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ORIGINAL ARTICLE

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A real-world, observational study of weekly exenatide added to basal insulin in patients with type 2 diabetes mellitus (NCT02895672)

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Summary

Aim: This is a pre-post observational study from an endocrinology ambulatory care practice which assessed the effectiveness and safety following the addition of a glucagon-like peptide-1 (GLP-1) agonist, weekly exenatide (Bydureon), to basal insulin therapy in patients with type 2 diabetes mellitus (T2DM). Liraglutide plus basal insulin served as a comparison group.

Materials and methods: A data collection form was utilized to collect study-related information. The primary study outcome was change in HbA_{1c} from baseline to 12 months after GLP-1 receptor agonist therapy was added to basal insulin therapy. Secondary outcomes were change in weight, percentage of patients achieving an HbA_{1c} of <7% (53 mmol/mol) or ≤6.5% (48 mmol/mol) and changes in blood pressure and lipid parameters. Safety was assessed by a collection of reported adverse events.

Results: One-hundred and fifty patients met inclusion criteria (seventy-five per treatment arm). After 1 year of therapy, HbA_{1c} decreased by 0.7% in the entire cohort (once-weekly exenatide: −0.7%; once-daily liraglutide: −0.8%; no significant between-group difference). More subjects in the weekly exenatide arm achieved an HbA_{1c} < 7% (53 mmol/mol) (P = .03), but a comparable number achieved an HbA_{1c} ≤ 6.5% (48 mmol/mol). Although significantly more patients achieved an HbA_{1c} < 7% (53 mmol/mol) in the once-weekly exenatide arm, the baseline HbA_{1c} was lower (7.9%) than the liraglutide arm (8.4%). No significant differences were observed between groups for other secondary outcomes. A similar number of subjects discontinued therapy, mainly due to gastrointestinal-ill effects, and hypoglycaemia incidence did not increase compared with the previous year.

Conclusion: The addition of once-weekly exenatide to basal insulin was associated with appreciable reductions in HbA_{1c} and weight without an increase in hypoglycaemia.

KEYWORDS

basal insulin, exenatide, glucagon-like peptide-1 agonist, liraglutide

1 | INTRODUCTION

It is estimated that nearly 30 million people in the United States, roughly 10% of the population, have diabetes.[1] Type 2 diabetes mellitus (T2DM), which makes up more than 90% of all diabetes cases, is a heterogeneous and progressive disease typically requiring the use of an increasing number of antidiabetic medications. Good glycaemic control results in a decreased incidence of diabetes-related complications.[2] However, just over half (52.5%) of people with diabetes achieve the American Diabetes Association's (ADA)-recommended HbA_{1c} of <7% (53 mmol/mol), and <20% meet combined HbA_{1c}, blood pressure and lipid goals.[3] Glucagon-like peptide-1 (GLP-1) receptor agonists are widely used as second-line agents in clinical practice, often after the failure of one or more oral antidiabetic agents. A recent meta-analysis demonstrated that GLP-1 receptor agonist and basal insulin combination treatment results in robust glycaemic control with one-third less hypoglycaemia and a significant decrease in weight compared with the addition of prandial insulin.[4] Agents that can improve glycaemic control, have a low risk for hypoglycaemia and promote weight loss are especially desirable in diabetes management.

There are currently five commercially available GLP-1 receptor agonists approved for use within the United States and they include albiglutide, dulaglutide, exenatide, liraglutide and lixisenatide. The first three have once-weekly formulations available and the latter three have twice- or once-daily formulations (exenatide has two formulations available). All agents are currently approved for the management of T2DM as an adjunct to diet and exercise, but albiglutide, dulaglutide and liraglutide are the only long-acting agents approved for concurrent use with basal insulin.[5-10] Liraglutide is also indicated to reduce the risk for major adverse cardiovascular events in patients with established cardiovascular disease.[9]

This is a real-world, pre-post observational study from an ambulatory endocrinology practice that assessed the efficacy and safety following the addition of a GLP-1 receptor agonist (once-weekly exenatide [Bydureon] or once-daily liraglutide [Victoza]), to the regimens of patients with T2DM who have already received a minimum of 1 year of basal insulin therapy. Liraglutide was chosen as a comparator because it is the market leader for GLP-1 receptor agonists. We hypothesize that GLP-1 receptor agonist therapy added to basal insulin therapy would result in a statistically significant improvement in glycaemic control and weight loss, with a similar risk of hypoglycaemia compared with baseline.

2 | MATERIALS AND METHODS

This is a pre-post observational study which assessed the efficacy and safety of 12 months of GLP-1 receptor agonist therapy added to the therapeutic regimen of a group of patients with T2DM from an ambulatory endocrinology practice who had received basal insulin therapy for a minimum of 1 year. This endocrinology practice consists of primarily middle-aged, commercially insured patients seen for a diverse range of endocrine-based disorders, although approximately one-third of patients are seen for primary care. Eleven medical doctors, five mid-levels, two pharmacists, three nurses and three nutritionists/diabetes educators comprise the clinical team at the practice site. This study was reviewed and approved by the Albany College of Pharmacy and Health Sciences' Institutional Review Board. Potential subjects were identified via a computerized text search of the medication and problem fields of patient electronic medical records (EMR). Search terms included Bydureon, Lantus, Levemir, NPH, T2DM and Victoza. Start and end dates for our data ranged from 25 January 2010 through 1 June 2015 for liraglutide and 1 January 2012 through 1 June 2015 for once-weekly exenatide. Individual records of identified patients were reviewed to ascertain whether all applicable study criteria were met. Inclusion criteria were as follows: T2DM, age 18-85 years old, documentation of basal insulin therapy for a minimum of 1 year prior to GLP-1 receptor agonist initiation and the addition of once-weekly exenatide or once-daily liraglutide to basal insulin therapy. Patients did not have to be on prandial insulin to be included in the study; however, the use of prandial insulin was not an exclusion to enrolment. Exclusion criteria included type 1 diabetes mellitus, patients receiving prescription medications for weight loss and initiation of additional antidiabetic, antihypertensive or lipid-lowering medications during the follow-up period.

A data collection form was utilized to collect the following patient information: baseline demographic information (gender, age, height, weight), duration of diabetes, medications, laboratory information (HbA_{1c}, lipid profile [total cholesterol {TC}, low-density lipoprotein cholesterol {LDL-C}, triglycerides {TG}, high-density lipoprotein cholesterol {HDL-C}]) and blood pressure. Safety, including incidents of hypoglycaemia, was assessed by collection of reported adverse effects.

The primary study outcome was change in HbA_{1c} from baseline to 12 months after GLP-1 receptor agonist therapy was added to basal insulin therapy. Secondary outcomes were change in weight, percentage of patients achieving an HbA_{1c} of <7% (53 mmol/mol) or ≤6.5% (48 mmol/mol), changes in systolic and diastolic blood pressure and changes in lipid parameters (TC, LDL-C, TG and HDL-C).

2.1 | Statistical analysis

A two-tailed *t* test was performed to compare outcome differences between the two GLP-1 receptor agonist groups and a *P*-value of <.05 was considered to be statistically significant. Assuming an HbA_{1c} change of −0.5% from baseline, a beta error of 0.8 and an alpha error of 0.05, a sample size of 60 patients per group was determined to be required.

3 | RESULTS

Three hundred and fifty-eight patients were identified from the clinic's EMR as potential subjects for review. After 75 patients in each group were identified as meeting study criteria, further study enrolment ceased, as the predefined sample size (sixty patients per treatment arm) had been met. The baseline characteristics of the study population are presented in Table 1. Overall, this was an older group

TABLE 1 Baseline characteristics of study subjects

Baseline characteristic	Overall (N = 150)	Once-weekly exenatide (n = 75)	Once-daily liraglutide (n = 75)
Mean age, y [SD]	62 [10]	63 [10]	61 [9]
Gender, n (%)			
Female	58 (39)	29 (39)	29 (39)
Male	92 (61)	46 (61)	46 (61)
Race, n (%)			
African American	8 (5)	3 (4)	5 (7)
Asian	2 (1)	1 (1)	1 (1)
Hispanic	0 (0)	0 (0)	0 (0)
White	137 (91)	70 (93)	67 (89)
Unknown	3 (2)	1 (1)	2 (3)
Mean duration of diabetes, y [SD]	15 [7]	16 [8]	14 [6]
History of microvascular disease, n (%)	104 (69)	54 (72)	50 (67)
History of macrovascular disease, n (%)	55 (37)	27 (36)	28 (37)
Mean HbA_{1c}, % [SD]	8.1 [1.6]	7.9 [1.6]	8.4 [1.6]
Mean weight, pounds [SD]*	249 [55]	237 [54]	261 [53]
Mean body mass index, kg/m^2 [SD]*	38 [8]	37 [8]	40 [7]
Mean systolic blood pressure, mm Hg [SD]	122 [10]	121 [9]	122 [10]
Mean diastolic blood pressure, mm Hg [SD]	72 [6]	72 [5]	72 [6]
Mean low-density lipoprotein cholesterol, mg/dL [SD]*	80 [28]	75 [25]	85 [30]
Mean total daily insulin dose, Units [SD]	62 [50]	57 [55]	67 [44]
Median daily number of injections [SD]	1 [1.5]	1 [1.6]	1 [1.4]
Mean basal insulin dose, units [SD]	48 [34]	44 [39]	52 [27]
Mean duration of basal insulin therapy, y [SD]	6.8 [5.9]	6.4 [5.8]	7.4 [6.0]

SD, standard deviation.
Conversions: HbA_{1c}: to convert from percentage to mmol/mol: 10.93 * HbA_{1c} (percentage) − 23.5; weight: to convert from pounds to kilograms, divide by 2.2; LDL-C: to convert from mg/dL to mmol/L, divide by 38.67.
*$P < .05$.

of predominately white, moderately controlled patients with T2DM. Patients had a long history of diabetes (mean of 15 years) with two-thirds having a history of diabetes-related microvascular complications and one-third with a history of macrovascular disease. Patients had received basal insulin for approximately 7 years prior to initiating GLP-1 receptor agonist therapy.

One-hundred and seven subjects completed at least 1 year of therapy with a GLP-1 receptor agonist (median dose of liraglutide was 1.8 mg [ie, top-dose]). Table 2 lists the efficacy data for the completer population. At 1 year, the mean difference in HbA_{1c} from baseline was -0.7%, with a 0.7% decrease in the once-weekly exenatide completer arm and 0.8% decrease in the liraglutide completer arm (absolute treatment difference: −0.1%; between-group treatment difference not statistically significant, $P = .43$). Once-weekly exenatide use was associated with more patients achieving an HbA_{1c} <7% (53 mmol/mol) compared with the liraglutide arm (once-weekly exenatide: 58%; liraglutide: 36%; $P = .03$). A comparable number of subjects in both the once-weekly exenatide and liraglutide arms achieved an $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) (once-weekly exenatide: 32%; liraglutide: 20%; $P = .27$). Weight decreased by a mean of 5 pounds (2.3 kg) or 2% in each group (between-group treatment difference not statistically significant, $P = .87$). The mean total daily insulin dose between groups did not significantly change with a mean decrease of 5 units from baseline in those receiving once-weekly exenatide and a 3-unit increase observed in those receiving liraglutide (between-group treatment difference not statistically significant, $P = .29$).

A similar number of subjects in each group discontinued therapy secondary to adverse events (Table 3) believed to be GLP-1

TABLE 2 Primary and secondary efficacy outcomes for the Completer Population

Outcome	Overall (N = 108)	Once-weekly exenatide (n = 50)	Once-daily liraglutide (n = 58)
Primary study outcome			
1-y HbA_{1c}, % (mmol/mol) [SD]	7.4 (57) [1.4]	7.3 (56) [1.3]	7.6 (60) [1.5][a]
Mean change in HbA_{1c} from baseline, %**	−0.7	−0.7	−0.8
Secondary outcomes			
Subjects achieving an HbA_{1c} < 7% (53 mmol/mol), n (%)*	49 (46)	29 (58)	20 (36)
Subjects achieving an HbA_{1c} ≤ 6.5% (48 mmol/mol), n (%)**	27 (25)	16 (32)	11 (20)
1-y mean weight, pounds [SD]	245 [58]	234 [53]	255 [61]
Mean change in weight from baseline, pounds**	−5	−5	−5
1-y mean systolic blood pressure, mm Hg [SD]	122 [9]	123 [9]	121 [9]
Mean change in systolic blood pressure from Baseline, mm Hg**	0	+2	−2
1-y mean diastolic blood pressure, mm Hg [SD]	71 [6]	71 [6]	71 [6]
Mean change in diastolic blood pressure from baseline, mm Hg**	−1	0	−2
1-y mean total daily insulin dose, units [SD]	59 [52]	50 [61]	67 [41]
Mean change in total daily insulin dose, units**	0	−5	+3
1-y Mean Total Cholesterol, mg/dL [SD]	152 [35]	153 [30]	151 [39]
Mean Change in Total Cholesterol from Baseline, mg/dL**	−5	−1	−8
1-y mean LDL-C, mg/dL [SD]	75 [29]	72 [26]	78 [32]
Mean change in LDL-C from baseline, mg/dL**	−4	−3	−5
1-y mean triglycerides, mg/dL [SD]	167 [127]	176 [149]	159 [106]
Mean change in triglycerides from baseline, mg/dL**	+1	+2	0
1-y mean HDL-C, mg/dL [SD]	47 [13]	49 [15]	44 [12]
Mean change in HDL-C from baseline, mg/dL**	0	+2	−1

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GLP-1, glucagon-like peptide-1; SD, standard deviation.
Conversions: HbA_{1c}: to convert from percentage to mmol/mol: 10.93 * HbA_{1c} (percentage) − 23.5; weight: to convert from pounds to kilograms, divide by 2.2; LDL-C, total cholesterol, HDL-C: to convert from mg/dL to mmol/L, divide by 38.67; triglycerides: to convert from mg/dL to mmol/L, divide by 88.57.
[a]1-y HbA_{1c} was unavailable for 1 patient in the liraglutide arm.
*P = .03.
**P > .05.

TABLE 3 Safety and discontinuation findings

Outcome	Overall (N = 150)	Once-weekly exenatide (n = 75)	Once-daily liraglutide (n = 75)
Number of subjects discontinuing GLP-1 therapy, n (%)	42 (28)	24 (32)	18 (24)
Number of subjects discontinuing GLP-1 therapy secondary to adverse effects, n (%)	32 (21)	18 (24)	14 (19)
Number of subjects reporting hypoglycaemia, n (%)	23 (15)	8 (11)	15 (20)
Number of subjects discontinuing GLP-1 therapy secondary to cost, n (%)	5 (3)	3 (4)	2 (3)

GLP-1, glucagon-like peptide-1.
P > .05 for all comparisons.

receptor agonist-related (once-weekly exenatide: 24%; liraglutide: 19%). Adverse effects resulting in discontinuation of once-weekly exenatide included the following (patients may have discontinued therapy due to more than one adverse effect): gastrointestinal-related symptoms (n = 13; abdominal pain, diarrhoea, nausea, vomiting, anorexia, belching, flatulence, heartburn), injection site nodules and itching (n = 3), hypoglycaemia (n = 8), allergic reaction, weight loss, fatigue, headache, soreness, heartburn, leg welts, muscle spasms and aches (each, n = 1). Adverse effects resulting in discontinuation of liraglutide included gastrointestinal-related symptoms (n = 11; abdominal discomfort, diarrhoea, nausea), hypoglycaemia (n = 15), altered taste, weakness, migraines and shortness of breath (each, n = 1).

Hypoglycaemia was reported in 15% of patients during this trial, compared with 17% the year prior to the addition of a GLP-1 analogue. Specifically, hypoglycaemia was reported by 9 patients during the year prior to the addition of weekly exenatide, compared with 8 during the

year of follow-up, and by 16 patients the year prior to initiation of liraglutide, compared with 15 patients during the year of follow-up.

4 | DISCUSSION

This was a pre-post observational study from an ambulatory endocrinology practice assessing the effectiveness and safety following the addition of a GLP-1 receptor agonist to the regimens of patients with T2DM who had already received a minimum of 1 year of basal insulin therapy. T2DM is a progressive disease that often requires therapeutic intensification using medications that are often associated with weight gain and a higher incidence of hypoglycaemia. Compared with the addition of prandial insulin, the addition of GLP-1 receptor agonist therapy to basal insulin results in improved glycaemic control, significant weight loss and a one-third lower rate of hypoglycaemia.[4]

This study consisted primarily of middle-aged Caucasians with a long duration of diabetes, which was moderately controlled at baseline. The addition of a GLP-1 receptor agonist to background basal insulin therapy was associated with a 0.7% decrease in HbA_{1c} from baseline. The use of GLP-1 receptor agonist was also associated with modest weight loss and greater achievement of ADA-recommended HbA_{1c} targets, with no greater increase in reported episodes of hypoglycaemia.

The results of this study are consistent with reported clinical trials. There are currently results available from four large studies assessing the utility of adding a long-acting GLP-1 receptor agonist to basal insulin. DURATION-7 was a phase III, multicentre, randomized, double-blind, placebo-controlled study assessing both the efficacy and safety of once-weekly exenatide to placebo in addition to titrated basal insulin glargine in patients with T2DM.[11] The study consisted of an equal number of male and female subjects in their late 50s with an 11-year history of T2DM whose baseline HbA_{1c} was 8.5% (69 mmol/mol). Following 28 weeks of treatment, HbA_{1c} decreased 1% in the once-weekly exenatide arm and −0.2% in the placebo arm (least-square mean difference −0.7%; $P < .001$). The HARMONY-6 study was a randomized, open-label, noninferiority, 26-week, active-controlled clinical study, which assessed the efficacy of once-weekly albiglutide vs thrice-daily prandial insulin lispro, both as an add-on to basal insulin.[12] The primary end-point was change in HbA_{1c} from baseline at week 26. HbA_{1c} decreased by 0.82% in the once-weekly albiglutide arm and 0.66% in the insulin lispro arm ($P < .0001$ for noninferiority). The BEGIN: Victoza Add-On study compared once-daily liraglutide vs once-daily insulin aspart with the largest meal of the day in patients with T2DM on basal insulin (degludec) requiring intensification of therapy.[13] At 26 weeks, HbA_{1c} was reduced by 0.74% in the liraglutide group compared with −0.39% in the insulin aspart group ($P = .0024$). AWARD-9 was a multicentre, double-blind, parallel-arm, placebo-controlled study which compared once-weekly dulaglutide in addition to insulin glargine to placebo plus insulin glargine.[14] After 28 weeks, patients' HbA_{1c} in the dulaglutide arm decreased by 1.44% and those in the placebo arm decreased by 0.67% ($P < .001$).

The 4B trial by Diamant et al was a randomized, open-label, noninferiority, 30-week study, which was the first to compare a GLP-1, twice-daily exenatide, to thrice-daily insulin lispro, both in addition to insulin glargine.[15] The primary end-point was change in HbA_{1c} from baseline at week 30. At the end of treatment, HbA_{1c} decreased by −1.13% in the once-daily exenatide arm and by −1.10% in the thrice-daily insulin lispro arm. Twice-daily exenatide was found to be noninferior to thrice-daily insulin when added to a basal insulin regimen (95% confidence interval −0.18-0.11).

Overweight and obesity are well-recognized public health concerns associated with an increased risk for dyslipidaemia, hypertension, T2DM and cardiovascular death.[16] For patients with T2DM, weight loss can be challenging. A patient's background antidiabetic regimen may be responsible, in part, for excess weight as insulin, meglitinides, sulphonylureas and thiazolidinediones are all associated with weight gain.[16,17] Efforts to reduce weight by as little as 5% can improve the weight-related complications mentioned above.[18] The 5 pound (2.3 kg) (2%) weight loss observed in this study was similar for both once-weekly exenatide and once-daily liraglutide. While this may be modest, there was no prandial insulin comparator group. Eng et al reported a mean 12 pound (5.4 kg) higher weight in patients when prandial insulin was added to basal insulin compared with the addition of a GLP-1 receptor agonist.[4] The addition of once-weekly exenatide to basal insulin was associated with an additional 3.3 pound (1.5 kg) weight loss compared with placebo ($P < .001$).[12] The modest but additional weight loss observed in this study compared with DURATION-7 may be attributable, in part, to a higher baseline body mass index (BMI) (BMI: 38 kg/m^2 vs 33.3 kg/m^2, respectively). In HARMONY-6, use of albiglutide was associated with a mean 1.6 pound (0.7 kg) decrease in weight compared with a mean 1.8 pound gain in patients receiving insulin lispro.[12] Use of liraglutide in the BEGIN: Victoza Add-On study was associated with a 6.1 pound (2.8 kg) decrease in weight compared with a 2 pound weight gain in the insulin aspart group.[13] Pozzilli et al reported a 4.2 pound (1.9 kg) weight loss and a 1.1 pound (0.5 kg) weight gain in the dulaglutide and placebo arms, respectively, in AWARD-9.[14] Diamant et al reported a 5.5 pound (2.5 kg) weight loss with twice-daily exenatide and a 4.6 pound (2.1 kg) weight gain with thrice-daily insulin lispro in the 4B study ($P < .001$).[15]

Hypoglycaemia has historically been an important clinical consideration in the treatment of diabetes, in addition to cost, side effects and adherence. This study showed a similar rate of reported hypoglycaemia over 1 year in patients receiving GLP-1 therapy compared with the year prior to initiating therapy, despite a 0.7% reduction in HbA_{1c}. Eng et al's meta-analysis showed a 33% reduction in reported hypoglycaemia with the use of GLP-1 therapy compared with when prandial insulin was added to basal insulin.[4] In DURATION-7, hypoglycaemia occurred in 29.7% of weekly exenatide-treated subjects and 29% of placebo-treated subjects.[11] There was 47% less documented symptomatic hypoglycaemia in the GLP-1 group compared with the prandial insulin group in the HARMONY 6 study[12] and a reported 87% decrease in hypoglycaemia with GLP-1 therapy vs prandial insulin in the BEGIN: Victoza Add-On study.[13] In AWARD-9, total

hypoglycaemia was similar between the two treatment arms (dulaglutide/basal insulin: 54.7%; placebo/basal insulin: 50.7%).[14] Minor and confirmed non-nocturnal hypoglycaemia occurred less frequency with twice-daily exenatide in the 4B study compared with prandial insulin (30% vs 41%; 15% vs 34%, respectively).[15]

No major significant changes were observed between groups for blood pressure (baseline 122/72 mm Hg) (change in systolic blood pressure, $P = .09$; change in diastolic blood pressure, $P = .29$) or lipid profiles (baseline LDL-C 80 mg/dL [2.1 mmol/L]) ($P \geq .18$). The use of the GLP-1 receptor agonist class has been associated with minor reductions in both systolic and diastolic blood pressure, in addition to favourable effects on lipids,[19] but clinically meaningful differences were not observed in this study, which is likely because patients were well controlled at baseline.

This study is not without limitations. Due to the observational design of the study, a cause-and-effect relationship of study results cannot be established and a lack of randomization may have resulted in an imbalance between the two GLP-1 cohorts (eg, baseline HbA_{1c}, basal insulin dose and weight). This study did not control for potentially confounding factors such as diet and exercise. Next, in this homogeneous study population of predominately older Caucasians with long-standing diabetes, results of this study may not be applicable to a more diverse population, or to patients with a shorter history of disease. Third, an intention-to-treat analysis was not completed for efficacy analysis of this study as 43 patients discontinued therapy due to adverse effects, expense or personal preference. We evaluated follow-up data for only patients who completed a minimum of 1 year on GLP-1 receptor agonist therapy (study completers) reasoning that this approach would allow a better assessment of the full potential utility of GLP-1 receptor agonist therapy added to basal insulin.

Although liraglutide was commercially available 2 years earlier than once-weekly exenatide, aside from weight, body mass index and LDL-C, no other significant differences were found between treatment arms at baseline (eg, age at therapy initiation, duration of T2DM, gender). Finally, data were collected by a retrospective review of an EMR, and only documented adverse reactions were captured.

It is possible that more adverse events occurred than were reported. These preliminary data support the idea that the addition of a GLP-1 receptor agonist to basal insulin is an effective and safe therapeutic strategy to glycaemic control, as demonstrated in previous clinical trials.[11-15] This study complements results reported in DURATION-7,[11] which was a large-scale randomized trial; however, the utility of the results reported here indicates that in a real-world clinical setting, once-weekly exenatide is safe and efficacious.

In this pre-post observational study, two GLP-1 analogue therapies added to basal insulin were associated with appreciable and comparable reductions in HbA_{1c} and weight without an increase in hypoglycaemia. These combination therapies were well tolerated. Overall, weekly exenatide and daily liraglutide therapy appear to be a safe and effective therapeutic add-on to basal insulin in patients with T2DM who are inadequately controlled.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTION

Drs. Stryker contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. Dr. Kane co-conceived the presented idea and contributed to the design and implementation of the research. Dr. Busch co-conceived the presented idea. All authors discussed the results and contributed to the final manuscript.

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REFERENCES

1. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA: US Department of Health and Human Services; 2014.
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853. Epub 1998/09/22. PubMed PMID: 9742976.
3. Stark CS, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting HbA1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36:2271-2279.
4. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014;384:2228-2234.
5. Tanzeum [package insert]. Research Triangle Park, NC: GlaxoSmithKline LLC; 2017.
6. Trulicity [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.
7. Bydureon [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.
8. Byetta [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
9. Victoza [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S; 2017.
10. Adlyxin [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2016.
11. Frias J, Rosenstock J, Somogyi A, et al. Efficacy and safety of exenatide qw versus placebo added to uptitrated basal insulin in uncontrolled type 2 diabetes: DURATION-7 trial [presentation]. Presented at: American Diabetes Association; June 9-13, 2017; San Diego, CA.
12. Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care*. 2014;37:2317-2325. Epub 2014/06/06. PubMed PMID: 24898300.

13. Mathieu C, Rodbard HW, Cariou B, et al. A Comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes Metab*. 2014;16:636-644. Epub 2014/01/22. PubMed PMID: 24443830.
14. Pozzilli P, Norwood P, Jodar E, et al. A placebo-controlled, randomised trial of the addition of once weekly GLP-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). *Diabetes Obes Metab*. 2017;19:1024-1031. Epub 2017/03/16. PubMed PMID: 28294499.
15. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care*. 2014;37:2763-2773. Epub 2014/07/12. PubMed PMID: 25011946.
16. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(Suppl 3):1-203. Epub 2016/05/25. PubMed PMID: 27219496.
17. American Diabetes Association. Standards of medical care in diabetes–2017. *Diabetes Care*. 2017;40:S1-S135.
18. Blackburn G. Effect of degree of weight loss on health benefits. *Obes Res*. 1995;3(Suppl 2):211s-216s. Epub 1995/09/01 PubMed PMID: 8581779.
19. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs Context*. 2015;4:212283. Epub 2015/07/28. PubMed PMID: 26213556; PubMed Central PMCID: PMCPMC4509428.

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