Implementing the NICE guideline for type 2 diabetes: Weight gain and hypoglycaemia

Anthony Barnett, Clifford Bailey, Marc Evans, David Haslam, Debbie Hicks, Eugene Hughes

In 2008, the current authors published a consensus statement on the newer antihyperglycaemic agents and their place in the type 2 diabetes treatment pathway (Barnett et al, 2008). The original consensus statement included a treatment algorithm and rationale for the positioning of the oral dipeptidyl peptidase-4 inhibitors and injectable glucagon-like peptide-1 receptor agonists. Subsequently, NICE updated its clinical guideline on the management of type 2 diabetes, providing its own treatment algorithm and recommendations on the positioning of newer antihyperglycaemic agents (NICE, 2009a). Based on a recent meeting of the original consensus panel, this article is intended to assist primary care practitioners in the implementation of the updated NICE guideline, with a focus on hypoglycaemia and weight gain in the context of blood glucose-lowering therapy.

Article points

1. The current iteration of the NICE guideline on the management of type 2 diabetes provides a clear framework for person-centred care, taking into account the dual challenges of iatrogenic hypoglycaemia and weight gain.
2. In circumstances where hypoglycaemia and weight gain are problematic, NICE provides recommendations on the use of thiazolidinediones and the incretin-based drug classes.
3. This consensus statement is intended to assist primary care professionals in implementing the updated NICE recommendations, with a focus on hypoglycaemia and weight gain.

Key words

- Antihyperglycaemic agents
- Hypoglycaemia
- Weight gain

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Type 2 diabetes is a condition characterised by insulin insensitivity coupled with a relative deficiency of compensatory insulin secretion from the pancreatic beta-cells, the net result of which is progressively worsening hyperglycaemia (UKPDS Group, 1995). It is well established that control of blood glucose concentrations with antihyperglycaemic agents, aiming for HbA_{1c} levels as close as possible to the non-diabetic range, is important in reducing the risk of microvascular complications (UKPDS Group, 1998; ADVANCE Collaborative Group et al, 2008).

The effect of glucose lowering on macrovascular complications and all-cause mortality is less clear,

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with trends towards improvements in these outcomes failing to reach statistical significance in the original results obtained in the UKPDS (UK Prospective Diabetes Study; UKPDS Group, 1998), and the finding that intensive lowering of HbA_{1c} was associated with an increased risk of mortality in the recent ACCORD (Action to Control Cardiovascular Risk in Diabetes) study (ACCORD Study Group et al, 2008). Newer data from the UKPDS (Holman et al, 2008) are an important addition to the story, with statistically significant improvements in the risk of myocardial infarction and mortality emerging in the originally intensively controlled participants over 10 years of post-trial monitoring.

Commentators have suggested that the apparent discrepancy between such results may be explained by the differences in the patient populations studied – in terms of diabetes duration and cardiovascular risk – as well as in the length of follow-up and intensity of glucose lowering assessed (Holman, 2008). As yet, no cause for the increased mortality rate in ACCORD has been proven, although severe hypoglycaemia was associated with increased mortality in both arms of the study (Skyler et al, 2009).

A recent meta-analysis of the four major macrovascular outcome trials in type 2 diabetes (ACCORD, ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], UKPDS and VADT [Veterans Affairs Diabetes Trial]) suggested that, overall, intensive glucose lowering resulted in a 9% relative risk reduction in major macrovascular events over 4.4 years of follow-up (Turnbull et al, 2009). However, this was also associated with an increase in the risk of severe hypoglycaemia, leading the authors to conclude that clinicians should tailor glucose-lowering regimens to individual patient circumstances.

Glycaemic control in practice: NICE and the Quality and Outcomes Framework

Given the above, in everyday practice, it is therefore more appropriate for people with type 2 diabetes to tightly control their blood glucose levels from the point of diagnosis, rather than attempting to aggressively "rescue" glycaemic control after it has been allowed to deteriorate (Holman, 2008).

The need to individualise targets for blood glucose control has been advocated by NICE in its recent guidance on the management of type 2 diabetes for clinicians in England and Wales (NICE, 2008). Clinical Guideline 66 (CG66) suggested an HbA_{1c} target of 6.5% (48 mmol/mol) for people at the early stages of diabetes – namely those managed by diet and lifestyle intervention, or with mono- or dual therapy for blood glucose lowering. In contrast, a target of 7.5% (58 mmol/mol) was suggested for those with longer diabetes duration – specifically, those on triple-oral or injectable therapy. The guideline also states that these targets may be individualised depending on what is agreed with the person with type 2 diabetes.

This individualised approach should be set against the glycaemic control indicators contained within the most recent iteration of the Quality and Outcomes Framework for 2009/2010, which awards maximal points for 50% of a practice's diabetes register achieving an HbA_{1c} level of ≤7% (≤53 mmol/mol) (NHS Employers, 2008). In light of the data discussed above, concern has been expressed among the diabetes community that indiscriminate pursuit of such tight glycaemic control may be dangerous for some groups of people with type 2 diabetes (Hadley-Brown, 2008).

Newer agents for blood glucose lowering

As well as new national clinical guidelines on the management of type 2 diabetes, two new classes of blood glucose-lowering agents have been added to the treatment armamentarium in recent years – oral dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin and, most recently, saxagliptin) and injectable glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide and liraglutide).

Both types of agent exploit the incretin effect, which is diminished in people with type 2 diabetes (Nauck et al, 1986), and as a result enhance endogenous insulin secretion in a glucose-dependent manner, thus offering a low risk of hypoglycaemia, particularly when they

Page points

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2. In everyday practice, it is therefore more appropriate for people with type 2 diabetes to tightly control their blood glucose levels from the point of diagnosis, rather than attempting to aggressively "rescue" glycaemic control after it has been allowed to deteriorate.
3. As well as new national clinical guidelines on the management of type 2 diabetes, two new classes of blood glucose-lowering agents have been added to the treatment armamentarium in recent years.

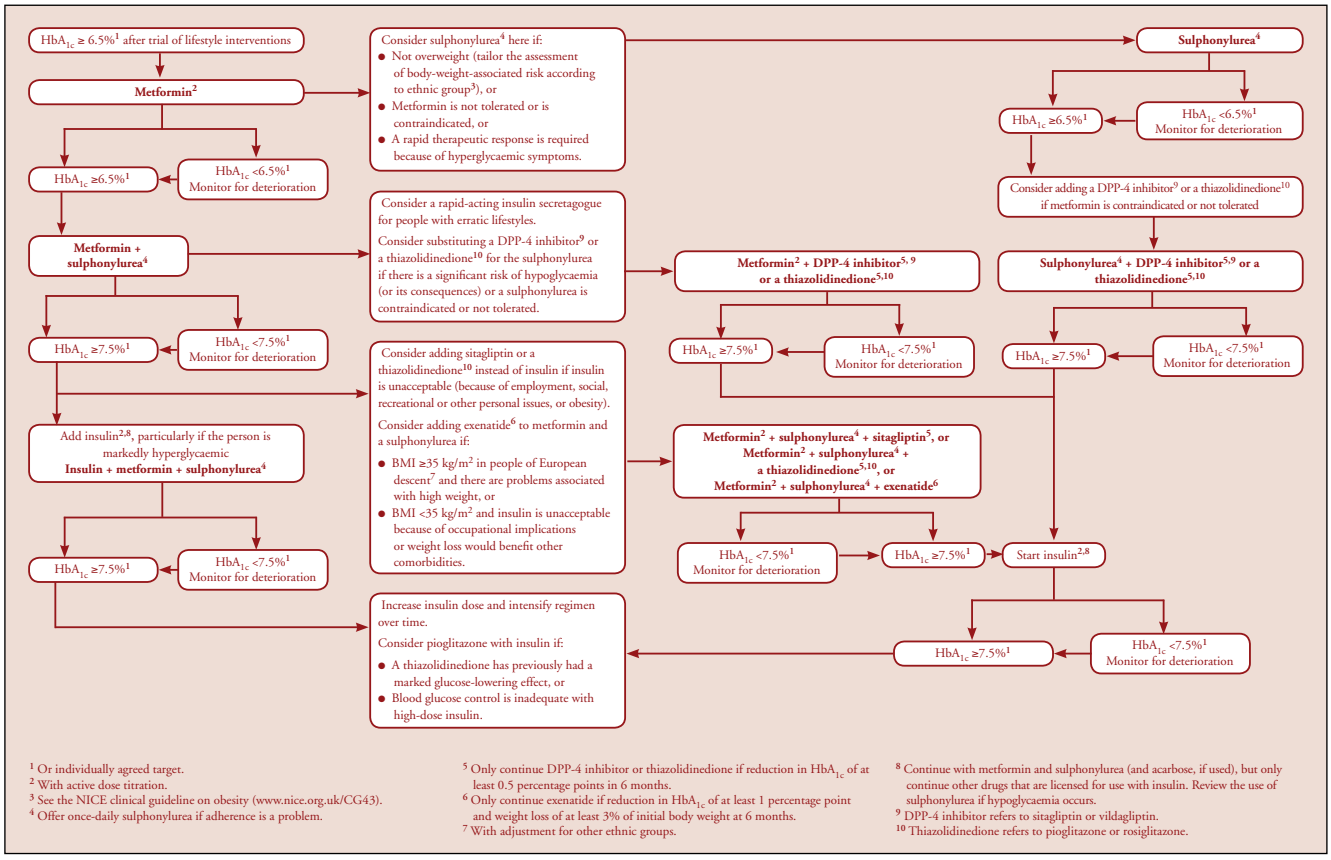

Figure 1. Updated NICE algorithm on the management of blood glucose levels in type 2 diabetes. (NICE, 2009b.) Adapted from* CG87 Type 2 diabetes: the management of type 2 diabetes. *NICE, London. Available from www.nice.org.uk/CG87. Reproduced with permission. DPP = dipeptidyl peptidase-4.

are not co-prescribed with a sulphonylurea. For example, in a head-to-head randomised clinical trial comparing the effect of adding either sitagliptin or glipizide to ongoing metformin monotherapy, the proportion of participants experiencing hypoglycaemia with the DPP-4 inhibitor was significantly lower than that in the sulphonylurea group (5% vs. 32%, respectively; $P<0.001$; Nauck et al, 2007). Indeed, in a Cochrane Library systematic review of 25 trials involving sitagliptin or vildagliptin, no severe hypoglycaemic events were identified in those randomised to either DPP-4 inhibitor (Richter et al, 2008). Furthermore, in a head-to-head comparison of liraglutide and glimepiride, the incidence of minor hypoglycaemia was significantly less in the group receiving the GLP-1 receptor agonist (approximately 3% vs. 17%, respectively; $P<0.001$; Nauck et al, 2009).

Unlike many other classes of antihyperglycaemic agent, these newer agents are not associated with weight gain. The DPP-4 inhibitors are generally regarded as "weight neutral", whereas GLP-1 receptor agonists are associated with progressive weight loss, resulting from reduced appetite and food intake. This difference is thought to result from the fact that the levels of active GLP-1 generated with DPP-4 inhibitors are lower than those obtained with GLP-1 receptor agonists (Holst et al, 2008). This concentration differential also explains the dissimilar tolerability profiles between these drug classes; while DPP-4 inhibitors are generally well tolerated, GLP-1 receptor agonist therapy may initially be associated with gastrointestinal side-effects such as nausea, diarrhoea and vomiting (Holst et al, 2008).

Position of the newer agents in the treatment algorithm

CG66, published in 2008, did not include recommendations on the use of DPP-4 inhibitors or some of the newer insulin preparations; however, some preliminary recommendations were made on the use of exenatide (NICE, 2008). The role played by the newer incretin-based

therapies in UK clinical practice has been subject to much debate, and so prior to the revision of the NICE guideline to include the omitted agents, the current authors published a consensus statement and treatment algorithm in September 2008 in an effort to provide a framework for primary care practitioners on the use of DPP-4 inhibitors and GLP-1 receptor agonists (Barnett et al, 2008).

NICE subsequently published a partially updated version of CG66 in the form of Clinical Guideline 87 (CG87), which includes clear recommendations on the use of sitagliptin, vildagliptin and insulin detemir and revised guidance regarding exenatide and some of the older antihyperglycaemic agents – notably pioglitazone, rosiglitazone and insulin glargine (NICE, 2009a). The document was accompanied by a revised treatment algorithm, which is reproduced in *Figure 1* (NICE, 2009b). Liraglutide and saxagliptin were not licensed for use in the UK at the time of publication of CG87, and so were not considered within it.

Key factors governing treatment decisions

In CG87, healthcare professionals in the UK have a clear framework for the use of the newer incretin-based therapies. It can be seen from *Figure 1* that while the treatment pathway offers a welcome degree of flexibility regarding treatment selection, the large number of agents now available necessitates several key "decision points" in the treatment algorithm. For example, as a second-line add-on therapy to metformin the guideline provides the options of a sulphonylurea, DPP-4 inhibitor or thiazolidinedione (TZD), depending on the specific circumstances. At most of these decision points, iatrogenic hypoglycaemia and weight gain are key factors to be taken into account.

Hypoglycaemia

In CG87, a sulphonylurea is the "standard" second-line therapy when blood glucose control becomes inadequate with metformin monotherapy; however, a DPP-4 inhibitor or a TZD may be considered as a second-line therapy when "the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone])" (NICE, 2009a).

Table 1. Signs and symptoms associated with hypoglycaemia. (Adapted from Krentz and Bailey, 2005).

Signs and symptoms	Approximate blood glucose concentration for onset (mmol/L)	Mechanism
Hunger Palpitations Sweating Tremor Dizziness	<4	Autonomic response
Atypical behaviour Cognitive dysfunction Drowsiness Uncoordination Speech difficulty	<3	Neuroglycopenia
Headache Malaise Nausea Reduced consciousness Coma Convulsions	<2	Severe neuroglycopenia

In order to effectively implement this recommendation, it is important that primary care professionals are knowledgeable about hypoglycaemia – not only having an awareness of its prevalence, signs and symptoms, but also being confident in strategies for treating hypoglycaemic episodes and eliciting appropriate information from the person with type 2 diabetes. These are considered in greater detail below.

Prevalence

While definitive data regarding the prevalence of hypoglycaemia in type 2 diabetes are lacking, it is known that the phenomenon is not restricted to those receiving insulin. For example, data from the UK Hypoglycaemia Study suggest that the prevalence of hypoglycaemia is equivalent in those treated with insulin for <2 years and in people treated with sulphonylureas (UK Hypoglycaemia Study Group, 2007). Over the 9–12 month study period, severe episodes of hypoglycaemia were experienced by 7% of the

Table 2. Authors' guide to hypoglycaemia for people with diabetes and their carers.

Signs and symptoms	Approximate blood glucose level (mmol/L)	Action required
Feeling "odd" Feeling "shaky" Tired Anxious	Below 5	**Caution**
As above, plus: Mood change Sweating Hungry Dizzy Palpitations	Below 4	**Take 10–20 g fast-acting carbohydrate** (e.g. 50–100 mL Lucozade®, 3–6 dextrose tablets or a small glass of sugary drink [e.g. cola, but not diet cola]). **Then take starchy carbohydrate** (e.g. a piece of fruit or a sandwich). **Repeat glucose measurement** after 10 min
As above, plus: Drowsy Tingly round the mouth Vision disturbed Speech difficult Disoriented Aggression Odd behaviour Unsteady movement	Below 3	**Take 10–20 g fast-acting carbohydrate** as above. **Then take starchy carbohydrate** as above. **Repeat blood glucose measurement** after 10 min and **take further fast-acting carbohydrate if below 4 mmol/L. Seek assistance**
As above, plus: Unable to function	Below 2	**Help from others required. Ambulance may be needed**

Note: Oral carbohydrate should be given only if the person is conscious and has a gag reflex.

insulin group as compared with 7% of those receiving sulphonylureas, and mild symptomatic episodes were recorded in 51% versus 39% of patients, respectively (UK Hypoglycaemia Study Group, 2007).

Furthermore, in the recent RECAP-DM (Real-Life Effectiveness and Care Patterns of Diabetes Management) study, approximately 38% of people with type 2 diabetes who added a sulphonylurea or a thiazolidinedione to ongoing metformin therapy experienced symptoms of hypoglycaemia over the course of 1 year (Alvarez Guisasola et al, 2008). In an older study, by Jennings et al (1989), 20% of people receiving sulphonylurea therapy reported experiencing hypoglycaemic symptoms in the previous 6 months, when questioned during routine diabetes clinics at a UK hospital. Thus, hypoglycaemia is potentially more common a problem in people treated with certain oral hypoglycaemic agents – particularly sulphonylureas – than may be appreciated by some healthcare professionals.

Consequences of hypoglycaemia

A full examination of the consequences of hypoglycaemia in type 2 diabetes was outside the scope of the panel's discussion, and readers are directed to recent reviews on the subject (Amiel et al, 2008). Briefly, severe episodes of hypoglycaemia can be serious, particularly in older people, and have been linked with a wide variety of neurological and cardiovascular sequelae, such as seizure, transient ischaemic attack and coma. Hypoglycaemia can also cause accident and injury – for example, it has been estimated that >40 road traffic accidents (RTAs) each month, and five RTA fatalities each year result from hypoglycaemic episodes (Hitchen, 2006).

Aside from the consequences above, hypoglycaemia has a detrimental impact on quality of life on a number of levels (in terms of fear and mood, for example), and also may affect concordance with therapy (Amiel et al, 2008), not to mention employment. In addition, hypoglycaemia is associated with significant economic cost to the health service – for example as a result of hospitalisation and ambulance call-out costs (Leese et al, 2003).

Symptoms, signs and treatment of hypoglycaemia

Given the above, vigilance for hypoglycaemia on the part of the healthcare professional and the person with type 2 diabetes or their carers is important. *Table 1*, adapted by the authors from Krentz and Bailey (2005), is designed to provide primary care professionals with an approximate guide to the signs and symptoms associated with hypoglycaemia. It should be noted, however, that the plethora of hypoglycaemia signs and symptoms, and the blood glucose levels at which

they manifest, is highly variable between people with diabetes, and indeed within the same person. Furthermore, the signs and symptoms may not be immediately obvious as being caused by hypoglycaemia.

The person with type 2 diabetes who is receiving hypoglycaemic medication (or his or her carers) should also be aware of the signs and symptoms of hypoglycaemia, along with having an understanding of how to act should an episode occur. With this in mind, the authors propose *Table 2* as a useful source of information to be shared with people with diabetes or their carers. As with *Table 1*, it is important to bear in mind that the blood glucose values given are approximate and the signs and symptoms highly variable from person to person.

Self-monitoring of blood glucose (SMBG) is an important tool for providing information on hypoglycaemia, and indeed CG87 states that it should be available to those on oral glucose-lowering medications for this reason, among others (NICE, 2009a). The guideline does not offer recommendations on specific testing frequency for different groups of patients, but readers can refer to a consensus statement published previously in this journal for further information (Owens et al, 2005).

Specific patient groups

As quoted above, CG87 provides some examples of specific groups in whom hypoglycaemia is a particular concern. The current authors have compiled *Table 3* to provide a more detailed guide – it should be noted that while some groups are more likely to experience hypoglycaemia with blood glucose-lowering therapy than others, there are also patients in whom hypoglycaemia is not necessarily more likely, but in whom it should be avoided due to the increased possibility of accident or injury, for example.

Appropriate questioning: engaging with the person with diabetes

It is incumbent upon primary care professionals to explore hypoglycaemia with people with type 2 diabetes; however, eliciting information may be difficult, particularly if patients do not understand the concept of hypoglycaemia or how and why it manifests. A series of questions that may help in teasing out the relevant information is provided in *Table 4*. The current authors believe that such questions should be

Table 3. Groups or circumstances in which susceptibility to hypoglycaemia is increased or in which hypoglycaemia must be avoided in the context of antihyperglycaemic therapy.

Hypoglycaemia more likely	Older people. Impaired renal function. Fasting (e.g. during Ramadan) or eating less to lose weight. Increased alcohol ingestion without carbohydrate consumption. Increased exercise. Co-medication with beta-blockers or ACE inhibitors. During illness.
Hypoglycaemia must be avoided	Drivers (LGV and PCV licence holders) and pilots. Those working at heights or depths. Machine workers. Those living alone.

ACE = angiotensin-converting enzyme. LGV = large goods vehicle. PCV = passenger carrying vehicle

Table 4. Exploring hypoglycaemia with the person with type 2 diabetes.

Issue	Questions that may be helpful
People with diabetes may not understand the term hypoglycaemia, nor the concept of low blood glucose levels.	"What do you understand by the term 'low blood sugar'?" "What do you call it when you have a low blood sugar?" "What do you understand by the term 'hypo' or hypoglycaemia?"
People with diabetes may not understand that hypoglycaemia is caused by their glucose-lowering medication, rather than their diabetes.	"What do you think causes hypoglycaemia?"
People with diabetes may not realise they have experienced hypoglycaemia, or know what to look for.	"How would you recognise hypoglycaemia?" "What are your experiences of hypoglycaemia?"
People with diabetes may not appreciate the implications of hypoglycaemia.	"What do you think the effects of hypoglycaemia are?" "Do you hold a driving license?"
People with diabetes may not understand how to act if they experience hypoglycaemia.	"What do you do when you experience a hypoglycaemic episode?" "How would you treat a hypo?"

Page points

1. Metformin excepted, until the introduction of the incretin-based agents, antihyperglycaemic agents were generally associated with weight gain.
2. The current authors believe that healthcare professionals focused on the management of blood glucose levels in diabetes should also reinforce the importance of lifestyle interventions, and consider the possible need for agents licensed specifically for weight loss at every treatment step.
3. Weight gain is an important consideration for healthcare professionals when prescribing antihyperglycaemic agents, and the current authors have compiled *Table 6* in an effort to assist primary care practitioners in identifying some of the specific circumstances and populations in which further weight gain, or indeed weight loss, is particularly relevant.

asked of people who are taking agents that may cause hypoglycaemia (not limited to insulin) in each and every consultation as a means of either providing information that may not have been given before, or reinforcing previous education.

Weight gain

In CG87, weight gain is also a factor at several decision points in the blood glucose-lowering algorithm. For example, at the second- and third-line therapy stages, where there may be a choice to be made between a DPP-4 inhibitor or a TZD, the guideline states that the former may be preferable "if further weight gain would cause or exacerbate significant problems associated with high body weight".

Similarly, weight gain is a factor at the third-line stage when considering injectable therapy. The guideline states that exenatide should be considered as an add-on to first-line metformin and second-line sulphonylurea for people who have:

- A BMI ≥35 kg/m^2 (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 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities (NICE, 2009a).

It is worthwhile exploring weight gain further if these recommendations are to be implemented appropriately.

Prevalence of high body weight and weight gain with type 2 diabetes treatments

The majority of people with type 2 diabetes have excess body weight or are obese (Lusignan et al, 2005). Indeed, a recent analysis of patients attending one secondary care diabetes clinic in the UK found that, overall, 86% of those with type 2 diabetes were overweight or obese (Daousi et al, 2006). While much attention is placed on the adverse health consequences of excess weight and obesity in general (e.g. type 2 diabetes and cardiovascular disease), little consideration has been given to the effects of weight gain in people who have been diagnosed with diabetes, and in the above study by Daousi et al (2006), obese people with type 2 diabetes had a significantly worse cardiovascular risk factor profile compared with their lower weight counterparts.

Metformin excepted, until the introduction of the incretin-based agents, blood glucose-lowering agents were generally associated with weight gain (*Table 5*). There are several reasons for this, one of which being simply that untreated type 2 diabetes is often associated with loss of glucose that cannot be utilised by the body via the urine; treatment with a blood glucose-lowering agent prevents this, as glucose uptake and storage is promoted instead. Indeed, it is possible to estimate likely weight gain based on the amount of glucose retained and the reduction in HbA_{1c}.

Implications of weight gain and relevant populations and circumstances

Barnett et al examined the effects of weight gain associated with blood glucose-lowering therapy, finding that it affected not only the physiological capability of people with type 2 diabetes to achieve glycaemic targets, but also their psychological health, quality of life and adherence to blood glucose-lowering therapy (Barnett et al, 2007).

As a result, the current authors believe that healthcare professionals focused on the management of blood glucose levels in diabetes should also reinforce the importance of lifestyle interventions, and consider the possible need for agents licensed specifically for weight loss at every treatment step. Modest weight reduction is also associated with improvements in glycaemic control in people with type 2 diabetes (Pi-Sunyer et al, 2007), and treatment with the antiobesity agents orlistat (Jacob et al, 2009) and sibutramine (Fujioka et al, 2000) leads to reductions in HbA_{1c} level also.

In summary, weight gain is an important consideration for healthcare professionals when prescribing antihyperglycaemic agents, and the current authors have compiled *Table 6* in an effort to assist primary care practitioners in identifying some of the specific circumstances and populations in which further weight gain, or indeed weight loss, is particularly relevant.

Table 5. Comparison of the currently available blood glucose-lowering agents for type 2 diabetes.

	Metformin	SUs (and †meglitinides)	†Alpha glucosidase inhibitors	TZDs	DPP-4 inhibitors	GLP-1 receptor agonists	Insulins
Efficacy (in terms of HbA_{1c} lowering)	++	++	+	++	++	++(+)	+++
Outcome studies?	Yes[1,2]	Yes[2,3]	Yes[4]	Yes[5,6]	Ongoing	Ongoing	Yes[2,3], with others ongoing[7]
Tolerability concerns	Gastrointestinal disturbance	Hypoglycaemia, weight gain	Gastrointestinal disturbance	Weight gain, oedema, heart failure, fractures	No specific problems yet established	Nausea, vomiting	Hypoglycaemia, weight gain
Weight gain?	No	Yes	No	Yes	No	Weight loss	Yes
Hypoglycaemia?*	No	Yes	No	No	No	No	Yes

†Not widely used in the UK.

*Relates to whether there is an increased risk of hypoglycaemia relative to placebo.

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DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SU = sulphonylurea; TZD = thiazolidinedione.

Table 6. Circumstances and populations in which further weight gain is particularly undesirable, or weight loss is particularly beneficial.

Those in whom further weight gain is a particular concern	Raised BMI or waist circumference. Ethnic minority groups (e.g. people of south Asian origin), in whom definitions of obesity and excess weight are tailored to reflect an increased cardiovascular risk. Specific psychological problems related to high body weight. Specific mental health issues (particularly bipolar disorders or schizophrenia).
Obesity-related conditions in which weight loss is a therapeutic priority	Chronic sleep apnoea. Polycystic ovarian syndrome. Mobility or joint problems. Established cardiovascular disease.

The increasing range of blood glucose-lowering agents

For many years, the only blood glucose-lowering agents available for treating type 2 diabetes were metformin, sulphonylureas and insulin. However, with the launches of newer agents over the past 10–15 years, there are now eight classes of glucose-lowering drugs at the healthcare professional's disposal, each with its own characteristics. While the large number of agents is undoubtedly useful from the perspective of tailoring the blood glucose-lowering strategy to the individual circumstances of the person with type 2 diabetes, it has the potential to cause uncertainty on the part of the healthcare professional in terms of when and how best to use each drug. The authors have therefore generated an at-a-glance comparison of the different drug classes in *Table 5*.

As well as efficacy, tolerability and the other factors considered in *Table 5*, it is worth noting that there is currently discussion and debate about various other facets of blood glucose-lowering therapy, such as the "durability" of action of the different agents, and furthermore whether or not they are able to influence the rate of progression of the type 2 diabetes disease process. For example, the concept of glycaemic durability was investigated in ADOPT (A Diabetes Outcomes Progression Trial; Kahn et al, 2006), in which the extent of 5-year monotherapy failure was compared for metformin, glibenclamide and rosiglitazone. In that study, monotherapy with rosiglitazone was found to have the greatest durability, and was associated with a slowing in the rate of beta-cell dysfunction.

The newer incretin-based therapies have also been associated with improvements in markers of beta-cell function (Raz et al, 2006), and, in animal experiments, increased beta-cell mass (Gedulin et al, 2005). Data regarding the possible role of the incretin-based agents in slowing the progression of type 2 diabetes are therefore awaited with interest. Related to this, a number of older antihyperglycaemic agents have already been shown to delay the progression from glucose intolerance to overt type 2 diabetes (Chiasson, 2006; Gerstein et al, 2006; Diabetes Prevention Program Research Group, 2009), and it will be interesting gauge the development of this facet of the story.

The vascular outcomes associated with each class of agent is another area of discussion. While the major relevant randomised controlled trials are cited in *Table 5*, it is worth noting that additional observational data have recently been published (Tzoulaki et al, 2009).

Conclusion

There are now a large number of agents available for treating the hyperglycaemia that characterises type 2 diabetes. The different properties of each class enable the blood glucose-lowering strategy to be tailored to the individual needs of people with type 2 diabetes to a greater extent than ever before. The current iteration of the NICE guideline on the management of type 2 diabetes provides a clear framework for person-centred care, taking into account the dual challenges of iatrogenic hypoglycaemia and weight gain, which are features of many of the older antihyperglycaemic agents. In circumstances where hypoglycaemia and weight gain are problematic, NICE provides recommendations on the use of the incretin-based drug classes. In this consensus document, the current authors have provided supplementary information and a number of tables on hypoglycaemia, weight gain and the currently available classes of antihyperglycaemic agents, which are intended to assist primary care practitioners in implementing CG87 in clinical practice. ■

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"In this consensus document, the current authors have provided supplementary information and a number of tables on hypoglycaemia, weight gain and the currently available classes of antihyperglycaemic agents, which are intended to assist primary care practitioners in implementing CG87 in clinical practice."