GLP-1 receptor agonists in type 2 diabetes - NICE guidelines versus clinical practice

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Abstract

Injectable glucagon-like peptide-1 receptor agonists (GLP-1ras) have the distinct advantage of promoting weight loss as well as lowering glucose in type 2 diabetes. Treatment with a GLP-1ra is costly, thereby necessitating a restriction on widespread use, thus in the UK the National Institute for Health and Care Excellence (NICE) has published guidance on the use of these drugs.

In the UK the Association of British Clinical Diabetologists (ABCD) conducted two nationwide audits on the use of exenatide twice daily and liraglutide once daily and noticed that deviations from NICE guidelines were common. Herein data have been used from both audits (following a combined total of 12,955 type 2 diabetes patients) to evaluate these treatment decisions, critically appraise the NICE guidelines and formulate recommendations for the use of GLP-1ras.

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Key words: Exenatide, liraglutide, GLP-1 receptor agonist, obesity, insulin, thiazolidinedione, type 2 diabetes

Introduction

In November 2006 exenatide (twice daily; Byetta®) was the first GLP-1ra to be approved in Europe for the treatment of type 2 diabetes.[1] It was introduced in 2007 and the next agent in the class, liraglutide (once daily, Victoza®), was introduced in 2009.[2] GLP-1ras mimic the actions of the natural gut hormone GLP-1 which enhances insulin secretion, reduces glucagon secretion, delays gastric emptying and suppresses appetite.[3] In addition to their glucose-lowering action, GLP-1ras promote weight reduction - unlike sulphonylureas, TZDs and insulins which cause weight gain. The weight loss aspect of GLP-1ras is particularly appealing in the treatment of type 2 diabetes since many patients are overweight or obese.

Abbreviations and acronyms

ABCD	Association of British Clinical Diabetologists
BMI	body mass index
GLP-1ra	glucagon-like peptide-1 receptor agonist
HbA_{1c}	glycated haemoglobin
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OAD	oral antidiabetic drug
SIGN	Scottish Intercollegiate Guidelines Network
TZD	thiazolidinedione

NICE guidelines on the use of exenatide and liraglutide

NICE aims to provide evidence-based guidance to optimise healthcare and promote effective use of resources in the UK.[4] The NICE guidelines for exenatide and liraglutide are similar both in terms of patient selection and defining a therapeutic response to justify continuing treatment (Table 1).[5,6]

These NICE guidelines are influenced by the cost of GLP-1ra treatment which is much higher than other add-on diabetes therapies.[7,8] Costs of GLP-1ras are typically higher than other third line diabetes therapies such as TZDs or basal insulin (Table 2).[9,10] A different model suggests liraglutide may be a cost-effective second line agent compared with glimepiride after taking into account reductions in systolic blood pressire, weight and cholesterol.[11]

The cost-effectiveness of GLP-1ra use is considered better in patients with higher BMI due to greater anticipated weight loss and the likelihood of higher doses of insulin being required if insulin was used as an alternative. In models considered by NICE, exenatide and liraglutide became cost-effective in comparison with insulin glargine in patients with BMI > 33 or 35 kg/m^2.[10,12,13] It is noteworthy that the liraglutide 1.8 mg dose was considered not cost-effective compared with the 1.2 mg dose.[13]

The ABCD nationwide GLP-1ra audits

The ABCD is the national society of diabetes specialists in the UK. It conducted nationwide audits of the use of exenatide (Byetta®) and liraglutide (Victoza®) to assess their safety and

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Table 1 Summary of NICE guidance for use of exenatide (twice daily) and liraglutide.

Exenatide (Byetta®)	Liraglutide (Victoza®)
"Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulphonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥7.5%, or other higher level agreed with the individual), and the person has: • *a body mass index (BMI) ≥35.0 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or* • *a BMI <35.0 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.* *Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months)."*	The guideline is identical to that for the use of exenatide as third line therapy and for continuing therapy; but with the addition of: *"Liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulphonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if:* • *the person is intolerant of either metformin or a sulphonylurea, or treatment with metformin or a sulphonylurea is contraindicated, and* • *the person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with thiazolidinediones and DPP-4 inhibitors is contraindicated."*

Table 2 The estimated NHS cost of 30 days supply of third line drug therapies[8]

Drug	Dosage	Cost
Exenatide	10 µg bd	£68.24
Liraglutide	1.2 mg od	£78.48
Pioglitazone (TZD)	30 mg od	£33.25
Glargine (basal insulin)	25 units od	£20.18

efficacy in real life clinical practice. Diabetes centres from across the UK were invited to participate. Data requested were obtained from routine clinical practice and were anonymised. From across the UK, 126 centres submitted data on 6717 patients treated with exenatide from 2007–2009 and 117 centres submitted data on 6238 patients treated with liraglutide from 2009–2013. Data from the ABCD audits showed that exenatide and liraglutide were being used in patients who were much heavier and had poorer glycaemic control than the patients in the phase 3 clinical trials.

Patients in the exenatide audit had mean ±SD BMI of 39.8 kg/m² ± 8.0 and HbA_{1c} of 9.47% ± 1.69, and 33.9% of patients were on insulin at exenatide initiation.[14] Patients in the liraglutide audit had mean ± SD BMI of 38.8 kg/m² ± 7.2 and HbA_{1c} of 9.39% ± 1.72 and 39.2% of patients were on insulin at liraglutide initiation. We think that the baseline characteristics of patients in the audit were influenced by NICE guidelines (recommending selection of patients with higher BMI) as well as the predominant participation and use of GLP-1ra therapies in specialist practice dealing with patients with more advanced diabetes.

Aims of this study

Several issues pertaining to the NICE guidelines and the use of exenatide and liraglutide became evident early in both ABCD audits, not least that the desire to use these agents commonly led to their use outside the NICE guidelines. It is not possible for us to present all instances of this. This study aimed to assess:

1. The use of exenatide or liraglutide with insulin
2. The use of exenatide or liraglutide in patients on three OADs
3. The frequency and consequences of discontinuing a third OAD (most commonly a TZD) or insulin when starting GLP-1ra therapy - to appear to be adhering to NICE guidelines
4. The merits and pitfalls of using BMI as a criterion for selecting patients to start exenatide or liraglutide
5. The frequency of patients meeting NICE criteria for a beneficial metabolic response at 6 months
6. The justification for the NICE requirement for ≥1% HbA_{1c} reduction with treatment

Methods of analyses

Results shown are a combination of newly analysed data, previously published data and presentations at scientific meetings.

Patients in real life practice were seen at highly variable intervals of follow-up. To standardise comparisons, we chose to only analyse patients with both HbA_{1c} and weight data at six months of treatment but accepted data from 20–32 weeks (26 ± 6 weeks). There were many more patients with data beyond this time point who were not included in the analyses.

Points 1, 2 and 4 above were analysed among patients using exenatide or liraglutide only as add-on therapy (ie without discontinuation of an OAD or reduction of insulin dose by > 20% at GLP-1ra initiation). Patients on liraglutide 1.8 mg or switching from exenatide were excluded from the analyses (see Figure 1).

Caveats

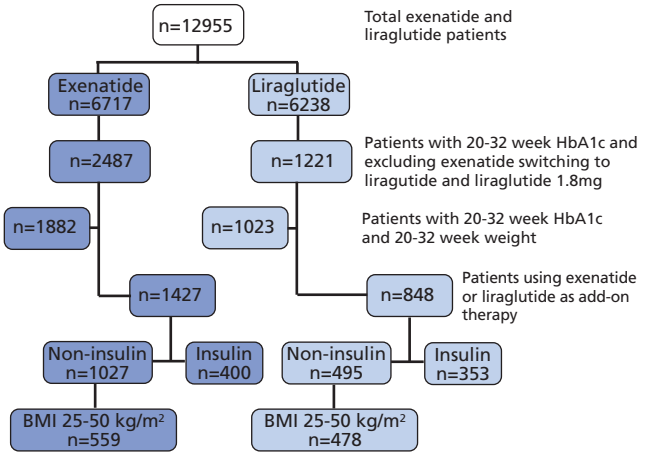
It must be emphasised that the data for exenatide and liraglutide are presented together for the purpose of discussing the NICE guidelines, they are not meant to be compared against each other. The audits were conducted at different time periods (exenatide 2007-2009; liraglutide 2009-2013), among different patients and against different prevailing diabetes experience with GLP-1ra treatment. Concurrent diabetes treatment reduction was often more excessive in the exenatide audit than in the liraglutide audit.

Results

1. The use of exenatide or liraglutide with insulin

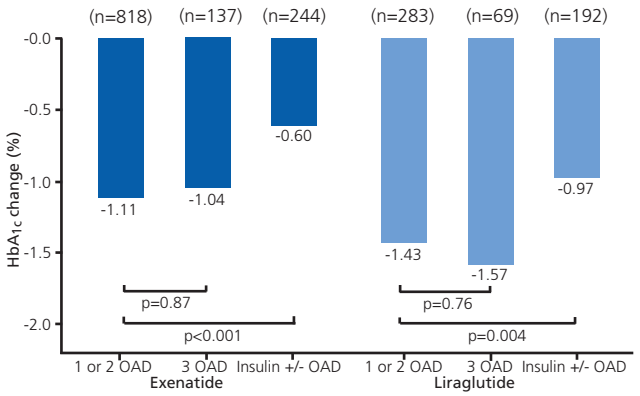
The use of GLP-1ras with insulin was the most common deviation from the NICE guidelines, and indeed from the drugs' licensed indications: 39.6% and 36.5% of patients in the

Figure 1. Patients in the ABCD nationwide exenatide and liraglutide audit



Numbers are different for number of patients with weight data. Non-insulin-treated patients included those on 0-4 oral antidiabetic drugs. Insulin-treated patients included those on basal, biphasic, basal bolus, or other insulin regimens.

Figure 2. HbA_{1c} change at 20-32 weeks with exenatide and liraglutide as add-on therapy to patients on 1 or 2 OADs, on 3 OADs, or on basal or biphasic insulin.



OAD; oral antidiabetes drug

Data are adjusted mean analysed by ANCOVA with baseline HbA_{1c} as a covariate

exenatide[15] and liraglutide audits, respectively, used insulin concurrently after taking into account patients stopping or starting insulin. While exenatide twice daily has since received licensing approval (in 2012) for use in conjunction with basal insulin,[16] this was not the case during the exenatide audit (2007-2009). Moreover, all types of insulin regimens were involved. The unlicensed use of a GLP-1ra was widespread across most participating centres, but how effective was this strategy of combining a GLP-1ra with insulin?

As reported in the exenatide audit, compared with non-insulin-treated patients, insulin-treated patients achieved lesser reductions in HbA_{1c} (mean ±SE: 0.51% ± 0.06 v 0.94% ± 0.04, $p < 0.001$), had similar weight reduction (5.8 kg ± 0.2 v 5.5 kg ± 0.1, $p = 0.28$), more than double the rate of exenatide discontinuation (31.0% v 13.9%, $p < 0.001$) and treatment dissatisfaction was more than threefold higher (20.8% v 5.7%, $p < 0.001$). There was a reduction of daily insulin dose of 42 ± 2 Units (mean ± SE) from a baseline of 120 ± 99 Units (mean ± SD), and 16.6% of patients discontinued insulin.[15]

Herein we have assessed even more specific subgroups of patients in the audits; noting the glycaemic efficacy of exenatide and liraglutide as add-on therapies to one or two OADs as compared with add-on therapy to basal insulin (± OAD) or biphasic insulin (± OAD) at six months of treatment. Data have been adjusted for baseline HbA_{1c}. HbA_{1c} changes were lesser among insulin-treated exenatide patients (adjusted mean ±SE: -0.60% ± 0.10 v -1.11% ± 0.06, $p < 0.001$) and insulin-treated liraglutide patients (-0.97% ± 0.11 v -1.43% ± 0.09, $p = 0.004$) when compared with their non-insulin-treated counterparts (Figure 2).

Comment

The situation can be considered either as a glass half empty or half full; half empty from the point of NICE which should aim to restrict the use of these expensive drugs to earlier stages of diabetes (but not too early as discussed above) whereby GLP-1ra treatment is likely to be more effective. The glass may be half full from the point of treating physicians, who now find a viable treatment for obese and poorly controlled insulin-treated patients. The widespread use of GLP-1ras in both audits suggests that there was a collective sense that no effective alternatives for improving glycaemic control were available.

Our audits suggest that GLP-1ras are less effective in insulin-treated than non-insulin-treated patients. However the pertinent question is whether, in poorly controlled, obese, insulin-treated patients, the addition of a GLP-1ra is a more effective strategy than further insulin up-titration or even a strategy of lifestyle optimisation without additional pharmacotherapy. There is currently a lack of clinical trial data in such patients to provide evidence for a clinical guideline. Furthermore, there is an emerging line of thought that some degree of insulin resistance protects tissues against chronic fuel excess; overcoming this insulin resistance with even higher doses of insulin does not reverse the pathophysiological process of type 2 diabetes and may even be harmful to skeletal muscle and organs such as the heart.[17]

The concurrent use of GLP-1ras with insulin analogues is likely to be costly. Cost savings may occur if there was a combination of weight loss, more effective HbA_{1c} reduction, fewer healthcare visits for insulin up-titration and lowering of high insulin dose requirements.

2. The use of exenatide and liraglutide in patients on three OADs

Figure 2 also shows the glycaemic efficacy of exenatide or liraglutide as add-on therapy to three OADs, as compared with one or two OADs. Data were adjusted for baseline HbA_{1c}. There was no difference in HbA_{1c} change comparing exenatide added to

three OADs with exenatide added to one or two OADs (adjusted mean ±SE: -1.04% ± 0.14 v -1.11% ± 0.06, p = 0.87). Similarly, there was no difference in HbA_{1c} change with liraglutide added to three OADs compared with liraglutide added to one or two OADs (-1.57% ± 0.18 v -1.43% ± 0.09, p = 0.76).

Comment

There is a lack of randomised trials and cost-effectiveness analyses of addition of a GLP-1ra to triple oral therapy and hence this treatment algorithm is unlikely to be supported in clinical guidelines. However, an equivalence in efficacy of a GLP-1ra being added to single or dual oral therapy points to a prescribing restriction that is more based on health economics than treatment efficacy.

3. Frequency of TZD or insulin discontinuation when starting GLP1-ra to adhere to NICE guidelines

Baseline diabetes treatment was known in 6085 patients in the exenatide audit, of which 1652 (27.1%) were on a TZD. Over half (54.3%) of these patients stopped TZDs at exenatide initiation. Adjusting for baseline HbA_{1c} and number of OADs, patients who stopped TZD as part of their dual or triple oral therapy achieved poorer HbA_{1c} responses compared with patients who continued TZD treatment (adjusted mean HbA_{1c} ±SE: -0.45% ± 0.09 v -1.09% ± 0.11, p < 0.001). Similarly, 1168 (19.0%) of the 6238 patients in the liraglutide audit were on a TZD and 47.0% of these patients stopped TZD therapy at liraglutide initiation. The HbA_{1c} reduction was also poorer among patients on liraglutide who stopped a TZD compared with those continuing a TZD (-0.41% ± 0.16 v -1.52% ± 0.14, p < 0.001).

We have reported on the dangers of substituting insulin with exenatide. Indeed, 26.2% of patients on insulin stopped insulin at exenatide initiation and approximately half of them experienced worsening HbA_{1c}. Of the 11 cases of ketosis or ketoacidosis reported in the exenatide audit, 7 were from this group.[18] In contrast, only 8.7% of patients on insulin in the liraglutide audit stopped insulin at liraglutide initiation.

Comment

The desire of some clinicians to appear to conform to NICE guidelines on use of GLP-1ras led to frequent treatment "switches" which were often associated with poorer glycaemic outcomes.

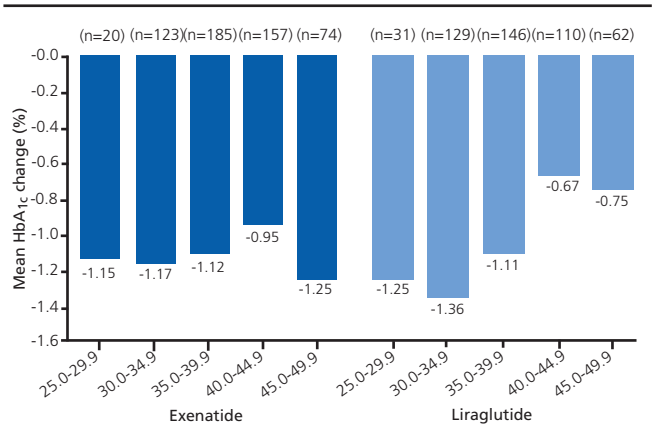
4. Merits and pitfalls of using a BMI as a criterion for selecting patients to start exenatide or liraglutide

In both the exenatide and liraglutide audits capture of BMI was poor (3554/6717 and 5703/6238 respectively).

In the exenatide audit 27.2% (967/3554) of patients with BMI data were below the NICE guidelines threshold of BMI > 35 kg/m^2. Only a minority of these patients had justification for starting a GLP-1ra with a BMI < 35 kg/m^2; 9.7% were non-Europid and fewer still were reported to have other indications for use of GLP-1ra, such as occupational implications for using insulin[19] or obesity-related comorbidities. Similarly, 32% of patients (1824/5703) in the liraglutide audit had BMIs < 35 kg/m^2, and only 11.1% of these patients were non-Europid.

Figure 3 shows the mean HbA1c change achieved with exenatide and liraglutide when used as add-on therapy to non-insulin-treated patients with BMI 25-50 kg/m^2; patients with BMIs outside this range were excluded for clarity. After adjusting for number of OADs, baseline HbA_{1c} , age, gender and ethnicity, no relationship was observed between BMI groups and HbA_{1c} change among exenatide treated patients (p = 0.67). However, a lesser HbA_{1c} reduction was observed with increasing BMI group among patients treated with liraglutide (p = 0.024). These longer term (6 months) liraglutide results contrast with our earlier analysis of short term data (3 months) showing no significant effect of BMI on HbA_{1c} reduction.[20]

Figure 3. HbA_{1c} change at 20-32 weeks with exenatide and liraglutide as add-on therapy to non-insulin-treated patients, results stratified by baseline BMI.



Data analysed by ANCOVA using BMI group and number of OAD as fixed effects, and baseline HbA_{1c}, age, gender, ethnicity as covariates.
Exenatide; p = 0.67 for effect of BMI group, liraglutide; p = 0.024 for effect of BMI group

Figure 4 shows the corresponding weight changes with exenatide and liraglutide treatment. There was increasing weight reduction seen in both treatment groups with increasing BMI group (p < 0.001 and p = 0.021, respectively).

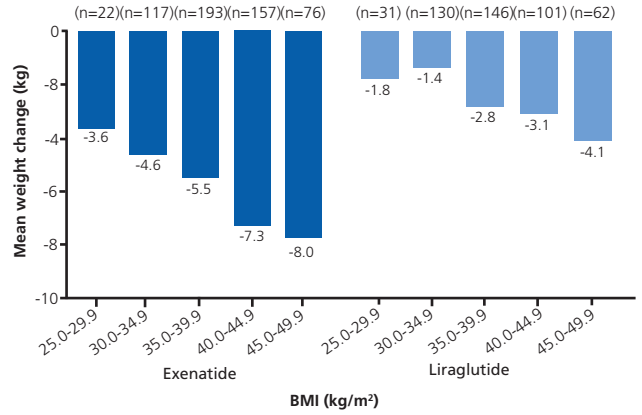
Expressed as a percentage of initial body weight, the change increased non-significantly with increasing BMI groups among patients on exenatide (from -3.8% to -5.9%, p = 0.08) and among patients on liraglutide (from -2.3% to -3.0%, p = 0.55).

Comment

The pivotal clinical studies leading to regulatory approval of exenatide and liraglutide studied patients who were less obese than those required by NICE (mean BMIs 34.0 kg/m^2 and 31.8kg/m^2 vs ≥35kg/m^2).[21,22] Most of the pre-registration studies also excluded patients with BMI > 45 kg/m^2.[23-28] Hence, the BMI restriction of ≥35 kg/m^2 adopted by NICE is not strictly evidenced-based.

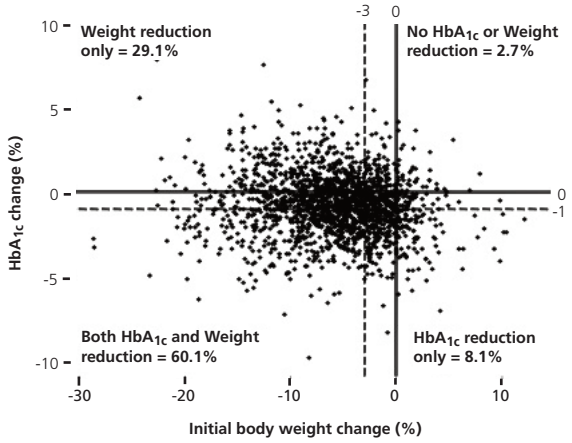
Our findings suggest that the NICE BMI restriction has merit based on greater weight reduction. However, the argument of increased cost-effectiveness is lost if HbA_{1c} reduction is less with greater BMI, as was seen with liraglutide at 6 months. The liraglutide audit finding is supported by a trial in which addition of exenatide (twice daily) to optimized insulin glargine generated

Figure 4. Weight change at 20-32 weeks with exenatide and liraglutide as add-on therapy to non-insulin-treated patients, results stratified by baseline BMI.



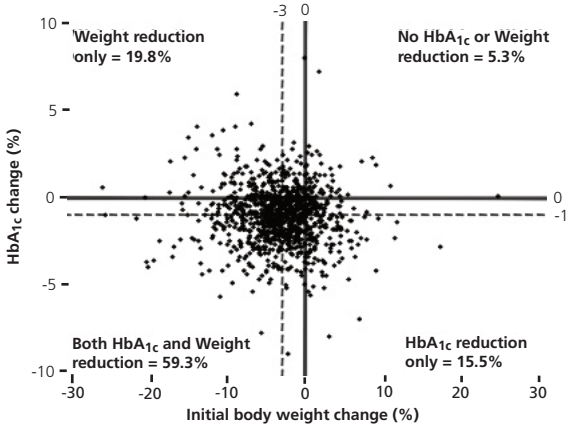
Data analysed by ANCOVA using BMI group and number of OAD as fixed effects, and age, gender, ethnicity as covariates.
Exenatide; $p < 0.001$ for effect of BMI group, liraglutide; $p = 0.021$ for effect of BMI group

Figure 5. Scatterplot of HbA_{1c} change and initial body weight change at 20-32 weeks of 1882 patients treated with exenatide



Dotted line indicates criteria of ≥1% HbA1c reduction and ≥3% IBW reduction require by NICE for continuation of therapy – while 60.1% of patients achieved both HbA1c and weight reduction, only 28.6% achieved this to the criteria level set by NICE.

Figure 6. Scatterplot of HbA_{1c} change and initial body weight change at 20-32 weeks of 1023 patients treated with liraglutide



Dotted line indicates criteria of ≥1% HbA_{1c} reduction and ≥3% IBW reduction require by NICE for continuation of therapy – while 59.3% of patients achieved both HbA_{1c} and weight reduction, only 25.0% achieved this to the criteria level set by NICE.

greater reductions in HbA_{1c} among subjects with lower BMI (<30 and 30-36 kg/m² versus >36 kg kg/m²).[29]

5. The frequency of patients meeting NICE criteria for a beneficial metabolic response at 6 months

In the exenatide audit (all diabetes therapies) there were data at 6 months for both HbA_{1c} and body weight for 1882/6717 patients (Figure 5). Of these 1882 patients 60.1% achieved reductions in both HbA_{1c} and body weight, 8.1% achieved HbA_{1c} reduction only, 29.1% achieved weight reduction only and 2.7% achieved neither. Only 28.6% of patients achieved the NICE criteria of both ≥1% HbA_{1c} reduction as well as ≥3% reduction of initial body weight.

In the liraglutide audit HbA_{1c} and weight data were recorded for 1023/6238 patients (Figure 6). Of these 59.3% achieved both HbA_{1c} and weight reductions, 15.5% achieved HbA_{1c} reduction only, 19.8% achieved weight reduction only and 5.3% achieved neither. Only 25.0% of patients achieved both HbA_{1c} and weight reduction in accordance with NICE criteria.

Comment

It is apparent that the vast majority of patients using GLP-1ras in clinical practice would require discontinuation of this therapy based on NICE criteria. The rates of exenatide and liraglutide discontinuation in the audits did not match this. Physicians may also face the dilemma of whether to stop treatment among patients who achieved significant HbA_{1c} reduction but not significant weight reduction or patients who achieved significant weight reduction but not significant HbA_{1c} reduction.

In our opinion, stopping GLP-1ra treatment in a patient who has achieved significant glycaemic improvement (but not significant weight reduction) would seem unwise. In this sense, GLP-1ra has worked as a diabetes treatment; it is only the requirement of weight reduction to justify cost-effectiveness that has deemed treatment to be a failure.

A somewhat more contentious situation would be that of patients who achieved significant reductions in weight and HbA_{1c} but with the latter not meeting NICE criteria. We would argue that if these patients started GLP-1ra treatment according to NICE criteria, they should continue GLP-1ra treatment until weight reduction has tapered off.

Table 3 Median HbA_{1c} change, proportion of patients achieving HbA_{1c} reduction of ≥1% and proportion of patients achieving target HbA_{1c} of 7% among patients treated with liraglutide in the ABCD audit; results stratified by baseline HbA_{1c} and use of insulin.

	Baseline HbA_{1c} (%)							
	7.0-7.9	**8.0-8.9**	**9.0-9.9**	**10.0-10.9**	**11.0-11.9**	**12.0-12.9**	**13.0-13.9**	**P value**
Non-insulin-treated								
n	91	158	161	106	60	35	11	
Median HbA_{1c} change, (%)	-0.7 [-1.1,-0.1]	-1.1 [-1.7,-0.5]	-1.4 [-2.2,-0.4]	-1.9 [-3.2,-0.9]	-2.6 [-3.9,-1.6]	-3.1 [-1.3,-4.5]	-2.0 [-0.3,-4.9]	< 0.001
Proportion achieving ≥1% reduction, n(%)	30 (33.0)	95 (60.1)	103 (64.0)	77 (72.6)	51 (85.0)	28 (80.0)	8 (72.7)	< 0.001
Proportion achieving HbA_{1c} of 7%, n(%)	50 (55.0)	58 (36.7)	35 (21.7)	25 (23.6)	11 (18.3)	4 (11.4)	1 (9.1)	< 0.001
Insulin-treated								
n	73	124	156	98	61	35	10	
Median HbA_{1c} change, (%)	-0.2 [-0.7,0.4]	-0.5 [-1.2,0.3]	-1.1 [-2.0,-0.2]	-1.3 [-2.6,-0.5]	-1.3 [-2.5,-0.5]	-1.8 [-3.4,-0.6]	-3.6 [-4.7,-1.6]	< 0.001
Proportion achieving ≥1% reduction, n(%)	11 (15.1)	41 (33.1)	82 (52.6)	61 (62.2)	36 (59.0)	24 (68.6)	9 (90.0)	< 0.001
Proportion achieving HbA_{1c} of 7%, n(%)	28 (38.4)	18 (14.5)	21 (13.5)	8 (8.2)	3 (4.9)	1 (2.9)	2 (20.0)	< 0.001

Median HbA_{1c} change results are shown as median [interquartile range]

Results show patients are more likely to achieve ≥1% HbA_{1c} reduction when baseline HbA_{1c} is higher and conversely more likely to achieve target HbA_{1c} of 7% if baseline HbA_{1c} is lower.

6. The lack of justification for requiring ≥1% HbA_{1c} reduction with GLP-1ra treatment

The liraglutide audit (Table 3) showed that the likelihood of achieving ≥1% HbA_{1c} reduction increased with increasing baseline HbA_{1c}. We investigated an alternative criterion which was that of achieving a target HbA_{1c} of 7%. In contrast, the likelihood of achieving this criterion increased with decreasing baseline HbA_{1c}.

Comment

In our opinion, the most serious flaw to the NICE criteria is that of a requirement for HbA_{1c} reduction with treatment that is not indexed to baseline HbA_{1c}. It is well established that the higher the baseline HbA_{1c} the greater the HbA_{1c} reduction on addition of a differently acting glucose lowering agent - including incretin-based therapies.[30,31] Hence, a requirement of ≥1% HbA_{1c} reduction unfairly favours patients with higher baseline HbA_{1c} levels.

Patients with lower baseline HbA_{1c} may also be penalised due to treatment considerations to avoid hypoglycaemia. The SIGN guidelines also miss the mark[32] by only requiring an HbA_{1c} reduction of ≥0.5% to continue treatment: this is easily achieved but not necessarily clinically meaningful in patients with higher baseline HbA_{1c}. In contrast, an alternative criterion of reaching a target HbA_{1c} of 7% unfairly favours patients with lower baseline HbA_{1c} instead and therefore should also not be used.

Hence, we conclude that a measure of HbA_{1c} reduction indexed to a patient's baseline HbA_{1c} is probably the fairest way to judge response, such as achieving an HbA_{1c} reduction that is better than the median HbA_{1c} reduction of a baseline HbA_{1c} group. Based on the results in Table 3, a simplified but graded criterion for non-insulin-treated patients may be that of a requirement of ≥0.5% reduction if baseline HbA_{1c} <8.0%, ≥1.0% if baseline HbA_{1c} 8.0-9.0% and ≥1.5% if HbA_{1c} >9.0%.

Conclusions and recommendations

The NICE guidelines for the use of diabetes therapies serve an important purpose of recommending use of treatments that are evidence-based and cost-effective. This is particularly pertinent in an era of rising healthcare costs. However, in their present form, the NICE guidelines for GLP-1ras essentially prevent their use in patients with more advanced diabetes who still require effective treatment. Specifically:

1. More clinical trials and cost-effectiveness analyses are needed in obese patients with more advanced diabetes. The issue is not the comparative costs of third line diabetes treatment, but that of the comparative costs and effectiveness in patients already on third line therapy who require treatment intensification (such as by escalating insulin doses or using a GLP-1ra). Creative solutions such as an agreement to combine cheaper human insulin with a GLP-1ra could be explored, but requires considerations of the potential disadvantages of older insulins compared with insulin analogues.

Key messages

- Exenatide (twice daily) and liraglutide were commonly prescribed outside NICE guidelines
- In practice less than a third of patients achieve NICE metabolic targets for continuation of a GLP-1ra.
- Restricting GLP-1ra therapy to patients with BMI ≥35 kg/m^2 to improve cost-effectiveness via greater weight loss may be counter-productive if glycaemic efficacy is not maintained
- Requiring ≥1% HbA_{1c} reduction with GLP-1ra treatment lacks justification because the HbA_{1c} reduction was closely associated with baseline HbA_{1c}.

2. The addition of a GLP-1ra to three oral antidiabetic drugs was as effective as adding a GLP-1ra to one or two drugs, thus the escalation to GLP-1ra rather than insulin should be considered a viable treatment algorithm among patients on three oral antidiabetic drugs.
3. Due to the risk of glycaemic deterioration we would caution clinicians against substituting concurrent diabetes treatment to appear to adhere to guidelines when a GLP-1ra is started.
4. The general requirement by NICE for BMI to be >35 kg/m^2 is not strictly evidenced-based. This strategy to improve cost-effectiveness may be counter-productive if glycaemic improvement is diminished in more obese patients.
5. Few patients also meet the criteria for continuing GLP-1ra therapy. We propose that patients who achieved significant HbA_{1c} reduction but not weight reduction be allowed to continue GLP-1ra treatment.
6. The NICE criterion of ≥1% HbA_{1c} reduction as a requirement for continued GLP-1ra treatment unfairly favours patients with higher baseline HbA_{1c}. This should be replaced by a target HbA_{1c} reduction that is indexed to an individual's baseline HbA_{1c}.

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Appendix 2. ABCD nationwide prospective liraglutide audit contributors. The following are those whom we know about.

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