Health-Related Quality of Life Assessments with Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists in Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes (T2DM) is associated with significant impairment in health-related quality of life (HRQoL). A patient-centered collaborative approach is recommended to optimize clinical outcomes, including HRQoL, in this patient population. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) provide effective glycemic control and have demonstrated beneficial effects on HRQoL and treatment satisfaction. Available once-weekly GLP-1 RAs may offer enhanced convenience compared with daily GLP-1 RAs and include exenatide extended-release (ER), dulaglutide, and semaglutide.

This article reviews the impact of once-weekly GLP-1 RAs on HRQoL and treatment satisfaction in patients with T2DM. Compared with oral antihyperglycemic drugs, insulin, and daily GLP-1 RAs, once-weekly GLP-1 RAs offer benefits with regard to HRQoL and treatment satisfaction. These benefits appear to be largely mediated by relative drug effects on glycemic control, weight, and hypoglycemia. While there was not an overall class benefit of once-weekly GLP-1 RAs compared with daily GLP-1 RAs on HRQoL and treatment satisfaction, results suggested that once-weekly GLP-1 RAs may enhance certain elements of treatment satisfaction and increase willingness to continue treatment. In 2 studies comparing once-weekly GLP-1 RAs with each other, semaglutide produced significantly greater improvement in overall treatment satisfaction compared with exenatide ER but not dulaglutide. Once-weekly GLP-1 RAs represent an effective and convenient treatment option that may potentially increase treatment satisfaction and enhance adherence, contributing to improved health outcomes.

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Type 2 diabetes (T2DM) is associated with significant impairments on a broad range of health-related quality of life (HRQoL) measures, including high rates of depression.¹⁻⁵ The concept of HRQoL takes into account the patient's perspectives of both physical and mental health.⁶ Diabetes management has undergone an increasing emphasis on the need to not just address clinical outcomes such as hyperglycemia but also to view improvement in HRQoL as a goal of treatment.^{6,7} In addition to the obvious benefits of improving patients' well-being and functioning, a positive impact of treatment on HRQoL may potentially lead to improvement in mood and to better lifestyle choices that translate to improvements in other health endpoints (e.g., glycemic control, obesity, blood pressure control, self-management, and education). Further, resulting improvements in physical function may lead to increased physical activity, which may improve health outcomes.

A patient-centered collaborative approach is recommended to optimize clinical outcomes and improve HRQoL in patients

with T2DM.⁷ Both pharmacologic and nonpharmacologic approaches are important in this regard. Weight loss, associated with lifestyle changes or pharmacotherapy, is one key component of diabetes management that may also contribute to improvements in HRQoL and treatment satisfaction, although HRQoL has many determinants.^{8,9} There is a wide range of pharmaceutical treatment options available for the management of T2DM, including both injectable and oral medications. However, many treatment regimens are associated with weight and blood glucose fluctuations as well as with high costs and administration issues (e.g., frequent dosing and high pill-burden load) that may potentially impair HRQoL.

Once-daily and twice-daily (BID) glucagon-like peptide-1 receptor agonists (GLP-1 RAs) effectively reduce hyperglycemia and have demonstrated beneficial effects on HRQoL and treatment satisfaction.^{7,10-14} This class of medication is also associated with reductions in body weight, which, along with other mechanisms, may contribute to improved psychological and emotional well-being, social/daily functioning, and health perceptions.¹⁰⁻¹² In recent years, once-weekly GLP-1 RAs have become available, including exenatide extended-release (ER), dulaglutide, albiglutide, and semaglutide. This article reviews the impact of once-weekly GLP-1 RAs, oral antihyperglycemic drugs (OADs), insulin, or daily GLP-1 RAs on HRQoL and treatment satisfaction in patients with T2DM.

Quality of Life and Treatment Satisfaction

In order to enable meaningful interpretation of data on the effects of treatments on HRQoL and treatment satisfaction, it is critical to use validated tools to assess HRQoL in diabetes outcomes studies.⁶ Table 1 provides a summary of the tools used to evaluate HRQoL and treatment satisfaction in studies of once-weekly (QW) GLP-1 RAs. Of note, some studies have employed validated tools to specifically examine the impact of treatment with once-weekly GLP-1 RAs on weight-related HRQoL^{27,28} and self-perception.^{29,30} For further reference, a recent review on T2DM and HRQoL describes a broad range of HRQoL assessment tools used in patients with diabetes.⁶ Tables 2, 3, and 4 summarize the effects on HRQoL and treatment satisfaction with exenatide ER, dulaglutide, and semaglutide, respectively.

Once-Weekly GLP-1 RAs Versus Placebo

Compared with placebo, dulaglutide 0.75 mg and 1.5 mg as add-on therapy to metformin and pioglitazone in AWARD-1 significantly improved measures of patients' self-perception related to body

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TABLE 1 Tools Used to Assess Effects of Once-Weekly GLP-1 RAs on Quality of Life and Treatment Satisfaction in Patients with Type 2 Diabetes

Assessment Tool		Description of Tool
Quality of life tools		
APPADL	Ability to Perform Physical Activities of Daily Living	7-item assessment of how difficult engagement in activities deemed integral to normal life is (e.g., walking, standing, and climbing stairs); rated on 5-point numeric scale from “not at all difficult” to “unable to do” ¹⁵
DHP-18	18-item Diabetes Health Profile	18-item questionnaire assessing psychological distress, barriers to activity, and disinhibited eating and including disease-specific health-related quality of life questions ¹⁶ Items are scored from 0 (never/not at all/very likely) to 3 (always/very often/very much/not at all likely) on a 4-point Likert-type; raw scale scores on each subscale are transformed to an overall (“common”) score ranging from 0-100, with 0 indicating no dysfunction ¹⁶
EQ-5D	EuroQol 5 Dimensions	2-part questionnaire 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression 3-level responses: no problem, some problem, extreme problem Visual analog scale component rating daily health from 0-100 (worst to best health imaginable) ¹⁷
IWQOL-Lite	Impact of Weight on Quality of Life-Lite	Questionnaire assessing effect of weight on various areas of life; brief version relating identified scales to impact on physical function (11 items), self-esteem (7 items), sexual life (4 items), public distress (5 items), and work (4 items) ¹⁸ Each item begins with the phrase “Because of my weight” and is rated on a Likert scale from 5 (always true) to 1 (never true) ¹⁸ Normalized IWQOL-Lite scores (separate scores for each of 5 domains and total score) range from 0 (worst outcome) to 100 (best outcome) ¹⁹
IW-SP	Impact of Weight on Self-Perception	Questionnaire assessing 3 items of body weight’s impact on how happy an individual is with his/her appearance and public self-consciousness; rated on a 5-point numeric scale from “never” to “always” ²⁰
PGWB	Psychological General Well-being Index	Brief questionnaire measuring subjective perception of well-being and distress over previous month ^{21,22} Dimensions and score ranges include anxiety (0-25), depressed mood (0-15), positive well-being (0-20), self-control (0-15), general health (0-15), and vitality (0-20); a 20 global score (sum of 6 dimensions) ranges from 0-110; normalized scores range from 0-100, with scores for each dimension and the global score indicating greater well-being ²²
SF-36	36-item Short-Form Survey	36-item questionnaire that assesses physical function, pain, general health, mental health, emotional function, and social function ²³ Each item is scored on a scale from 1 to either 2, 3, 5, or 6; each item score is then converted to a scale of 0-100, representing the percentage of total possible score achieved and with higher scores indicating a higher health status; items on the same scale are then averaged to obtain the 8 scale scores (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health) ^{23,24}
Treatment satisfaction tool		
DTSQ	Diabetes Treatment Satisfaction Questionnaire	Questionnaire measuring satisfaction with diabetes treatment consisting of 8 items evaluating 6 aspects of treatment satisfaction and 2 perceived recent event rates of hyperglycemia/hypoglycemia ^{25,26} Each item is scored on a 7-point Likert scale ranging from 0 (very dissatisfied) to 6 (very satisfied) ²⁶ Items evaluating 6 aspects of treatment satisfaction are summed to produce a total treatment satisfaction score; DTSQ status total scores range from 0-36, with higher scores indicating greater satisfaction; the perceived frequency of hyperglycemia/hypoglycemia items are scored separately, with lower scores indicating better perceived blood glucose control ²⁶

weight (based on the Impact of Weight on Self-Perceptions Questionnaire [IW-SP]), HRQoL, treatment satisfaction, and perceived hyperglycemia (Table 3).^{29,36} A 28-week, multicenter, randomized, double-blind study comparing dulaglutide 1.5 mg with placebo as background therapy to insulin glargine with or without metformin (AWARD-9) found that, compared with placebo, dulaglutide was associated with significant improvements on the IW-SP and less disinhibited eating (Diabetes Health Profile [DHP-18]) but not on other patient-reported outcomes (PROs), including HRQoL (EuroQol-5D [EQ-5D]), psychological distress (DHP-18), and barriers to activity (DHP-18).³⁰

In SUSTAIN-5, QW semaglutide 0.5 mg and 1.0 mg, as add-on therapy to basal insulin ± metformin, were associated with significant improvements in overall treatment satisfaction from baseline to week 30 compared with placebo (Diabetes Treatment Satisfaction Questionnaire [DTSQ]; Table 4).³¹

Once-Weekly GLP-1 RAs Versus Oral Antihyperglycemic Drugs

A 26-week, multicenter, randomized, double-dummy study (DURATION-2) compared exenatide ER 2 mg with maximum daily doses of sitagliptin (100 mg) or pioglitazone (45 mg) as add-on therapy to metformin in 491 patients with T2DM.^{28,37}

Exenatide ER reduced glycated hemoglobin (A1c; -1.5%) and weight (-2.3 kg) to a significantly ($P < 0.05$) greater degree than pioglitazone (-1.2%, +2.8 kg) and sitagliptin (-0.9%, -0.8 kg); no episodes of major hypoglycemia were reported.³⁷ Weight-related HRQoL as measured by the Impact of Weight on Quality of Life-Lite (IWQoL-Lite) questionnaire improved significantly from baseline in patients receiving exenatide ER or sitagliptin but not pioglitazone (Table 2).²⁸

Improvement in weight-related HRQoL (IWQoL-Lite) was significantly greater with exenatide versus pioglitazone. Similarly, general health utility scores (EQ-5D) improved significantly for patients receiving exenatide ER or sitagliptin but not pioglitazone, although there were no significant differences between treatment groups. All treatment groups demonstrated significant improvements in psychological well-being (Psychological General Well-being Index [PGWB]) and diabetes treatment satisfaction (DTSQ), with no significant differences between exenatide ER and either comparator. Across the entire study population, the development of nausea/vomiting did not affect treatment satisfaction. However, reduction in body weight was found to correlate significantly with improvements in overall weight-related HRQoL ($r = -0.26$, $P < 0.0001$).

AWARD-3 was a 52-week, multicenter, randomized, double-blind, double-dummy study comparing dulaglutide 0.75 mg, dulaglutide 1.5 mg, and metformin in patients with T2DM managed with diet and exercise.^{29,36,38} Both doses of dulaglutide (-0.7% [dulaglutide 0.75 mg], -0.8% [dulaglutide 1.5 mg]) produced significantly greater reductions in A1c than metformin (-0.6%) at 26 weeks, whereas mean weight reduction at 26 weeks was similar between dulaglutide 1.5 mg (-2.3 kg) and metformin (-2.2 kg) but was less with dulaglutide 0.75 mg (-1.4 kg). No severe hypoglycemic events occurred. At week 26, there were no significant differences between dulaglutide and metformin with regard to improvements in impact of weight on self-perception (IW-SP), Ability to Perform Physical Activities of Daily Living scale (APPADL), or treatment satisfaction, with the exception of significantly ($P < 0.05$) greater improvement in perceived hyperglycemia (DTSQs-hyperglycemia score) in the dulaglutide 1.5 QW group (Table 3).^{29,36} The latter finding is consistent with the greater reductions in A1c observed with dulaglutide compared with metformin. Although there was a statistically significant relationship between change in A1c and change in treatment satisfaction, the strength of the relationship was of questionable clinical significance (slope estimate for regression analysis, -1.058; $P \leq 0.001$).³⁶ There was no significant relationship between weight or hypoglycemia incidence and change in treatment satisfaction.

In AWARD-5, a 104-week, multicenter, randomized, double-blind, placebo-controlled study with a primary endpoint of 52 weeks, dulaglutide 0.75 mg and 1.5 mg were compared with sitagliptin in patients with T2DM on background metformin therapy.³⁹ Placebo-treated patients were switched to sitagliptin

after 26 weeks. At 52 weeks, both dulaglutide doses were associated with significantly greater reductions in A1c (-0.9% [dulaglutide 0.75 mg], -1.1% [dulaglutide 1.5 mg]) and weight (2.6 kg [dulaglutide 0.75 mg], -3.0 kg [dulaglutide 1.5 mg]) compared with sitagliptin (A1c: -0.4%; body weight: -1.5 kg). No severe hypoglycemic events occurred. However, there were no significant differences at 52 weeks between either dose of dulaglutide and sitagliptin on measures of HRQoL and impact of weight on quality of life (Table 3).²⁹

SUSTAIN-2 was a 56-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled study that compared semaglutide 0.5 mg and 1.0 mg with sitagliptin as add-on therapy to metformin, a thiazolidinedione, or a combination of metformin with a thiazolidinedione in patients with T2DM.³³ Compared with sitagliptin, both doses of semaglutide produced significantly greater reductions from baseline to week 56 in A1c (-1.3% [semaglutide 0.5 mg], -1.6% [semaglutide 1.0 mg], -0.5% [sitagliptin]) and body weight (-4.3 kg [semaglutide 0.5 mg], -6.1 kg [semaglutide 1.0 mg], -1.9 kg [sitagliptin]). Severe hypoglycemia occurred in no semaglutide-treated patients and in 2 patients receiving sitagliptin. Overall treatment satisfaction and perceived hyperglycemia (DTSQ) improved to a significantly greater extent in the semaglutide groups than in the sitagliptin group (Table 4). Compared with patients taking sitagliptin, responses to individual DTSQ items indicated that those taking semaglutide found their treatment to be more convenient (1.0 mg dose) and more flexible (both doses), were more satisfied with their understanding of their diabetes (1.0 mg dose), were more willing to continue their current treatment (1.0 mg dose), and were more likely to recommend their treatment (both doses). Further, several aspects of HRQoL, as measured on the 36-item Short-Form Survey (SF-36), improved with semaglutide versus sitagliptin (Table 4).

Once-Weekly GLP-1 RAs Versus Insulin

Dulaglutide (0.75 and 1.5 mg) was compared with insulin glargine at week 26 (primary endpoint) as add-on therapy to insulin lispro with or without metformin (AWARD-4)⁴⁰ and at week 52 (primary endpoint) in patients receiving metformin and glimepiride (AWARD-2).⁴¹ In AWARD-4, both doses of dulaglutide were associated with significantly greater reductions in A1c than insulin glargine at week 26 (-1.6% [dulaglutide 0.75 mg], -1.6% [dulaglutide 1.5 mg], -1.4% [insulin glargine]).⁴⁰ Body weight decreased with dulaglutide 1.5 mg (-0.9 kg) and increased slightly with dulaglutide 0.75 mg (+0.2 kg), but both doses were significantly different versus insulin glargine (+2.3 kg; i.e., greater weight gain was observed with insulin). Compared with insulin glargine, incidence rates of hypoglycemia (plasma glucose ≤ 3.9 mmol/L) at week 26 were similar with both doses of dulaglutide (88.4% [dulaglutide 0.75 mg], 85.9% [dulaglutide 1.5 mg], 89.5% [insulin glargine]). At week 26, the only significant difference between dulaglutide and insulin glargine in PROs

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TABLE 2 Changes from Baseline in Patient-Reported Outcomes in the DURATION Clinical Trial Program with Once-Weekly Exenatide ER Compared with Other Antidiabetic Therapies

Variable	DURATION-1 (Week 30) ²⁷		DURATION-1 (Week 30-52) ²⁷	
	Exenatide ER 2 mg (n = 148) LSM Change (SE)	Exenatide BID 10 µg (n = 147) LSM Change (SE)	Exenatide ER 2 mg LSM Change (SE)	Exenatide 10 µg BID→Exenatide ER 2 mg LSM Change (SE)
DTSQ				
DTSQs total score	5.17 (0.54) ^a	3.97 (0.53) ^a	0.65 (3.8)	1.16 (6.1) ^b
Treatment satisfaction—current	1.29 (0.12) ^a	1.11 (0.11) ^a	0.10 (0.77)	0.01 (1.2)
Perceived frequency hyperglycemia	-1.86 (0.15) ^{a,c}	-1.42 (0.15) ^a	-0.04 (1.9)	-0.15 (1.8)
Perceived frequency hypoglycemia	0.08 (0.12)	0.14 (0.11)	-0.18 (1.4)	-0.21 (1.4)
Treatment convenience	0.25 (0.13) ^d	0.14 (0.13)	0.30 (1.2) ^e	0.42 (1.6) ^e
Treatment flexibility	0.49 (0.13) ^a	0.27 (0.13) ^d	0.24 (1.2) ^b	0.39 (1.7) ^b
Understanding of diabetes	0.50 (0.10) ^a	0.56 (0.10) ^a	0.06 (0.94)	0.04 (1.2)
Treatment recommend	0.98 (0.10) ^a	0.83 (0.10) ^a	-0.05 (0.94)	0.07 (1.1)
Treatment satisfaction—continue	1.43 (0.13) ^{a,c}	0.99 (0.12) ^a	-0.01 (0.93)	0.24 (1.3) ^b
IWQOL-Lite				
IWQOL-Lite total score	10.23 (0.89) ^a	8.61 (0.88) ^a	0.36 (7.1)	1.44 (8.7)
Physical function	12.06 (1.20) ^a	9.55 (1.21) ^a	0.08 (9.5)	2.13 (11.5) ^b
Self-esteem	13.60 (1.31) ^a	13.71 (1.30) ^a	0.83 (10.9)	1.12 (11.5)
Sexual life	7.34 (1.51) ^a	6.95 (1.50) ^a	0.64 (17.3)	0.91 (15.2)
Public distress	6.05 (1.00) ^a	4.07 (1.00) ^a	6.96 (13.2) ^f	5.04 (11.2) ^f
Work	8.17 (1.13) ^a	5.81 (1.12) ^a	0.42 (9.8)	1.10 (11.2)
Variable	DURATION-2 (Week 26) ²⁸			
	Exenatide ER 2 mg (n = 160) LSM Change (SE)	Sitagliptin (n = 166) LSM Change (SE)	Pioglitazone (n = 165) LSM Change (SE)	
DTSQ				
Total score	3.96 (0.60) ^d	2.35 (0.59) ^d	2.50 (0.61) ^d	
Perceived frequency hyperglycemia	-1.63 (0.17) ^d	-1.30 (0.17) ^d	-1.28 (0.17) ^d	
Perceived frequency hypoglycemia	0.22 (0.15)	-0.05 (0.15)	-0.12 (0.15)	
IWQOL-Lite				
IWQOL-Lite total score	5.15 (1.04) ^d	4.56 (1.02) ^d	1.20 (1.06) ^g	
Physical function	6.78 (1.35) ^d	5.81 (1.33) ^d	2.00 (1.38) ^g	
Self-esteem	5.88 (1.39) ^d	5.79 (1.36) ^d	3.11 (1.41)	
Sexual life	5.80 (1.61) ^d	5.02 (1.61) ^d	2.41 (1.63)	
Public distress	3.86 (1.17) ^d	2.40 (1.14) ^d	-0.63 (1.18) ^g	
Work	2.79 (1.28) ^d	3.02 (1.25) ^d	-1.28 (1.29) ^g	
EQ-5D				
Index score	0.04 (0.02) ^d	0.05 (0.02) ^d	0.02 (0.02)	
Visual analog scale score	4.46 (1.34) ^d	6.04 (1.32) ^d	2.54 (1.37)	
PGWB				
Global score	6.82 (1.00) ^d	6.97 (0.98) ^d	4.78 (1.02) ^d	
Anxiety	8.40 (1.31) ^d	8.20 (1.28) ^d	5.10 (1.33) ^d	
Depressed mood	3.84 (1.33) ^d	3.80 (1.30) ^d	3.73 (1.36) ^d	
Positive well-being	4.65 (1.42) ^d	7.86 (1.39) ^d	5.02 (1.45) ^d	
Self-control	5.53 (1.37) ^d	4.30 (1.34) ^d	3.68 (1.40) ^d	
General health	9.46 (1.40) ^d	6.95 (1.37) ^d	6.37 (1.43) ^d	
Vitality	7.46 (1.37) ^d	8.98 (1.35) ^d	6.23 (1.41) ^d	

^aP<0.001 from baseline to week 30.

^bP≤0.05 from week 30 to week 52.

^cP<0.05 exenatide ER versus exenatide BID.

^dP≤0.05 versus baseline to week 30/26.

^eP<0.01 from week 30 to week 52.

^fP<0.001 from week 30 to week 52.

^gP≤0.05 versus exenatide ER.

BID=twice weekly; DTSQ=Diabetes Treatment Satisfaction Questionnaire; DTSQs=Diabetes Treatment Satisfaction Questionnaire–Status version; EQ-5D=EuroQol 5 Dimensions; ER=extended release; LSM=least squares mean; IWQOL-Lite=Impact of Weight on Quality of Life–Lite; PGWB=Psychological General Well-Being Index; SE=standard error.

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TABLE 3 Changes from Baseline in Patient-Reported Outcomes in the AWARD Clinical Trial Program with Once-Weekly Dulaglutide Compared with Other Antidiabetic Therapies²⁹

Variable	AWARD-3 (Week 26)			AWARD-5 (Week 52)		
	Dulaglutide 1.5 mg (n = 269)	Dulaglutide 0.75 mg (n = 270)	Metformin (n = 268)	Dulaglutide 1.5 mg (n = 279)	Dulaglutide 0.75 mg (n = 280)	Sitagliptin (n = 276)
IW-SP ^a	6.0 (1.6) ^b	5.3 (1.5) ^b	6.6 (1.5) ^b	–	–	–
APPADL ^a	0.3 (1.2)	0.7 (1.2)	0.1 (1.2)	–	–	–
IWQOL-Lite ^a	–	–	–	3.3 (0.7) ^b	2.7 (0.7) ^b	2.1 (0.7) ^b
EQ-5D UK Index	–	–	–	0.00 (0.01)	0.01 (0.01)	0.00 (0.01)
EQ-5D VAS	–	–	–	2.1 (0.8) ^b	1.5 (0.8)	1.2 (0.8)
DTSQs ^c	1.9 (0.4) ^b	1.8 (0.4) ^b	2.0 (0.4) ^b	–	–	–
DTSQs-Hyperglycemia	-1.3 (0.1) ^{b,d}	-1.1 (0.1) ^b	-0.9 (0.1) ^b	–	–	–
DTSQs-Hypoglycemia	-0.1 (0.1)	-0.1 (0.1)	0.1 (0.1)	–	–	–
DSC-R	0.2 (0.4)	-0.2 (0.4)	0.4 (0.4)	–	–	–
Variable	AWARD-2 (Week 52)			AWARD-4 (Week 26)		
	Dulaglutide 1.5 mg (n = 273)	Dulaglutide 0.75 mg (n = 272)	Insulin glargine (n = 262)	Dulaglutide 1.5 mg (n = 295)	Dulaglutide 0.75 mg (n = 293)	Insulin glargine (n = 296)
IW-SP ^a	3.8 (1.3) ^b	2.0 (1.3)	1.2 (1.4)	4.9 (1.4) ^{b,d}	3.0 (1.4) ^b	1.5 (1.4)
APPADL ^a	3.4 (1.1) ^{b,d}	1.4 (1.1) ^d	-2.1 (1.1)	-1.8 (1.1)	-2.1 (1.1)	-3.1 (1.1) ^b
EQ-5D UK Index	0.01 (0.01) ^d	0.00 (0.01) ^d	-0.04 (0.01) ^b	-0.03 (0.01) ^b	-0.02 (0.01)	-0.03 (0.01) ^b
EQ-5D VAS	3.2 (0.9) ^b	2.3 (0.9) ^b	1.1 (0.9)	-1.4 (1.0)	-1.0 (1.0)	-0.4 (1.0)
ALBSS ^c	-4.2 (0.8) ^{b,d}	-4.1 (0.8) ^{b,d}	-1.0 (0.9)	3.5 (1.3) ^b	3.3 (1.3) ^b	3.3 (1.3) ^b
ALBSS-Worry	-2.2 (0.5) ^{b,d}	-2.1 (0.5) ^{b,d}	-0.3 (0.5)	2.1 (0.9) ^b	1.1 (0.9)	2.1 (0.9) ^b
ALBSS-Behavior	-2.1 (0.5) ^{b,d}	-2.1 (0.5) ^{b,d}	-0.8 (0.5)	1.3 (0.6) ^b	2.2 (0.6) ^b	1.2 (0.6) ^b
Variable	AWARD-1 (Week 26)			AWARD-6 (Week 26)		
	Dulaglutide 1.5 mg (n = 279)	Dulaglutide 0.75 mg (n = 280)	Exenatide (n = 276)	Placebo (n = 141)	Dulaglutide 1.5 mg (n = 299)	Liraglutide 1.8 mg (n = 300)
IW-SP ^a	4.7 (1.2) ^b	3.9 (1.2) ^b	3.9 (1.2) ^b	3.7 (1.6) ^b	7.4 (1.3) ^b	7.7 (1.3) ^b
APPADL ^a	0.6 (1.0)	0.4 (1.0)	1.7 (1.0)	0.1 (1.3)	2.6 (1.1) ^b	0.5 (1.1)
EQ-5D UK Index	0.01 (0.01)	0.01 (0.01)	0.00 (0.01)	0.00 (0.02)	0.02 (0.01) ^b	0.01 (0.01)
EQ-5D VAS	4.5 (0.9) ^{b,e}	2.4 (0.9) ^b	3.9 (0.9) ^{b,e}	0.7 (1.2)	2.8 (0.8) ^b	1.8 (0.8) ^b
DTSQs ^c	2.4 (0.3) ^{b,d,e}	2.6 (0.3) ^{b,d,e}	0.9 (0.3) ^b	0.5 (0.5)	–	–
DTSQs-Hyperglycemia	-1.9 (0.1) ^{b,d,e}	-1.8 (0.1) ^{b,d,e}	-1.1 (0.1) ^{b,e}	-0.5 (0.2) ^b	–	–
DTSQs-Hypoglycemia	0.1 (0.1) ^d	0.2 (0.1) ^d	0.5 (0.1) ^b	0.3 (0.2)	–	–
Variable	AWARD-9 (Week 28)					
	Dulaglutide 1.5 mg (n = 150)	Placebo (n = 150)				
IW-SP ^a	6.14 (2.25) ^{b,e}	0.07 (2.20)				
EQ-5D UK Index	-0.03 (0.02)	-0.02 (0.02)				
EQ-5D VAS	2.73 (1.37) ^e	0.65 (1.33)				
DHP-18 (psychological distress domain)	0.13 (1.39)	0.89 (1.35)				
DHP-18 (barriers to activity domain)	-0.63 (1.48)	2.21 (1.43)				
DHP-18 (disinhibited eating domain)	-5.69 (1.70) ^{b,e}	-1.18 (1.65)				

Note: Data are presented as least squares mean (standard error).

^aTotal score transformed.

^bP < 0.05 versus placebo.

^cTotal score.

^dP < 0.05 versus active comparator.

^eP < 0.05 versus baseline.

ALBSS = Adult Low Blood Sugar Survey; APPADL = Ability to Perform Physical Activities of Daily Living; DTSQs = Diabetes Treatment Satisfaction Questionnaire–Status version; DSC-R = Diabetes Symptom Checklist–Revised; EQ-5D = EuroQol 5 Dimensions; IWQOL-Lite = Impact of Weight on Quality of Life–Lite; IW-SP = Impact of Weight on Self-Perception; VAS = visual analog scale.

TABLE 4 Changes from Baseline in Patient-Reported Outcomes in the SUSTAIN Clinical Trial Program with Once-Weekly Semaglutide Compared with Other Antidiabetic Therapies

Variable	SUSTAIN-5 (30 Weeks) ³¹			SUSTAIN-3 (56 Weeks) ³²	
	Semaglutide 0.5 mg (n = 132) Mean Change	Semaglutide 1.0 mg (n = 131) Mean Change	Placebo (n = 133) Mean Change	Semaglutide 1.0 mg (n = 404) Mean Change	Exenatide ER 2.0 mg (n = 405) Mean Change
DTSQs	2.7 ^a	3.5 ^b	1.2	5.0 ^b	4.0
Variable	SUSTAIN-2 (56 Weeks) ³³		SUSTAIN-4 (30 Weeks) ³⁴		
	Semaglutide 0.5 mg (n = 409) Mean (95% CI) ETD vs. Sitagliptin	Semaglutide 1.0 mg (n = 409) Mean (95% CI) ETD vs. Sitagliptin	Semaglutide 0.5 mg (n = 362) Mean (95% CI) ETD vs. Insulin Glargine	Semaglutide 1.0 mg (n = 360) Mean (95% CI) ETD vs. Insulin Glargine	
DTSQ					
DTSQs total score	0.83 (0.18, 1.48) ^a	1.46 (0.81, 2.11) ^a	0.87 (0.11, 1.63) ^a	1.38 (0.60, 2.15) ^a	
Treatment satisfaction—current	0.16 (0.01, 0.30) ^a	0.28 (0.14, 0.42) ^a	0.03 (-0.16, 0.21)	0.16 (-0.03, 0.34)	
Perceived frequency hyperglycemia	-0.38 (-0.64, -0.12) ^a	-0.61 (-0.87, -0.35) ^a	-0.44 (-0.70, -0.17) ^a	-0.71 (-0.97, -0.44) ^a	
Perceived frequency hypoglycemia	0.08 (-0.13, 0.29)	-0.02 (-0.22, 0.19)	-0.02 (-0.25, 0.20)	-0.07 (-0.30, 0.16)	
Treatment convenience	0.13 (-0.02, 0.28)	0.21 (0.06, 0.37) ^a	0.20 (0.03, 0.37) ^a	0.17 (-0.00, 0.34)	
Treatment flexibility	0.18 (0.02, 0.33) ^a	0.19 (0.04, 0.35) ^a	0.16 (-0.01, 0.34)	0.33 (0.15, 0.51) ^a	
Understanding of diabetes	0.02 (-0.14, 0.18)	0.16 (0.01, 0.32) ^a	0.04 (-0.11, 0.19)	0.07 (-0.09, 0.22)	
Treatment recommendation	0.21 (0.07, 0.35) ^a	0.31 (0.17, 0.44) ^a	0.14 (-0.02, 0.30)	0.24 (0.08, 0.40) ^a	
Treatment satisfaction—continue	0.10 (-0.04, 0.24)	0.25 (0.11, 0.39) ^a	0.28 (0.09, 0.47) ^a	0.36 (0.17, 0.56) ^a	
SF-36					
Physical component summary	-0.11 (-1.04, 0.83)	0.21 (-0.71, 1.14)	0.00 (-0.97, 0.98)	0.91 (-0.07, 1.89)	
Mental component summary	1.72 (0.54, 2.89) ^a	1.64 (0.47, 2.81) ^a	0.98 (-0.28, 2.25)	1.08 (-0.20, 2.35)	
Physical functioning	0.10 (-0.88, 1.09)	0.44 (-0.54, 1.42)	0.96 (-0.21, 2.12)	0.08 (-0.37, 1.97)	
Role physical	0.30 (-0.80, 1.40)	0.92 (-0.17, 2.02)	0.12 (-1.12, 1.36)	1.19 (-0.06, 2.44)	
Bodily pain	0.71 (-0.68, 2.10)	-0.13 (-1.51, 1.25)	0.05 (-1.34, 1.43)	0.86 (-0.53, 2.25)	
General health	0.40 (-0.65, 1.45)	0.96 (-0.09, 2.01)	0.33 (-0.70, 1.35)	1.15 (0.12, 2.18) ^a	
Vitality	1.52 (0.36, 2.68) ^a	1.31 (0.16, 2.47) ^a	0.75 (-0.49, 2.00)	1.13 (-0.12, 2.38)	
Social functioning	0.62 (-0.53, 1.77)	1.06 (-0.09, 2.21)	0.77 (-0.52, 2.06)	0.68 (-0.62, 1.98)	
Role emotional	0.81 (-0.46, 2.08)	1.43 (0.17, 2.70) ^a	0.83 (-0.63, 2.29)	1.67 (0.20, 3.14) ^a	
Mental health	2.03 (0.78, 3.28) ^a	1.24 (-0.00, 2.49)	1.15 (-0.11, 2.40)	0.62 (-0.64, 1.89)	

continued on next page

was significantly greater improvement in impact of weight on self-perception (IW-SP) with dulaglutide 1.5 mg (Table 3).^{29,40} In AWARD-2, the higher dulaglutide dose (-1.1%) produced a significantly greater reduction in A1c than insulin glargine (-0.6%) at week 52.⁴¹ Both doses of dulaglutide were associated with weight loss (-1.3 kg [dulaglutide 0.75 mg], -1.9 kg [dulaglutide 1.5 mg]), while insulin glargine was associated with weight gain (1.4 kg); the difference versus insulin glargine was significant for both dulaglutide doses. Incidence rates of total hypoglycemia were significantly lower for dulaglutide 0.75 mg (54.4%) and 1.5 mg (55.3%) compared with insulin glargine (69.1%), although severe hypoglycemia was rare. At week 52, both doses of dulaglutide were associated with significantly greater improvement compared with insulin glargine in HRQoL (on the EQ-5D), in ability to perform physical activities of daily living (APPADL), and on PROs related to hypoglycemia.²⁹

SUSTAIN-4 was a 30-week, multicenter, randomized, open-label study comparing semaglutide 0.5 mg and 1.0 mg with insulin glargine against a background of metformin with or without sulfonylurea in patients with T2DM.³⁴ At 30 weeks, both doses of semaglutide were associated with significantly greater reductions in A1c compared with insulin glargine (-1.2% [semaglutide 0.5 mg], -1.6% [semaglutide 1.0 mg], -0.8% [insulin glargine]). Body weight decreased with both semaglutide doses but increased with insulin glargine (-3.5 kg [semaglutide 0.5 mg], -5.2 kg [semaglutide 1.0 mg]; +1.2 kg [insulin glargine]), and the difference was statistically significant ($P < 0.0001$) for both semaglutide doses. Significantly greater percentages of patients developed severe or blood glucose-confirmed hypoglycemia with insulin glargine (11%) compared with semaglutide 0.5 mg (4%) or semaglutide 1.0 mg (6%), although the incidence of severe hypoglycemia was similar and low ($\leq 1\%$) in all treatment groups. Both doses of semaglutide were associated with significantly greater overall

TABLE 4 Changes from Baseline in Patient-Reported Outcomes in the SUSTAIN Clinical Trial Program with Once-Weekly Semaglutide Compared with Other Antidiabetic Therapies (*continued*)

Variable	SUSTAIN-7 (40 weeks) ³⁵	
	Semaglutide 0.5 mg (n = 301) Mean (95% CI) ETD vs. Dulaglutide 0.75 mg (n=299)	Semaglutide 1.0 mg (n = 300) Mean (95% CI) ETD vs. Dulaglutide 1.5 mg (n = 299)
DTSQ		
DTSQs total score	0.08 (-0.71, 0.86)	-0.10 (-0.89, 0.70)
Treatment satisfaction—current	-0.13 (-0.31, 0.06)	0.00 (-0.19, 0.19)
Perceived frequency hyperglycemia	-0.32 (-0.60, -0.04) ^c	-0.40 (-0.68, -0.12) ^c
Perceived frequency hypoglycemia	0.04 (-0.20, 0.28)	0.22 (-0.03, 0.46)
Treatment convenience	0.13 (-0.04, 0.30)	-0.03 (-0.21, 0.14)
Treatment flexibility	-0.00 (-0.18, 0.17)	0.02 (-0.16, 0.19)
Understanding of diabetes	0.07 (-0.08, 0.23)	-0.00 (-0.16, 0.15)
Treatment recommendation	0.09 (-0.08, 0.26)	-0.00 (-0.18, 0.17)
Treatment satisfaction—continue	-0.06 (-0.26, 0.13)	-0.05 (-0.25, 0.15)
SF-36		
Physical component summary	-0.72 (-1.81, 0.37)	0.75 (-0.35, 1.85)
Mental component summary	0.50 (-0.84, 1.84)	0.15 (-1.20, 1.50)
Physical functioning	-0.92 (-2.12, 0.29)	0.95 (-0.26, 2.17)
Role physical	-0.41 (-1.72, 0.90)	1.21 (-0.12, 2.53)
Bodily pain	-0.73 (-2.15, 0.69)	0.77 (-0.67, 2.21)
General health	0.79 (-0.39, 1.97)	-0.21 (-1.41, 0.98)
Vitality	-0.91 (-2.29, 0.47)	0.14 (-1.25, 1.54)
Social functioning	0.40 (-0.94, 1.75)	0.20 (-1.15, 1.56)
Role emotional	0.07 (-1.51, 1.64)	0.48 (-1.11, 2.08)
Mental health	0.46 (-0.88, 1.81)	0.69 (-0.67, 2.04)

^aP<0.05 versus placebo/sitagliptin/insulin glargine.

^bP<0.01 versus placebo/exenatide ER.

^cP<0.05 versus dulaglutide.

CI = confidence interval; DTSQ = Diabetes Treatment Satisfaction Questionnaire; DTSQs = Diabetes Treatment Satisfaction Questionnaire—Status version; ETD = estimated treatment difference; SF-36 = 36-item Short-Form Survey.

treatment satisfaction than insulin glargine (DTSQ; Table 4). Additionally, the 1.0 mg dose of semaglutide demonstrated significant improvement compared with insulin glargine in the role-emotional (measure of role limitations due to emotional problems) and general health domains of the SF-36 but not on other SF-36 domains.

Once-Weekly Versus Daily GLP-1 RAs

A 52-week, multicenter, open-label study of patients with T2DM managed with diet and exercise and/or OADs randomized patients to exenatide QW or BID during weeks 1 to 30 (DURATION-1).^{27,42} Subsequently, all patients received exenatide QW from week 30 to week 52. At 30 weeks, patients receiving exenatide QW had significantly greater reductions in A1c compared with those receiving exenatide BID (-1.9% vs. -1.5%), and a greater proportion of patients treated with exenatide QW achieved A1c ≤ 7% (77% vs. 61%).⁴² Similar reductions in weight and rates of hypoglycemia were observed with exenatide QW (-3.7 kg) and exenatide BID (-3.6 kg). Patients continuing on

exenatide QW had sustained reductions in A1c (2.0% at week 52), while those who switched from exenatide BID to QW experienced improvements in A1c (-2.0% at week 52); body weight was similarly reduced in both treatment arms by week 52 (-4.1 kg [exenatide QW only]; -4.5 kg [exenatide BID to exenatide QW]).⁴³ From baseline to week 30, significant improvements in weight-related HRQoL (IWQOL-Lite) and treatment satisfaction (DTSQ) were observed in both treatment groups, with no significant differences between groups (Table 2).²⁷ However, at week 30, treatment satisfaction (DTSQ) had improved significantly more in the exenatide QW group than the exenatide BID group with respect to perceived hyperglycemia frequency and willingness to continue current treatment. Patients who switched from exenatide BID to exenatide QW at week 30 experienced improvements from week 30 to week 52 (IWQOL-Lite) in physical function and public distress HRQoL domains as well as in overall treatment satisfaction, treatment convenience, treatment flexibility, and satisfaction with continuing current treatment. Between weeks 30 and 52, those

patients initially taking exenatide QW reported significant improvements in the public distress domain (IWQOL-Lite) as well as in satisfaction with treatment convenience and flexibility (DTSQ). The development of nausea or injection-site reactions did not moderate the effects of treatment on HRQoL or treatment satisfaction.

In a 32-week, multicenter, randomized, open-label study in patients receiving 1 or more OADs (HARMONY-7), albiglutide 30 mg QW was inferior to liraglutide 1.8 mg once daily (QD) with respect to decrease from baseline in A1c (-0.8% [albiglutide]; -1.0% [liraglutide]) and also produced significantly less weight loss than liraglutide (-0.6 kg [albiglutide], -2.2 kg [liraglutide]).⁴⁴ Treatment satisfaction scores on the Diabetes Medication Satisfaction Questionnaire improved to a similar degree with both treatments (3.3 for albiglutide, 4.4 for liraglutide, $P=0.207$).

AWARD-1 was a 52-week, multicenter, randomized, double-blind, placebo-controlled study in patients with T2DM that compared dulaglutide (0.75 mg and 1.5 mg) with exenatide BID against a background of metformin and pioglitazone therapy.⁴⁵ At 26 weeks (primary endpoint), both doses of dulaglutide reduced A1c to a significantly greater degree than exenatide BID (-1.3% [dulaglutide 0.75 mg], -1.5% [dulaglutide 1.5 mg], -1.0% [exenatide]). Compared with exenatide BID (-1.1 kg), dulaglutide 1.5 mg (-1.3 kg) produced similar mean weight loss, and dulaglutide 0.75 mg (+0.2 kg) was associated with significant weight gain. No severe hypoglycemic events occurred with dulaglutide, but 2 were reported with exenatide BID.⁴⁵ Both doses of dulaglutide resulted in significantly greater improvement in treatment satisfaction (DTSQs) compared with exenatide BID at weeks 26 and 52 in AWARD-1, although there were no differences between treatment groups in improvement on HRQoL (EQ-5D), impact of weight on self-perception (IW-SP), or impact of weight on ability to perform physical ADL 881 (APPADL; Table 2).^{29,36} At weeks 26 and 52, both doses of dulaglutide were associated with significantly greater reductions in perceived frequency of hyperglycemia (DTSQs-Hyperglycemia) compared with exenatide BID. Perceived frequency of hypoglycemia (DTSQs-Hypoglycemia) increased with exenatide BID but not with dulaglutide, and differences for both doses were significant at weeks 26 and 52. There was no linear association between change in A1c and change in overall treatment satisfaction (DTSQ total score), and there also were no significant correlations between change in overall treatment satisfaction and changes in weight or hypoglycemia incidence.³⁶

A 26-week, multicenter, randomized, open-label study (AWARD-6) compared dulaglutide 1.5 mg QW with liraglutide 1.8 mg QD as add-on therapy to metformin in patients with T2DM.⁴⁶ Reduction in A1c with dulaglutide 1.5 mg was noninferior to that of liraglutide 1.8 mg (1.4% for both drugs), although significantly greater weight loss was observed with liraglutide (-3.6 kg vs. -2.9 kg with dulaglutide). No severe

hypoglycemic events occurred. There were no significant differences between dulaglutide 1.5 mg QW and liraglutide 1.8 mg QD with respect to improvement in HRQoL (EQ-5D), impact of weight on self-perception (IW-SP), or impact of weight on APPADL (Table 3).²⁹

Comparison Between Once-Weekly GLP-1 RAs

A randomized, open-label, multicenter, 56-week trial (SUSTAIN-3) compared semaglutide 1.0 mg with exenatide ER 2.0 mg as add-on therapy to 1 or 2 OADs in patients with T2DM.³² Compared with exenatide ER, semaglutide produced significantly greater reductions in A1c and weight at week 56. Improvement in overall treatment satisfaction was significantly greater with semaglutide versus exenatide ER (Table 4).

SUSTAIN-7 was an open-label, multicenter, 40-week study that compared semaglutide 0.5 mg versus dulaglutide 0.75 mg and semaglutide 1.0 mg versus dulaglutide 1.5 mg as add-on therapy to a stable metformin regimen in adults with T2DM.³⁵ Changes from baseline to week 40 in A1c and body weight were significantly greater with semaglutide 0.5 mg versus dulaglutide 0.75 mg (A1c: -1.5% [semaglutide 0.5 mg], -1.1% [dulaglutide 0.75 mg]; body weight: -4.6 kg [semaglutide 0.5 mg], -2.3 kg [dulaglutide 0.75 mg]) and with semaglutide 1.0 mg versus dulaglutide 1.5 mg (A1c: -1.8% [semaglutide 1.0 mg], -1.4% [dulaglutide 1.5 mg]; body weight: -6.5 kg [semaglutide 1.0 mg], -3.0 kg [dulaglutide 1.5 mg]). Rates of severe or blood glucose-confirmed hypoglycemia were low (1%-2%) across treatment groups. Total treatment satisfaction scores (DTSQ) were high at baseline, and changes from baseline in overall treatment satisfaction did not differ between semaglutide and dulaglutide (Table 4). In contrast to the greater benefit of semaglutide on A1c levels, the only DTSQ item on which there was a significant difference involved perceived hyperglycemia, with responses favoring dulaglutide ($P<0.05$; Table 4). HRQoL, as assessed with the SF-36, did not differ between semaglutide and dulaglutide.

Treatment Adherence

Once-weekly GLP-1 RAs may potentially support greater adherence than daily GLP-1 RAs because of the convenience of less frequent dosing.⁴⁷ Accordingly, studies have demonstrated greater adherence with exenatide QW versus exenatide BID^{48,49} and liraglutide QD.⁴⁸⁻⁵⁰ A retrospective study using U.S. administrative claims data found that, relative to patients receiving exenatide QW, the odds of achieving $\geq 80\%$ adherence over 6 months were lower with exenatide BID (odds ratio [OR]=0.41) and liraglutide (OR=0.80, both $P<0.001$), and the odds of achieving $\geq 90\%$ adherence were lower with exenatide BID (OR=0.31) and liraglutide (OR=0.60, both $P<0.001$).⁴⁸ Similarly, a retrospective cohort study using medical and pharmacy claims data reported that, over 6 months, significantly higher percentages of patients treated with exenatide QW

had $\geq 80\%$ adherence (43.2%) versus exenatide BID (39.0%, $P < 0.01$) and liraglutide (35.0%, $P < 0.001$), and patients receiving exenatide QW were also more likely to have $\geq 90\%$ adherence (37.2%) compared with exenatide BID (20.6%) or liraglutide (23.3%; $P < 0.001$ for both comparisons).⁴⁹ In an analysis of adherence data from a German prescriptions database, patients receiving exenatide ER were significantly more likely than those receiving liraglutide to achieve $\geq 80\%$ adherence over 6 months (OR = 1.78, $P < 0.0001$).⁵⁰ Greater adherence (percentage achieving $\geq 80\%$ adherence over 6 months, with propensity score matching used to account for possible selection bias: 54.2% [dulaglutide] vs. 37.9% [exenatide QW], $P < 0.0001$; 53.5% [dulaglutide] vs. 44.3% [liraglutide], $P < 0.0001$) and persistence (percentage of patients who discontinued treatment, with propensity score matching used to account for possible selection bias: 26.2% [dulaglutide] vs. 48.4% [exenatide QW], $P < 0.0001$; 28.0% [dulaglutide] vs. 35.6% [liraglutide], $P < 0.0001$) have also been observed with dulaglutide versus exenatide QW or liraglutide QD.⁵¹ Further research is needed to better define the benefits of once-weekly GLP-1 RAs with regard to HRQoL and treatment satisfaction and to clarify the relationship of these benefits to treatment adherence.

Discussion

It is important to understand the impact of diabetes treatments on HRQoL given the treatment goal of reducing diabetes-related impairment in HRQoL and considering that treatment-related improvements in HRQoL may enable patients to better manage their self-care and engage in health-promoting activities, such as exercise and healthy diet. Improvements in treatment satisfaction may enhance HRQoL and may also potentially translate to better treatment adherence, which in turn may improve disease control and lead to better health outcomes.

Studies of once-weekly GLP-1 RAs have employed a variety of tools to assess the effects of medications on HRQoL and treatment satisfaction, as well as on various aspects of these PROs. When compared with OADs, once-weekly GLP-1 RAs demonstrated some advantages with regard to glycemic control, weight, and hypoglycemia risk that, in some but not all cases, were associated with significantly greater improvement in corresponding aspects of HRQoL and treatment satisfaction. For example, in DURATION-2, exenatide ER significantly reduced weight compared with both sitagliptin and pioglitazone and also significantly improved weight-related HRQoL versus pioglitazone (but not sitagliptin).²⁸ In this study, there was a significant correlation between changes in weight and changes in weight-related HRQoL. AWARD-3 found that dulaglutide improved A1c relative to metformin, and the 1.5 mg dose of dulaglutide was associated with greater improvement in perceived hyperglycemia versus metformin.^{29,36}

Insulin has the advantage of theoretically unlimited efficacy but also has several disadvantages, including weight gain and

hypoglycemia risk, among others, that may adversely affect HRQoL.⁷ At 52 weeks (AWARD-2), dulaglutide was associated with significantly greater improvement compared with insulin glargine in HRQoL, in ability to perform physical activities of daily living, and on PROs related to hypoglycemia. Similarly, in SUSTAIN-4, semaglutide was associated with greater treatment satisfaction than insulin glargine, and the higher semaglutide dose (1.0 mg) also demonstrated significant improvement compared with insulin glargine in the role-emotional and general health domains of the SF-36.³⁴ These findings indicate that once-weekly GLP-1 RAs may have some benefits over insulin in relation to HRQoL and treatment satisfaction, although studies are needed to further elucidate the reasons underlying these benefits (i.e., by examining changes in weight-related HRQoL) and to explore whether once-weekly GLP-1 RAs reduce the distress associated with disease management compared with insulin.

It has been hypothesized that the requirement for fewer injections with once-weekly versus daily GLP-1 RAs may increase patient satisfaction and HRQoL.⁵² Accordingly, in surveys, patients with T2DM have reported a preference for once-weekly over daily dosing.^{47,53,54} Comparison of exenatide ER with exenatide in DURATION-1 identified no significant differences between groups at 30 weeks with respect to changes in weight, weight-related HRQoL, or treatment satisfaction.²⁷ However, treatment satisfaction improved more with exenatide ER with regard to perceived hyperglycemia frequency (likely related to differential effects on A1c) and willingness to continue current treatment, which may reflect the convenience of once-weekly treatment. Further, between weeks 30 and 52, patients who switched from exenatide to exenatide ER experienced improvements in physical function and public distress HRQoL domains as well as in overall treatment satisfaction, treatment convenience, treatment flexibility, and satisfaction with continuing current treatment. When additionally considering results of studies comparing dulaglutide with exenatide^{29,36} and dulaglutide or albiglutide with liraglutide,^{29,44} evidence suggests that there is not a class benefit of improved HRQoL and treatment satisfaction associated with once-weekly GLP-1 RAs; there is, however, a signal that certain elements of treatment satisfaction and willingness to continue treatment may be enhanced with once-weekly GLP-1 RAs.

Only 2 studies (SUSTAIN-3 and SUSTAIN-7) were identified comparing once-weekly GLP-1 RAs with each other with respect to treatment satisfaction^{32,35} and/or HRQoL.³⁵ Semaglutide produced significantly greater reductions in A1c and weight than exenatide ER and dulaglutide and was also associated with significantly greater improvement in overall treatment satisfaction compared with exenatide, but not with dulaglutide.^{32,35} There were no significant differences between semaglutide and dulaglutide in HRQoL.³⁵ Additional comparative trials are warranted.

Conclusions and Clinical Implications

T2DM is associated with considerable impairment in HRQoL.¹⁻⁴ In addition, adverse effects of the medications used to control T2DM, such as weight gain and hypoglycemia, and practical aspects such as cost and administration burden may further impair patients' HRQoL. Thus, as a component of a comprehensive management plan, it is critical to assess and monitor the impact of diabetes and its treatment on HRQoL. Screening for depression (e.g., with the 2-item⁵⁵ or the 9-item Patient Health Questionnaire⁵⁶) is increasingly being incorporated into clinical practice, and more systematic assessment of HRQoL and psychological well-being using validated tools, although time-consuming, may enhance overall patient management.

When selecting a medication regimen for patients with T2DM, it is important to consider the impact of treatment on HRQoL. Once-weekly GLP-1 RAs appear to offer benefits with regard to HRQoL and treatment satisfaction compared with OADs, insulin, and daily GLP-1 RAs. The observed benefits are often related to relative drug effects on glycemic control, weight, and hypoglycemia, and their detection is dependent on the use of appropriate assessment tools. Differences in patient populations/background medications and assessment tools employed would make it difficult to interpret any indirect comparisons across studies between once-weekly GLP-1 RAs. Once-weekly GLP-1 RAs represent an effective and convenient treatment option that may potentially enhance treatment adherence, leading to improved health outcomes.

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