosis of advanced chronic kidney disease can also negatively impact a patient's QoL, with the introduction of dietary restrictions (eg potassium, phosphates), and for those with end-stage renal disease, the additional logistical challenges that come with being on haemodialysis (eg travelling to dialysis centre three times weekly).[69,70]

3.3.4 | QW GLP-1 RAs and QoL

The impact of QW GLP-1 RAs on HRQoL is presumed to be directly related to the increased propensity for weight loss, low risk of hypoglycaemia when not used concurrently with a sulphonylurea or insulin, and the relatively infrequent need to administer the medication.[71] The increased likelihood of weight loss can be especially beneficial for patients with T2D and obesity, as these were the individuals who had lower HRQoL scores compared to people with T2D who were not obese.[61] Lastly, the addition of a QW GLP-1 RA is able to provide effective glucose lowering[8] without the need for an increase in self-monitored blood glucose frequency, which would be necessary with the addition of multiple daily injection (MDI) insulin.

This may help patients who are at risk of the regimen-related components of diabetes distress by introducing a medication that does not require frequent administration or monitoring of glucose levels. Overall, however, further research is needed into exactly how QW GLP-1 RAs impact diabetes distress and therefore HRQoL.

3.3.5 | The economic impact of diabetes on patients

Lastly, the economic impact of diabetes on patients should be considered, which has multiple components. In 2017, it was estimated that approximately USD 16 750 per person with diabetes was spent each year on their healthcare needs; 2.3 times higher than for individuals without diabetes.[72] This amount has increased steadily from 2007,[72] consisting largely of direct medical costs arising from diabetes treatments, as well as care for related chronic complications.[72-74] As such, although patients with diabetes have reduced life expectancy, they have substantially higher direct lifetime medical expenditures, with those diagnosed at the age of 40 estimated to spend an additional USD 124 600 on medical costs over the course of their remaining lifetime, vs those without a diabetes diagnosis.[75]

Importantly, direct, diabetes-related medical costs vary per patient, depending on the relative severity of a person's condition, the frequency of medical appointments, the pharmacologic interventions (Table 2) required to manage blood glucose levels and the degree of monitoring required to do so safely.[8,72,76] As such, out-of-pocket costs to the individual may differ[76] dependent on the highly variable retail value of different medications[8] and on their healthcare coverage/insurance plan.[77] Diabetes-related costs can therefore remain very high for some individuals, to the extent that one in four Americans with T2D taking insulin reported reducing their dosage or stopping it altogether because they simply could not afford it.[77,78]

In addition, although comorbidity costs also account for a significant proportion of the economic burden of diabetes, these can often be overlooked by patients and perhaps even some HCPs.[72,79,80] For example, if CVD is present in a patient with T2D, the cost of annual treatment is 112% greater than in patients without CVD.[80] In the US, if patients have diabetes and one other chronic condition (namely, neurological, vascular, or renal), then 29-39% of their healthcare costs may be spent on managing these chronic complications.[72] It should be noted, however, that if glucose levels are managed appropriately, then some of the direct medical costs (both comorbidity treatment costs as well as diabetes treatment costs) may be avoided, in addition to extending patients' life span, as seen in the intensive treatment group within the Steno-2 trial.[81-83]

When discussing the economic impact of T2D with patients, the indirect costs (estimated to account for 36.3% of the overall costs of this disease in North America[73]) should be considered. While the indirect costs, which include absenteeism or drop-out from the workforce, may not be evident to individual patients immediately, they are an important consideration in assessing the long-term benefits (eg remaining in employment) vs short-term costs of different treatments.

3.3.6 | QW GLP-1 RAs and economic impact

The immediate short-term cost evident to patients is likely to be the price of the treatment. Compared with other pharmacologic agents used for T2D that have a generic alternative available, the QW GLP-1 RAs continue to be one of the more expensive treatment options available in terms of direct wholesale cost (Table 2).[8] Due to differences in out-of-pocket expenses and insurance coverage,[76,77] such wholescale costs may not be directly relevant to patients.[8] Also, as discussed, direct medical cost of diabetes treatment is just one component contributing to the economic impact on patients. For this reason, cost-effectiveness studies within diabetes take more than prescription costs into consideration. Within the diabetes research field, there are many validated cost-effectiveness models (eg BRAVO,[84] CORE,[85] UKPDS[86]),[87] which include factors such as disease progression, mortality, macrovascular events, microvascular events and hypoglycaemia.[84-86] Through inclusion of such variables, researchers provide evidence-based data to support diabetes management at national level.[84]

A systematic review of 85 cost-effectiveness studies of newer anti-hyperglycaemia treatments demonstrated that GLP-1 RAs (including dulaglutide and exenatide ER) were cost-effective compared with dipeptidyl peptidase-4 inhibitors and sodium-glucose cotransporter-2 inhibitors.[87] Each of these three classes of newer treatments was cost-effective compared with insulin, thiazolidinediones and sulphonylureas.[87] Due to semaglutide s.c. receiving US Food and Drug Administration approval in late 2017,[10] there were not many cost-effectiveness studies completed at the time of preparing this review; however, a few studies suggested that it was cost-effective compared with the other two QW GLP-1 RAs.[88-90] When discussing QW GLP-1 RAs with patients, it may be worthwhile for pharmacists to explain the results of such cost-effectiveness studies in simple terms, reminding patients that prescription costs for glucose management treatments are not the only aspect of treating this chronic condition that need to be considered.

4 | WHAT IS NEW AND CONCLUSION

In addition to the high prevalence and associated clinical impact of T2D in the US, there is also a large impact on the individual patient and society. It is important to understand the long-term impact of complications of T2D, be aware of the recent advances in treatments that can postpone or reduce both micro- and macrovascular complications, and appreciate the short- vs long-term costs of treatment and prevention. As a result of this individual impact and the frequency with which pharmacists see such patients, it is important for pharmacists to have a complete understanding of the disease impact and treatment options, including QW GLP-1 RAs. Individual agents within this therapy group have been shown to provide CV benefits without increasing the risk of hypoglycaemia, compared with other treatments. Pharmacists can listen to patients' concerns about individual complications or comorbidities when using QW GLP-1 RAs

and advise them on how to maximize their use of medications and minimize any potential impact of the life-long challenges when living with these chronic conditions. As members of diabetes care teams, pharmacists play an important role in working with patients to improve their outcomes using a holistic management strategy that looks beyond glucose lowering, by also looking to lower patients' overall cardiometabolic risk and increase their psychosocial well-being.

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CONFLICT OF INTEREST

A Bzowyckyj has no relevant conflicts of interest to declare.

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