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ORIGINAL ARTICLE

Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit*

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Aim: To assess the extent, safety, efficacy and tolerability of reported off-licence exenatide use through a nationwide audit.
Methods: The Association of British Clinical Diabetologists hosted a password-protected, online collection of anonymized data of exenatide use in real clinical practice. Three hundred and fifteen contributors from 126 centres across UK provided data on 6717 patients. HbA1c and weight changes, exenatide discontinuation, adverse events and treatment satisfaction were compared between non-insulin and insulin-treated patients.
Results: Four thousand eight hundred and fifty-seven patients had baseline and follow-up treatment status with mean (±s.d.) baseline HbA1c 9.45 ± 1.69% and BMI 40.0 ± 8.2 kg/m^2. Of the 4857 patients, 1921 (39.6%) used exenatide with insulin. Comparing patients who continued insulin with exenatide with non-insulin-treated patients, mean (±s.e.) latest HbA1c and weight reduction (median 26 weeks) were 0.51 ± 0.06 versus 0.94 ± 0.04% ($p < 0.001$) and 5.8 ± 0.2 versus 5.5 ± 0.1 kg ($p = 0.278$). Insulin-treated patients had higher rates of exenatide discontinuation (31.0 vs. 13.9%, $p < 0.001$), hypoglycaemia (8.9 vs. 6.1%, $p < 0.001$), gastrointestinal side effects (28.4 vs. 25.0%, $p = 0.008$) and treatment dissatisfaction (20.8 vs. 5.7%, $p < 0.001$). However, 34.2% of the patients continuing insulin still achieved HbA1c reduction ≥1%. There was significant insulin discontinuation, dose reduction and greater sulphonylurea discontinuation among insulin-treated patients.
Conclusions: Addition of exenatide to obese, insulin-treated patients can improve glycaemia and weight. Adverse events were statistically but probably not clinically significantly higher, but combination treatment was less well tolerated. Overall, exenatide was less effective in lowering HbA1c among insulin-treated patients, although significant number of insulin-treated patients still achieved significant HbA1c, weight and insulin reductions. Further research into identifying obese, insulin-treated patients who will tolerate and benefit from exenatide treatment is urgently needed.
Keywords: exenatide, GLP-1 analogue, incretin therapy, insulin therapy, type 2 diabetes

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Introduction

Exenatide, a GLP-1 agonist, has proven efficacy in combination with various oral diabetes treatment in the management of type 2 diabetes [1–4]. In the UK, the National Institute for Health and Clinical Excellence has endorsed its use mainly as third-line treatment in patients with BMI ≥35 kg/m^2 [5]. However, exenatide is not licensed for use in combination with insulin, with insulin treatment being, in essence, considered a surrogate marker of significant β-cell decline [6]. With as many as 27.4% of patients with type 2 diabetes treated with insulin in a population-based study [7], this potentially excludes exenatide treatment to a substantial number of patients. The lack of clinical data on combination use makes it difficult to judge whether this restriction is justified.

There is uncertainty about the effectiveness of exenatide in insulin-treated patients. Exenatide stimulates insulin secretion especially after meals [8], a process that is probably diminished if β-cell function has declined. This action is also potentially redundant in patients receiving sufficient doses of treatment insulin. However, in the case of basal insulin being added to oral hypoglycaemic agents, postprandial glycaemic excursions may be insufficiently controlled; the addition of exenatide to basal insulin may prove a logical combination [9–11]. Moreover, exenatide also inhibits postprandial glucagon secretion, delays gastric emptying and suppresses appetite [8]. Whether these effects, and its *in vitro* effects on β-cell preservation, aid glycaemic control even in insulin-deficient patients is not clear [12,13]. Exenatide and insulin have opposing weight effects [9,14]; the net effect of the combination should be

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*The intention-to-treat HbA1c and weight data of patients analysed in this article were presented as a poster in the 46th EASD 2010 Annual Meeting in Stockholm.

†See Appendix for list of contributors in the ABCD nationwide exenatide audit.

clarified. Finally, the burden and cost of added injections would also need to be justified.

The Association of British Clinical Diabetologists (ABCD) is a national diabetes specialist society aimed at promoting high-quality care in diabetes. To learn from the experience of exenatide in real clinical use, ABCD launched a nationwide audit in December 2008. It became apparent that exenatide was commonly used with insulin by many patients. With the issues above in mind, we report on the safety, efficacy and tolerability of the combination treatment.

Methods

Patient Selection

The design and overall findings of the ABCD nationwide exenatide audit have been previously reported [15]. Over a period of 1 year, anonymized data of patients who were on exenatide treatment were collected via a website-hosted, password-protected, online questionnaire. Three hundred and fifteen contributors from 126 centres across the UK sent information on 6717 patients using exenatide in clinical practice. Among other information, data on HbA1c, weight, diabetes treatment, adverse events and treatment satisfaction were requested in the audit. For this analysis, patients were divided according to insulin treatment status at baseline and end of audit while patients with insufficient treatment details were excluded (figure 1). Patients who continued insulin at baseline were used for comparisons of HbA1c and weight changes with non-insulin-treated patients, whereas comparisons of adverse events and treatment satisfaction included patients adding insulin after exenatide initiation.

Endpoints Analysed

Contributors sent HbA1c and weight data at progressive intervals; these were accepted from a minimum of 6 weeks after exenatide start and were excluded if off-exenatide treatment.

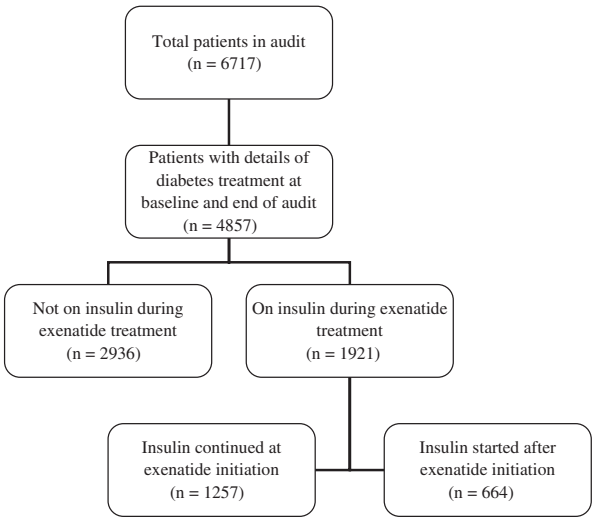

Figure 1. Distribution of patients on exenatide based on insulin use in the Association of British Clinical Diabetologists nationwide exenatide audit.

The latest HbA1c and weight data of each patient, as well as data grouped at 3, 6, 9 and 12 months were compared with baseline. The mean latest HbA1c and weight changes were compared between insulin continued and non-insulin-treated patients. The proportions of patients achieving an HbA1c reduction of $\geq$1% and weight loss $\geq$3% of initial body weight were also compared. Exenatide discontinuation in the span of the audit and in the first 3 months was compared, as were rates of oral hypoglycaemic agent discontinuation. Among patients who continued insulin, the proportion of patients eventually coming off insulin and insulin dose reduction was quantified.

Descriptive statistics were provided for all patients receiving at least one dose of exenatide, and adverse events and patient satisfaction were analysed as intention-to-treat (exenatide). These were compared between insulin and non-insulin-treated patients. Contributors provided details of hypoglycaemia based on local working definitions while severe hypoglycaemia in the analysis was episodes requiring external assistance. All gastrointestinal side effects including nausea, vomiting and diarrhoea were analysed collectively as a group. Patient satisfaction with exenatide treatment was specified in the audit as extremely unhappy, very unhappy, unhappy, ambivalent, happy, very happy and extremely happy. These were grouped into negative, neutral or positive responses for ease of comparison. Satisfaction with exenatide treatment was also assessed according to the change in insulin status with regard to the addition or stopping of insulin, as well as the total number of injections per day required by patients (exenatide + insulin) in groups of 2–3, 4–5 and 6–7 injections per day.

Statistical Analysis

HbA1c and weight changes from baseline to latest as well as at 3, 6, 9 and 12 months were assessed using paired *t*-tests. Differences in mean HbA1c and weight changes and the mean of continuous baseline variables were compared between insulin continued and non-insulin-treated patients using Student's *t*-test. Analysis of variance (ANOVA) was used to compare the mean latest HbA1c and weight changes with those at 3, 6, 9 and 12 months after checking residuals for normality. Median diabetes duration was compared between non-insulin and insulin-treated patients using Mann–Whitney *U*-test, whereas the proportion reaching HbA1c and weight change cut-offs, exenatide and oral hypoglycaemic discontinuation, categorical baseline variables, adverse events and exenatide treatment satisfaction were compared using chi-squared tests. p-Values <0.05 were deemed to be statistically significant. Statistical calculations were performed using MINITAB® Release 14.11 (Minitab Ltd, Coventry, UK).

Results

Number of Patients on Exenatide and Insulin

The distribution of patients is shown in figure 1. Four thousand eight hundred and fifty-seven patients had detailed baseline and follow-up diabetes treatment with median (range) follow-up of 31 (0.4–136) weeks. Of the 4857 patients, 2936 (60.4%) were not on insulin during exenatide treatment, whereas

Table 1. Baseline characteristics of patients on exenatide based on insulin use.

	Data (n)	All patients in analysis (n = 4857)	Non-insulin-treated patients (n = 2936)	Insulin-treated patients (n = 1921)	p-Value
Males (%)	4857	55.1	57.8	51.0	<0.001
Caucasian (%)	3742	90.2	92.2	86.7	<0.001
Age (years)	4838	54.7 (10.6)	54.1 (10.6)	55.8 (10.4)	<0.001
Diabetes duration (years)	3910	9.0 (5.0–13.0)	7.1 (5.0–11.0)	11.0 (7.0–15.0)	<0.001
HbA1c (%)	4833	9.45 (1.69)	9.40 (1.67)	9.52 (1.72)	0.025
Weight (kg)	4792	113.9 (23.5)	114.1 (24.1)	113.6 (22.4)	0.451
BMI (kg/m^2)	2565	40.0 (8.2)	39.7 (8.5)	40.4 (7.8)	0.028
Insulin dose (U/day)	1222	—	—	118 (104)*	—
Insulin dose (U/kg/day)	1192	—	—	1.0 (0.9)*	—

Continuous values are quoted as mean (s.d.) except for diabetes duration which is expressed as median (interquartile range).
*Excludes patients who started insulin after exenatide initiation.

1921 of 4857 patients (39.6%) used insulin with exenatide. Among those on the combination, 1257/1921 patients continued insulin at exenatide initiation and 664/1921 patients started insulin after.

Baseline Patient Characteristics

The baseline patient characteristics are outlined in Table 1. Insulin-treated patients had longer diabetes duration and were more probably female and non-Caucasian. Mean age, HbA1c and BMI were marginally, but statistically higher, because of large sample sizes with similar standard deviations.

HbA1c and Weight Results

Excluding patients who started insulin after exenatide initiation, there were 2855 and 2759 paired baseline and latest HbA1c and weight data, at median (range) of 26 (7–164) and 27 (7–151) weeks, respectively. Patients continuing insulin achieved mean (±s.e.) HbA1c reduction of $0.51 \pm 0.06\%$ ($p < 0.001$) and weight reduction of 5.8 ± 0.2 kg ($p < 0.001$). Non-insulin-treated patients achieved mean HbA1c reduction of $0.94 \pm 0.04\%$ ($p < 0.001$) and weight reduction of 5.5 ± 0.1 kg ($p < 0.001$). Comparing the two groups, the difference in HbA1c reduction (0.51 vs. 0.94%) was statistically significant ($p < 0.001$) but not weight reduction (5.8 vs. 5.5 kg, $p = 0.278$). The proportions of patients between the two groups who achieved HbA1c reduction of ≥1% were 34.2 versus 49.0% ($p < 0.001$) (Table 2).

The mean latest HbA1c reductions in both groups were not statistically different to mean HbA1c reductions at 3, 6, 9 and 12 months. The mean latest weight reductions in both groups were statistically greater than those at 3 months but less than those at 9 months (and 12 months for non-insulin-treated patients) (Table 3). The residuals of the ANOVA models had approximate normal distributions.

Reduction of Diabetes Treatment

The proportions of all patients on metformin, sulphonylureas and thiazolidinediones at baseline and end of audit were 84.2 versus 84.0% ($p = 0.718$), 48.6 versus 43.1% ($p < 0.001$) and 27.9 versus 9.8% ($p < 0.001$), respectively. The use of oral hypoglycaemic agents other than metformin, sulphonylureas and thiazolidinediones was low, with each of these other agents being used in <3% of patients. As a proportion of treatment use, insulin-treated patients had greater discontinuation of metformin (5.1 vs. 2.5%, $p < 0.001$), sulphonylureas (34.5 vs. 15.5%, $p < 0.001$) but not thiazolidinediones (64.9 vs. 65.6%, $p = 0.808$) when compared with non-insulin-treated patients.

Among 1257 patients who continued insulin at exenatide initiation, total daily insulin dose reduced by mean (±s.e.) 42 ± 2 U/day from mean (±s.d.) 120 ± 99 U/day at baseline to 78 ± 85 U/day at the end of the audit ($p < 0.001$). Expressed by baseline and latest weight, insulin dose decreased from 1.0 ± 0.8 to 0.7 ± 0.7 U/kg/day ($p < 0.001$).

Of the 1257 patients, 209 (16.6%) came off insulin by the end of the audit. This subgroup had an HbA1c reduction of $0.49 \pm 0.17\%$ ($p = 0.003$) and a weight reduction of 8.8 ± 0.7 kg ($p < 0.001$).

Table 2. Latest HbA1c, weight and BMI changes of patients on exenatide comparing non-insulin-treated patients with patients who continued insulin.

	Non-insulin-treated	Continued insulin	p-Value
n	2016	839	—
Baseline HbA1c (%)	9.42 (1.68)	9.55 (1.70)	0.058
Latest HbA1c (%)	8.48 (1.74)	9.04 (1.90)	—
HbA1c difference (%)	−0.94 (0.04)	−0.51 (0.06)	<0.001
Proportion with HbA1c reduction ≥1%	49.0%	34.2%	<0.001
n	1957	802	—
Baseline weight (kg)	114.1 (23.9)	112.7 (22.5)	0.161
Latest weight (kg)	108.6 (23.2)	106.9 (22.6)	—
Weight difference (kg)	−5.5 (0.1)	−5.8 (0.2)	0.278
Proportion with ≥3% body weight loss	59.0%	61.1%	0.613
n	994	309	—
Baseline BMI (kg/m^2)	39.5 (8.5)	39.5 (7.3)	0.916
Latest BMI (kg/m^2)	37.6 (8.2)	37.2 (6.9)	—
BMI difference (kg/m^2)	−1.9 (0.1)	−2.3 (0.1)	0.008

Baseline and latest HbA1c, weight and BMI quoted as mean (s.d.) and differences as mean (s.e.). All latest HbA1c, weight and BMI changes were significant with $p < 0.001$ compared with baseline.

Table 3. Mean latest HbA1c and weight changes compared with changes at 3, 6, 9 and 12 months after exenatide treatment among non-insulin-treated patients and patients who continued insulin.

	Latest data	3 months	6 months	9 months	12 months
Non-insulin					
n	2016	1512	1037	491	405
HbA1c change (%)	−0.94 (0.04)	−0.97 (0.04)****	−1.00 (0.06)****	−0.95 (0.08)****	−0.81 (0.09)****
n	1957	1425	968	416	341
Weight change (kg)	−5.5 (0.1)	−4.0 (0.1)***	−5.8 (0.2)****	−6.7 (0.3)**	−7.5 (0.4)***
Continued insulin					
n	839	662	418	205	126
HbA1c change (%)	−0.51 (0.06)	−0.56 (0.06)****	−0.40 (0.09)****	−0.56 (0.12)****	−0.32 (0.15)****
n	802	625	378	172	105
Weight change (kg)	−5.8 (0.2)	−4.5 (0.2)***	−6.5 (0.3)****	−7.6 (0.6)*	−7.6 (0.9)****

HbA1c and weight changes quoted as mean (s.e.). Median (range) latest HbA1c—non-insulin-treated patients: 27 (7–151) weeks; continued insulin: 26 (7–164) weeks. Median (range) latest weight—non-insulin-treated patients: 26 (7–151) weeks; continued insulin: 25 (7–143) weeks.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****not significant; compared with latest mean change.

The 34.2% of patients who continued insulin with exenatide and achieved an HbA1c reduction of ≥1%, also achieved a mean weight loss of 6.0 ± 0.4 kg ($p < 0.001$), an insulin dose reduction of 44 ± 4 U/day ($p < 0.001$) and 17.1% discontinued insulin. Among those patients on sulphonylureas and thiazolidinediones, 23.1 and 54.3% discontinued these treatments, respectively.

Exenatide Discontinuation

Table 4 summarizes the rates of exenatide discontinuation, adverse events and treatment satisfaction among non-insulin and insulin-treated patients. Insulin-treated patients had greater exenatide discontinuation in the whole audit (31.0 vs. 13.9%, $p < 0.001$), within 3 months (12.8 vs. 3.5%, $p < 0.001$), and stopping of exenatide because of the lack of glycaemic efficacy (41.0 vs. 33.6%, $p = 0.017$).

Adverse Events

Insulin-treated patients had higher rates of hypoglycaemia before and after exenatide treatment (Table 4). Two cases of severe hypoglycaemia were reported, both among patients on insulin. The first occurred in a patient 9 months after exenatide start and coincided with an unexplained episode of acute renal failure. The second case occurred in a patient who had profuse vomiting after her first injection of exenatide. There were also more patients reporting gastrointestinal side effects among insulin-treated patients (28.4 vs. 25.0 %, $p = 0.008$), while reported rates of acute renal failure were low in both groups (0.3 vs. 0.2%, $p = 0.459$). Cases of adverse events reported in the audit, but not among the 4857 patients in the analysis, were not listed for comparison.

Treatment Satisfaction

Treatment satisfaction with exenatide was recorded in 1645 patients with predominant responses being positive, of which 8.4% were extremely pleased, 37.9% very pleased, 23.0% pleased, 20.2% ambivalent, 6.9% unhappy, 2.6% very unhappy and 1.0% extremely unhappy with overall 69.3% of responses being positive, 20.2% neutral and 10.5% negative. More insulin-treated patients had a negative response (20.8 vs. 5.7%, $p < 0.001$) compared with non-insulin-treated patients. Patients who required the addition of insulin after exenatide initiation had the worst satisfaction with 38.8% recording a negative response, compared with 15.4% in those who continued insulin and 8.1% in those who came off insulin ($p < 0.001$

Table 4. Exenatide discontinuation, adverse events and exenatide treatment satisfaction comparing non-insulin and insulin-treated patients.

	Non-insulin-treated% (95% CI)	Insulin-treated% (95% CI)	p-Value
Exenatide discontinuation			
Whole audit	13.9 (12.7, 15.2)	31.0 (28.9, 33.1)	<0.001
Lack of glycaemic efficacy*	33.6 (29.0, 38.4)	41.0 (37.0, 45.1)	0.017
GI side effect*	31.9 (27.3, 36.6)	35.8 (31.9, 39.8)	0.197
Non-GI side effect*	17.4 (13.8, 21.4)	14.5 (11.7, 17.5)	0.207
Patient choice/ inability to manage injections*	5.6 (3.6, 8.3)	3.0 (1.8, 4.7)	0.040
Before 3 months	3.5 (2.9, 4.3)	12.8 (11.3, 14.4)	<0.001
Adverse events			
Pre-exenatide hypoglycaemia	2.9 (2.3, 3.6)	6.6 (5.5, 7.8)	<0.001
Postexenatide hypoglycaemia	6.1 (5.3, 7.1)	8.9 (7.7, 10.2)	<0.001
All GI side effects	25.0 (23.4, 26.6)	28.4 (26.4, 30.5)	0.008
Transient GI side effects†	75.6 (72.3, 78.7)	56.4 (52.1, 60.6)	<0.001
Acute renal failure	0.2 (0.1, 0.4)	0.3 (0.1, 0.7)	0.459
Treatment satisfaction			
Positive response	74.4 (71.7, 77.0)	58.0 (53.6, 62.3)	<0.001
Neutral response	19.8 (17.5, 22.0)	21.2 (17.7, 25.0)	As a group
Negative response	5.7 (4.5, 7.3)	20.8 (17.3, 24.6)	—

CI, confidence interval; GI, gastrointestinal.
*As a percentage of discontinuation in the whole audit of the group, percentages do not add up to 100% as there were other reasons for exenatide discontinuation.
†As a percentage of patients with GI side effects.

for group). Poorer satisfaction was also associated with more injections per day with 29.4, 20.7 and 7.9% being dissatisfied when using 6–7, 4–5 and 2–3 injections per day, respectively ($p < 0.001$ for group).

Discussion

This article examined the prevalence and outcomes of combined exenatide and insulin treatment in a nationwide audit of exenatide use. Outcomes were compared with non-insulin-treated patients starting exenatide. To our knowledge, this is the largest analysis to date documenting the experience of the combination, with a median patient follow-up of more than 6 months. Nearly 40% of patients were on the combination despite exenatide not being licensed for use with insulin. This was a surprising finding in view of exenatide being only newly available to the UK market at the time of the audit. Possible contributing factors include the difficulty in controlling weight gain among insulin-treated patients in clinical practice, a probably higher frequency of patients on insulin in secondary care centres, as well as the hope by contributors to wean patient off insulin after starting exenatide.

We compared HbA1c and weight changes of patients continuing insulin with non-insulin-treated patients as HbA1c changes among patients who later started insulin probably instigated the addition of insulin, rather than reflect the glycaemic effects of combination treatment. However, these patients were included for subsequent analysis on adverse events and treatment satisfaction as a result of using exenatide and insulin concurrently. To avoid excluding patients with shorter duration of follow-up, the latest HbA1c and weight data for each patient were used for comparisons. ANOVA showed that the mean latest HbA1c reduction was representative of those from 3 to 12 months, but the mean latest weight reduction was an underestimate when the period of exenatide treatment approached 12 months.

The addition of exenatide to patients continuing insulin resulted in a mean HbA1c reduction of 0.51%, a weight reduction of 5.8 kg, an insulin dose reduction of 42 U/day and 16.6% discontinued insulin. However, mean HbA1c reduction was less when compared with non-insulin-treated patients (0.94%), and there were higher rates of exenatide discontinuation because of the lack of glycaemic efficacy among insulin-treated patients. Inclusion of HbA1c results of patients who stopped exenatide early for this reason could have potentially shown an even weaker HbA1c reduction among patients on insulin. Possible reasons alluded to in the introduction, such as lower endogenous β-cell function or redundant effects of exenatide with insulin, could potentially account for the diminished response.

Nevertheless, the lesser HbA1c reduction among patients continuing insulin in the audit needs to be evaluated with several important considerations. First, the audit population was characterized by patients who were very obese, had poorly controlled diabetes and long duration of diabetes (mean HbA1c 9.45%, BMI 40.0 kg/m^2, duration 9 years), more so among insulin-treated patients. Insulin-treated patients also had high insulin dose requirements as a group. These characteristics are likely to represent a more treatment-resistant population of patients that is seen in everyday clinical practice and stand in contrast to patients enrolled in phase III trials of exenatide, with baseline HbA1c and BMI values ranging from 7.9 to 8.6% and 30 to 36 kg/m^2 [16].

Second, the lower HbA1c reduction seen in patients who continued insulin may in part reflect the diabetes treatment reduction occurring in this group. One in six patients (16.6%) who continued insulin with exenatide eventually came off insulin alongside achieving HbA1c reduction, albeit mean HbA1c levels were still not to target. The remaining patients who continued insulin achieved significant insulin dose reduction, even after correction of the reduction in body weight. Furthermore, there were high rates of discontinuation of thiazolidinedione treatment in both insulin and non-insulin groups (>60%), whereas sulphonylurea discontinuation was greater among patients on insulin. Clinicians adding exenatide to insulin may be concerned about the possibility of causing hypoglycaemia and be particularly motivated to reduce insulin. It would appear that in poorly controlled patients, over-reduction of diabetes treatment should be avoided when starting exenatide.

Third, despite a lower proportion of patients achieving an HbA1c reduction of ≥1%, more than one third of patients (34.2%) who continued insulin still achieved this target. Furthermore, this group achieved this while losing a mean of 6 kg weight despite the weight-gaining effects of insulin treatment, and with significant discontinuation of insulin, sulphonylureas and thiazolidinediones. Thus, while exenatide was overall less effective among insulin-treated patients, a broad restriction on combination use would have excluded a substantial number of insulin-treated patients who would benefit significantly from the addition of exenatide. It may be that more reliable clinical markers of treatment response are needed beyond insulin status in determining the potential benefit of exenatide.

The mean HbA1c reduction in patients continuing insulin with exenatide in the audit was marginally lower when compared with studies looking at the treatment combination [10,11,17–19]. In a randomized trial of 48 patients with type 2 diabetes, Arnolds et al. showed greater HbA1c reduction of 0.6% when adding exenatide to patients on metformin and insulin glargine, as well as 0.9 kg weight reduction, when compared with patients on metformin and glargine alone [10]. A more recent 30-week randomized trial by Buse et al. involving 261 patients showed a treatment group HbA1c change difference of 0.69% when comparing patients adding exenatide versus placebo to background insulin glargine [11]. The between-group weight change difference was 2.7 kg. Smaller retrospective studies involving 52 [17], 124 [18] and 188 [19] patients on exenatide and insulin have shown mean HbA1c and weight reductions between 0.6 and 0.87% and 2.4 and 6.4 kg, at follow-up intervals of 6–12 months. In contrast to this audit, patients in these studies had lower baseline HbA1c (7.7–8.4%) and some had lower (31.2–33.8 kg/m^2) [10,11] or similar (39.0–43.3 kg/m^2) BMI [17–19]. In trials of dipeptidyl peptidase-4 inhibitors, another class of incretin-based therapy, the addition of sitagliptin or vildaglitpin to insulin-treated patients resulted in a mean HbA1c reduction of 0.6 and 0.5%, respectively, as compared with placebo [20,21].

Patients on exenatide treatment for only a short duration were included in the analysis of adverse events as these events can often occur soon after starting exenatide. Hypoglycaemia was more frequent among insulin-treated patients but was probably because of background insulin therapy, as suggested by the higher rate of hypoglycaemia before exenatide treatment. As incretin-based therapies tend to be antihyperglycaemic rather than hypoglycaemic, the increase in hypoglycaemia probably reflects the concomitant actions of insulin or insulin secretagogue therapy when glycaemic control improved, rather than because of the addition of exenatide *per se*. Overall, rates of hypoglycaemia were low and comparable to other retrospective studies of exenatide and insulin [18,19] but lower in comparison with trials utilizing concurrent sulphonylurea therapy [2,3] and the recent randomized trial by Buse et al. involving uptitration of basal insulin [11]. The higher rate of gastrointestinal side effects among insulin-treated patients, however, was an unexpected finding. We could not provide an adequate physiological explanation for this finding, except that the threshold of unacceptable gastrointestinal side effects may have been lower if patients perceive a lack of glycaemic or weight response. Caution is needed in interpreting this result until this could be prospectively evaluated. Furthermore, while statistically significant, the 3.4% difference in the rate of gastrointestinal side effects may not be clinically significant.

Among respondents, treatment satisfaction was poorer among insulin-treated patients as well as those who required more total injections per day. Of note, the need for adding insulin subsequent to exenatide initiation was associated with more dissatisfaction than those who continued insulin when exenatide was started. We believe that it is crucial to correctly manage patients' expectations of exenatide treatment; that it may be a useful adjunct, but not a way of avoiding insulin treatment, in many insulin-treated patients. Previous studies comparing exenatide to insulin glargine had not found differences in quality of life assessment with the additional one injection required for exenatide [22]. It would be of interest to see whether the use of the newer, less frequently administered GLP-1 agonists would lead to similar rates of dissatisfaction when used with insulin.

As an audit of exenatide use in clinical practice, several limitations to the analysis need to be considered. First, participation in the audit was entirely voluntary and therefore selective. Nevertheless, data from the audit are still probably a better representation of real life clinical practice than those from phase III clinical trials. Second, participants were not subject to strict protocols of research studies and diabetes treatment changes were tailored to individuals rather than made in a controlled fashion. Although we were able to analyse the degree of oral diabetes medication discontinuation in the audit, it was more difficult to account for the many dose changes occurring among patients throughout the periods being reported, which were contributed by different formulations of sulphonylureas and thiazolidinediones used. It may be that the significant reduction or discontinuation of insulin, sulphonylureas and thiazolidinediones that accompanied the addition of exenatide in insulin-treated patients significantly attenuated the HbA1c response. Third, as the audit was also not a prospective research study, we did not capture information on markers of endogenous β-cell function, such as serum C-peptide, to determine whether this influenced the glycaemic response of insulin-treated patients. Fourth, data on the duration of insulin treatment among patients who started insulin after exenatide were also incomplete thereby limiting the interpretation of the adverse events and tolerability of treatment in this group. Finally, a validated diabetes satisfaction questionnaire such as the Diabetes Treatment Satisfaction Questionnaire [23] was not used in order to simplify the requirements from a contributor. Hence, with these limitations, the results presented in this article provide important information on the combination use of exenatide and insulin but requires validation in prospective research studies.

In conclusion, in the ABCD nationwide audit of exenatide in real clinical use in the UK, the off-licence combination of exenatide and insulin was commonly used. Patients were heavier and had worse glycaemic control than patients studied in clinical trials of exenatide. Despite the statistically higher rates of adverse events including higher rates of hypoglycaemia mainly driven by background insulin therapy, no evidence of safety concerns was uncovered in this large-scale audit. However, combination treatment appeared less well tolerated by patients. Although the average HbA1c reduction was lower when compared with non-insulin-treated patients, glycaemic improvement may have been attenuated by concurrent reductions in other hypoglycaemic agents, especially insulin. Nevertheless, a significant proportion of insulin-treated patients still had a significant glycaemic response, alongside important reductions in weight and insulin requirements. Although it may be better to try exenatide in overweight patients with poorly controlled type 2 diabetes before insulin, patients already on insulin may still obtain benefit with the addition of exenatide treatment. Hence, a therapeutic trial of the addition of exenatide to insulin may be justified in some obese patients. Further research is urgently needed to help identify such patients who will tolerate and benefit from exenatide treatment.

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Conflict of Interest

The authors remained independent in the analysis and the writing of this article. K. Y. T. structured and analysed data and wrote the manuscript. B. J., N. S., T. S., W. S. and A. S. R. analysed the data. M. L. C. and A. P. M. collected data for the audit. C. W. designed the audit, and reviewed and edited the manuscript. R. E. J. R. designed the audit, conducted the audit, collected data for the audit, analysed data and reviewed and edited the manuscript.

K. Y. T. is employed as ABCD research fellow and M. L. C. as data administrator in the Nationwide ABCD audit programme (which include audits of exenatide and liraglutide) by the Sandwell and West Birmingham Hospitals NHS Trust. These posts are funded by ABCD from grants provided by Eli Lilly and Novo Nordisk. B. J. has previously received an

honorarium from Eli Lilly. A. P. M., T. S., W. S., A. S. R. and C. W. have no conflict of interests to declare. R. E. J. R. has previously received educational sponsorship, speaker fees and consultancy fees from a number of pharmaceutical companies including Eli Lilly, Novo Nordisk, Sanofi-Aventis, Takeda and GlaxoSmithKline.

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Appendix

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