Insulin therapy in type 2 diabetes – update

Jill Hill

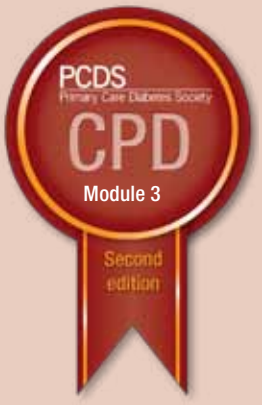
Insulin therapy is ultimately required by many people with type 2 diabetes. Unlike in type 1 diabetes, the aim of insulin therapy in people with type 2 diabetes is initially to supplement the endogenous insulin produced by pancreatic beta-cells against a background of insulin resistance. Over time, the progressive nature of type 2 diabetes necessitates the intensification of the insulin regimen. This module covers the different types of insulin and insulin regimen currently in use in the UK for people with type 2 diabetes, summarises current clinical guidance and evidence, and presents potential advances on the horizon. The article updates and replaces the previous version, published in 2009.

Type 2 diabetes is a progressive condition characterised by initial insulin resistance followed by gradual loss of beta-cell insulin secretory ability. The UKPDS (UK Prospective Diabetes Study) demonstrated that no matter how type 2 diabetes is treated, there is a progressive increase in HbA_{1c} (UKPDS Group, 1995). This means that oral antidiabetes drugs (OADs) become less effective over time, and eventually most people with type 2 diabetes need insulin to achieve or maintain their ideal HbA_{1c} level (Turner et al, 1999). The UKPDS confirmed that glycaemic control of a level nearing that of people without diabetes reduces the risk of microvascular and macrovascular complications and mortality (UKPDS Group, 1998; Holman et al, 2008), and insulin therapy will therefore be necessary to achieve this in many cases. *Box 1* provides some key facts and practical considerations relevant to insulin therapy in type 2 diabetes.

As insulin therapy is likely to be ultimately required in people with type 2 diabetes, it should be discussed early after diagnosis so that, when it is needed, it is not seen as failure of self-management or a punishment for non-adherence. In the author's experience, people may be fearful of starting insulin as a result of previous experiences of older members of the family (for example, a grandmother using glass syringes with large needles, who started insulin after amputation), a fear of needles, concern about possible hypoglycaemia and weight gain, or the perception that they now have "serious diabetes" (in contrast to "mild diabetes" controlled by diet and tablets). These concerns need to be addressed early to avoid delay in starting insulin therapy when it is needed.

Unlike in type 1 diabetes, which is characterised by a complete lack of endogenous insulin, insulin therapy in type 2 diabetes does not completely replace, but instead supplements, the insulin still being produced by

Supported by an educational grant from Boehringer Ingelheim and Eli Lilly and Company. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with *Diabetes & Primary Care*. Boehringer Ingelheim and Eli Lilly and Company had no input into the modules and are not responsible for their content.



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Learning objectives

After reading this article, the participant should be able to:

1. Explain why insulin requirements differ in type 1 and type 2 diabetes.
2. Outline the different types of insulins and explain why they are used in different ways.
3. Describe the various insulin regimens used by people with type 2 diabetes, with an appreciation of the pros and cons of each.

Key words

- Insulin
- Insulin regimens
- Hypoglycaemia
- Weight gain

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Box 1. Insulin therapy in type 2 diabetes: key facts and practical considerations.

- Offers rapid lowering of blood glucose levels and an improved lipid profile (Nathan et al, 2006).
- Typically reduces HbA_{1c} levels by 17–38 mmol/mol (1.5–3.5 percentage points; Nathan et al, 2006).
- Administered by subcutaneous injection.
- Multiple regimens of varying complexity, involving between one and four or more daily injections.
- Associated with weight gain and hypoglycaemia.
- Requires self-monitoring of blood glucose levels.

Page points

1. Insulin is the oldest of the currently available medications for glycaemic control, with the most clinical experience.
2. It has also been used in the treatment of type 2 diabetes since the 1930s.
3. It is a 51-amino acid polypeptide hormone that has an extensive and fundamental role in metabolism.

the beta-cells. How much insulin is required, and how many injections, will depend on a person's remaining endogenous insulin production capacity and the extent of the progression of the condition. Although people with type 2 diabetes still produce some insulin, compared with people with type 1 diabetes, bigger doses of exogenous insulin are often required, as obesity and insulin resistance are common.

Insulin regimens in type 2 diabetes vary from a single daily injection of insulin in combination with OADs to multiple injection regimens that may involve four or more daily injections. In contrast, in type 1 diabetes, a multiple injection regimen or insulin pump therapy is usually used to mimic the physiological insulin profile of someone without diabetes.

Insulin therapy is supported by a number of outcome studies in type 2 diabetes (Ohkubo et al, 1995; UKPDS Group, 1998) and is the only current blood glucose-lowering therapy for which there is no maximum dose or limit to efficacy (Inzucchi et al, 2012). More recent data from studies such as ACCORD (Action to Control Cardiovascular Disease in Diabetes; Gerstein et al, 2008) and the VADT (Veterans Affairs Diabetes Trial; Duckworth et al, 2009) have raised some concerns among healthcare professionals regarding the possible dangers of intensive glucose lowering in people with type 2 diabetes, and in many areas of the UK, primary care teams will be involved in the initiation and intensification of insulin therapy for people with type 2 diabetes in an effort to tighten glycaemic control.

An understanding of the different types of insulin, the various insulin regimens and whether or not OAD therapy should be adjusted is therefore important.

History

Insulin is the oldest of the currently available medications for glycaemic control, with the most clinical experience. Its discovery in 1921 at the University of Toronto, Canada, led to the award of the Nobel Prize in Physiology or Medicine in 1923 for Frederick Banting and J Macleod, who shared the prize with Charles Best and James Collip. The famous experiment to "cure" diabetes with "isletin" in Marjorie the dog (who had her pancreas removed to induce diabetes) led Collip to comment:

> *"We have obtained from the pancreas of animals a mysterious something which when injected into totally diabetic dogs completely removes all the cardinal symptoms of the disease […] If the substance works on the human, it will be a great boon to Medicine" (Bliss, 1982).*

The therapeutic use of insulin began with the treatment of a 14-year-old boy called Leonard Thompson in January 1922 (Bliss, 1982), and its role in the management of hyperglycaemia in type 1 diabetes is undisputed.

Insulin has also been used in the treatment of type 2 diabetes since the 1930s (Himsworth and Kerr, 1939). Indeed, until the 1940s, insulin was the only treatment available for both types of diabetes, at which point OADs were introduced in the form of the first generation of sulphonylureas. Metformin use followed in the late 1950s. The introduction of other OADs has meant that the role of insulin therapy in type 2 diabetes is less ubiquitous than in type 1 diabetes.

Mode of action

Insulin is a 51-amino acid polypeptide hormone that has an extensive and fundamental role in metabolism. It is secreted from pancreatic beta-cells in response to increases in blood glucose

levels arising from the ingestion of carbohydrate-containing food, and has a number of effects on glucose homeostasis. A detailed description of all its physiological effects is beyond the scope of this article, but, notably, insulin promotes the uptake of glucose by the liver, muscle and adipose tissue, and stimulates the storage of glucose as glycogen in the liver and muscle.

As insulin is inactivated by gut enzymes, it is not suitable for oral administration, and is given by subcutaneous injection in most circumstances. Since the introduction of insulin therapy in the 1920s, a number of types of insulin preparation with different pharmacodynamic properties have been developed. These are considered in more detail in the "Types of insulin" section.

Indications and licence

While the exact wording of the therapeutic indications of different insulins varies, broadly speaking, the different insulin preparations are indicated for the treatment of diabetes where insulin is required for glucose homeostasis. Some insulins, particularly the newer ones, are indicated for treatment in people above a certain age only.

Contraindications and side effects

Hypoglycaemia is a contraindication for many insulin preparations, and is also an important side effect. Although less common than in people with type 1 diabetes, it is still a problem with insulin therapy in type 2 diabetes, especially in older people, in whom the symptoms may not be recognised. Hypoglycaemia risk increases with the duration of insulin treatment (Zammitt and Frier, 2005), and in the UKPDS, at least one severe hypoglycaemic episode per year occurred in 2.3% of recipients (UKPDS Group, 1998).

Many people gain weight when starting insulin (Inzucchi et al, 2012), which is a significant issue for people with type 2 diabetes as many are already overweight. In the UKPDS, insulin therapy was associated with an average weight gain of 4 kg (UKPDS Group, 1998). This leads to increased cardiovascular risk (Russell-Jones and Khan, 2007) and can reduce adherence with treatment. A care plan and education when initiating insulin are essential to minimise the risks of weight gain and hypoglycaemia.

Other safety-related issues relevant to insulin use in type 2 diabetes that have arisen more recently are covered later in this module in their own section.

Types of insulin

Insulin preparations differ in terms of:

- **Their origin.** The amino acid sequences of animal insulins, human insulins and human insulin analogues are different. "Insulin analogues" are so called because their amino acid sequences are different from those occurring in nature, yet they retain the ability to interact with the human insulin receptor. Different techniques are also used to produce different insulin preparations. Human insulin, for example, may be generated by recombinant DNA technology using yeast or bacteria, or by enzymatic modification of porcine insulin (BMJ Group and RPS Publishing, 2012).
- **Their time–action profiles.** In prescribing resources, such as the *British National Formulary (BNF)* and *MIMS,* insulin preparations are typically categorised according to their time–action profiles. The categorisation in these resources differs slightly. For example, pre-mixed insulins aside, while the *BNF* (BMJ Group and RPS Publishing, 2012) considers short-acting and intermediate- and long-acting insulins, *MIMS* (Haymarket Medical, 2012) divides the preparations into very rapidly, short-, intermediate- and long-acting insulins. This article also categorises the different insulin preparations on the basis of their time–action profiles.

There are four manufacturers supplying insulin in the UK. Eli Lilly and Company Limited (Basingstoke), Novo Nordisk Limited (Crawley) and Sanofi (Guildford) manufacture a variety of genetically engineered human insulins and human insulin analogues. Wockhardt UK Limited (Wrexham) is now the only supplier of animal (pork and beef) insulins.

Page points

1. Insulin promotes the uptake of glucose by the liver, muscle and adipose tissue, and stimulates the storage of glucose as glycogen in the liver and muscle.
2. Hypoglycaemia is a contraindication for many insulin preparations, and is also an important side effect.
3. Many people do gain weight when starting insulin, which is a significant issue for people with type 2 diabetes as many are already overweight.
4. Insulin preparations differ in terms of their origin and their time–action profiles.
5. There are four manufacturers supplying insulin in the UK.

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Page points

1. Short- and rapid-acting insulins mimic the short burst of insulin associated with eating carbohydrate-containing meals produced by individuals without diabetes.
2. Intermediate- and long-acting insulins are also called basal insulins as their function is to provide a relatively steady supply of insulin to maintain blood glucose levels overnight and between meals, mimicking the background insulin produced by individuals without diabetes.

Short- and rapid-acting insulins

Short- and rapid-acting insulins mimic the short burst of insulin associated with eating carbohydrate-containing meals produced by individuals without diabetes. They are usually injected with meals (and are therefore known also as prandial insulins), but additionally are useful in managing hyperglycaemia during periods of illness. As the name suggests, they are relatively short acting, and are usually used in combination with an intermediate- or long-acting insulin. They can be further sub-divided into short-acting (or soluble) insulins and the more recently available rapid-acting insulin analogues.

Short-acting (soluble) insulins

Soluble insulins are clear solutions that are injected between approximately 15 and 30 minutes before meals, have a rapid onset of action (approximately 30–60 minutes), have a peak action between approximately 2 and 4 hours and can last for up to approximately 8 hours. *Figure 1* lists the soluble insulin preparations currently available in the UK.

Rapid-acting insulin analogues

Rapid-acting insulin analogues have been developed using genetic and protein engineering techniques, with the aim of changing the amino acid sequence of the human insulin molecule to reduce its tendency to self-associate (Williams and Pickup, 2004). Such changes give these preparations a faster onset of action and a shorter duration, allowing them to be injected immediately before or even after a meal, which may be more convenient for users.

There is evidence that, compared with soluble insulins, they are associated with a lower risk of hypoglycaemia (Zammitt and Frier, 2005) and can lower 2-hour postprandial blood glucose levels, lower the risk of late postprandial hypoglycaemia, and give a better quality of life through greater flexibility in timing and dosing of insulin (Rossetti et al, 2008). The currently available rapid-acting insulin analogues are listed in *Figure 1*.

Intermediate- and long-acting insulins

Intermediate- and long-acting insulins are also called basal insulins as their function is to provide a relatively steady supply of insulin to maintain blood glucose levels overnight and between meals, mimicking the background insulin produced by individuals without diabetes. Collectively, they have an onset of action within approximately 1–2 hours and a duration of between around 16 and 35 hours (BMJ Group and RPS Publishing, 2012). A number of different methods of prolonging the effect of insulin after injection have been developed over the years, including suspending human insulin with protamine or zinc and altering the amino acid sequence of human insulin.

Depending on the insulin used, they are usually given: once or twice daily; before breakfast, at bedtime or both; and often in combination with OADs or short- or rapid-acting insulins. There are a number of types of intermediate- and long-acting insulin.

NPH (isophane) insulins

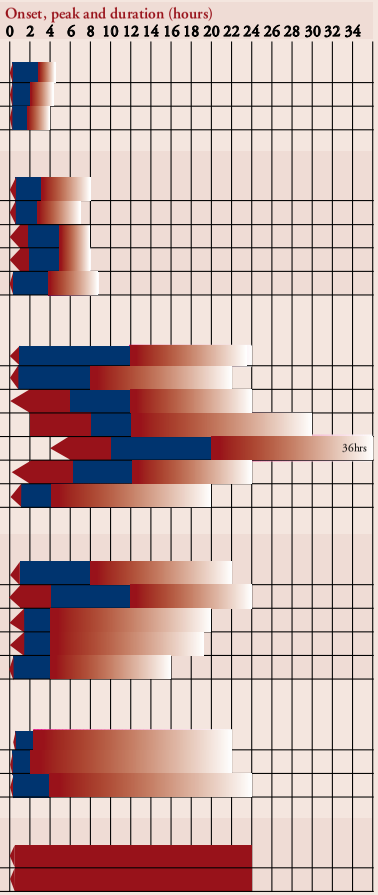
Isophane insulins are the "traditional" cloudy insulins, which comprise a suspension of insulin with protamine. They are commonly classified as intermediate-acting insulins and are also known as neutral protamine Hagedorn (NPH) insulin. NPH insulin must be re-suspended before use, it has quite a marked peak in its time–action profile and there may be large day-to-day variability in absorption after injection (Yki-Jarvinen, 2004), which, compared with long-acting insulin analogues, may result in variability in blood glucose levels and a higher risk of hypoglycaemia (Rossetti et al, 2008).

Information on the five NPH insulins available in the UK (Humulin I, Hypurin Bovine Isophane, Hypurin Porcine Isophane, Insulatard and Insuman Basal) is provided in *Figure 1*.

Long-acting insulin analogues

The long-acting insulin analogues are formed by alteration of the amino acid sequence of human insulin to give the desired prolonged

Name	Manufacturer	Source	Delivery system	Taken
RAPID-ACTING ANALOGUE				
NovoRapid	Novo Nordisk	Analogue	Vial, cartridge, prefilled device (two types)	Just before / with / just after food
Humalog	Eli Lilly and Company	Analogue	Vial, cartridge, prefilled device	Just before / with / just after food
Apidra	Sanofi	Analogue	Vial, cartridge, prefilled device	0–15 min before, or soon after a meal
SHORT-ACTING INSULINS/NEUTRAL INSULIN				
Actrapid	Novo Nordisk	Human	Vial	30 min before food
Humulin S	Eli Lilly and Company	Human	Vial, cartridge	20–45 min before food
Hypurin Bovine Neutral	Wockhardt UK	Bovine	Vial, cartridge	30 min before food
Hypurin Porcine Neutral	Wockhardt UK	Porcine	Vial, cartridge	30 min before food
Insuman Rapid	Sanofi	Human	Cartridge	15–20 min before food
MEDIUM- AND LONG-ACTING INSULINS				
Insulatard	Novo Nordisk	Human	Vial, cartridge, prefilled device	About 30 min before food or bed
Humulin I	Eli Lilly and Company	Human	Vial, cartridge, prefilled device	About 30 min before food or bed
Hypurin Bovine Isophane	Wockhardt UK	Bovine	Vial, cartridge	As advised by your healthcare team
Hypurin Bovine Lente	Wockhardt UK	Bovine	Vial	As advised by your healthcare team
Hypurin Bovine PZI	Wockhardt UK	Bovine	Vial	As advised by your healthcare team
Hypurin Porcine Isophane	Wockhardt UK	Porcine	Vial, cartridge	As advised by your healthcare team
Insuman Basal	Sanofi	Human	Vial, cartridge, prefilled device	45–60 min before food
MIXED INSULINS				
Humulin M3	Eli Lilly and Company	Human	Vial, cartridge, prefilled device	20–45 min before food
Hypurin Porcine 30/70 Mix	Wockhardt UK	Porcine	Vial, cartridge	As advised by your healthcare team
Insuman Comb 15	Sanofi	Human	Cartridge	30–60 min before food
Insuman Comb 25	Sanofi	Human	Vial, cartridge, prefilled device	30–45 min before food
Insuman Comb 50	Sanofi	Human	Cartridge	20–30 min before food
ANALOGUE MIXTURE				
Humalog Mix25	Eli Lilly and Company	Analogue	Vial, cartridge, prefilled device	Just before / with / just after food
Humalog Mix50	Eli Lilly and Company	Analogue	Cartridge, prefilled device	Just before / with / just after food
NovoMix 30	Novo Nordisk	Analogue	Cartridge, prefilled device	Just before / with / just after food
LONG-ACTING ANALOGUE				
Lantus	Sanofi	Analogue	Vial, cartridge, prefilled device	Once a day, anytime (but at same time each day)
Levemir	Novo Nordisk	Analogue	Cartridge, prefilled device (two types)	Once or twice daily



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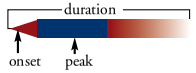

Times are approximate and may vary from person to person. This is a guide only.

Figure 1. Table of insulins available in the UK. Originally created by Diabetes UK based on information provided by insulin manufacturers. Information was correct to Diabetes UK's knowledge at the time of original publication in Spring 2009. Adapted and updated here with kind permission of Diabetes UK. Categorisation of the insulins differs slightly from that used in the main body of this article.

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Page points

1. As the name suggests, pre-mixed (biphasic) insulins are a mixture of a short-acting insulin or rapid-acting insulin analogue with a longer-acting protaminated version of the same insulin in a fixed ratio.
2. Insulin therapy in type 2 diabetes is not as straightforward as it is in type 1 diabetes and there are a variety of insulin regimens in use in clinical practice.
3. Evidence of the long-term benefits of achieving tight glycaemic control in the early stages of type 2 diabetes (the "legacy effect") may encourage early use of insulin.

duration of action. These preparations are clear and do not require re-suspension before use. HbA_{1c} attainment is similar to that achieved with NPH insulins, but long-acting insulin analogues may have some advantages in that their use can result in comparatively reduced fasting blood glucose levels with a lower risk of nocturnal hypoglycaemia and lower variability of blood glucose levels (Rossetti et al, 2008). However, they are more expensive than NPH.

There is evidence to suggest that treatment with insulin detemir is associated with slightly less weight gain than insulin glargine or NPH insulin (Haak et al, 2005; Dornhorst et al, 2007; Rosenstock et al, 2008), but otherwise use of the long-acting insulin analogues results in similar HbA_{1c} levels and risk of hypoglycaemia (Rosenstock et al, 2008).

They are often injected at bedtime but can be given first thing in the morning (Standl et al, 2006), and where required, insulin detemir can be given in two daily doses depending on the person's needs. There is some evidence that insulin glargine given in the morning may be more effective in reducing HbA_{1c} than that administered at bedtime (Fritsche et al, 2003).

Other preparations

Long-acting suspensions of animal insulins with zinc, or protamine and zinc, are also in use. Currently, two bovine preparations, Hypurin Bovine Lente and Hypurin Bovine PZI, are available in the UK (*Figure 1*).

Pre-mixed (biphasic) insulins:

As the name suggests, pre-mixed (biphasic) insulins are a mixture of a short-acting insulin or rapid-acting insulin analogue with a longer-acting protaminated version of the same insulin in a fixed ratio. The number in the brand name denotes the proportion of short-acting insulin in the mixture (*Figure 1*). These insulins are designed to provide a peak of activity to address postprandial hyperglycaemia, as well as a basal component to address hyperglycaemia between meals or overnight in a single injection.

The insulin appears cloudy and needs to be thoroughly re-suspended before each injection. They are usually given twice a day, before breakfast and before the evening meal, but can be given once or three times daily, with a meal (Kilo et al, 2003).

Mixtures containing soluble insulin should ideally be given 15–30 minutes before the meal. In contrast, pre-mixed insulins containing a rapid-acting insulin analogue can be given just before a meal and so may be more convenient to use than human mixtures (Garber et al, 2007). Pre-mixed insulin analogues are, however, more expensive than their human or animal counterparts.

The aim of insulin therapy in type 2 diabetes

The philosophy of insulin therapy for people with type 1 diabetes, who do not produce any insulin, is to mimic as closely as possible with exogenous insulin the insulin secretion pattern of someone who does not have diabetes. This includes a continuous, steady flow of insulin (basal) with rapid bursts of insulin (bolus) following carbohydrate consumption. Multiple injection regimens (one or two injections of intermediate- or long-acting insulin, and short-or rapid-acting insulin with meals) or insulin pumps are used to achieve this.

However, insulin therapy in type 2 diabetes is not as straightforward and there are a variety of insulin regimens in use in clinical practice. Adding insulin to type 2 diabetes treatment can significantly improve glycaemic control (Wright et al, 2002), but when and how to do so is the subject of considerable debate.

When to initiate insulin therapy in type 2 diabetes?

Evidence of the long-term benefits of achieving tight glycaemic control in the early stages of type 2 diabetes (the "legacy effect") may encourage early use of insulin (Holman et al, 2008). This is endorsed in the American Diabetes Association (ADA) and European Association of the Study of Diabetes (EASD) consensus guidelines, where insulin is considered as an option for second-line add-on

therapy after metformin has failed (Inzucchi et al, 2012).

However, NICE, in its revised type 2 diabetes guidelines (NICE, 2009), positioned it as a third-line treatment option for most people. Similarly, the subsequently published update on newer therapies for blood glucose lowering in type 2 diabetes positioned insulin as a third-line therapy option (NICE, 2009).

In practice, the degree of hyperglycaemic symptoms, especially unintentional weight loss, and level of HbA_{1c} will influence how quickly insulin is introduced in a person with type 2 diabetes.

Types of insulin regimen: Evidence and clinical guidance

Evidence

Table 2 describes a number of the insulin regimens currently used by people with type 2 diabetes in the UK. There still remain some gaps in the evidence directly comparing the different insulin regimens in people with type 2 diabetes. NICE has provided guidance on how to initiate insulin therapy and some direction on subsequent intensification (NICE, 2009).

The previous version of this module presented a non-exhaustive description of some of the notable trials examining insulin therapy regimens in type 2 diabetes, covering: direct comparisons of different insulin initiation regimens; direct comparisons of human insulin and insulin analogue regimens; and comparisons of titration method. The reader is directed to the previous version for those details (Hill, 2009).

Subsequent developments in research into the analogues include: publication of 3-year results for the 4T (Treating to Target in Type 2 Diabetes) study, which was conducted to directly compare the effects of different insulin analogue regimens in type 2 diabetes (Holman et al, 2009); presentation of results from the 24-month maintenance phase of DURABLE (Durability of Basal Versus Lispro Mix 75/25 Insulin Efficacy; Buse et al, 2011); and an upload onto ClinicalTrials.gov of results from the "All to Target" trial (ClinicalTrials.gov, 2011).

What does NICE recommend?

Recommendations for OADs when used in combination with insulin

It seems sensible to continue OADs that are insulin sparing (i.e. those that reduce insulin requirements) when initiating insulin therapy, and the evidence demonstrates achievement of a significantly lower HbA_{1c}, a lower injection dose requirement and less weight gain in regimens where insulin is combined with OADs compared with insulin monotherapy (Goudswaard et al, 2004), although a contrasting view as presented in a recent meta-analysis (Hemmingsen et al, 2012).

Specifically, NICE made the following recommendations for OADs in combination with insulin in its 2009 guidance on type 2 diabetes (NICE, 2009):

- When starting basal insulin therapy, continue with metformin and sulphonylureas (and acarbose, if used) but review the use of sulphonylurea if hypoglycaemia occurs.
- When starting pre-mixed insulin therapy (or basal–bolus regimens), continue with metformin and sulphonylurea initially, but discontinue the latter if hypoglycaemia occurs.
- Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to a thiazolidinedione, and in people on high-dose insulin therapy whose blood glucose is inadequately controlled.

Recommendations for insulin therapy

Box 2 provides an abbreviated version of NICE recommendations for insulin therapy in type 2 diabetes (NICE, 2009).

Regimens summary

In summary, no single regimen is the best. In practice, there is often a compromise to be struck between the achievement of HbA_{1c} targets and minimising the risk of hypoglycaemia and weight gain, and the frequency of daily injections a person is willing to accept. The chosen regimen needs to be individualised to take account of personal choice, lifestyle, job and work shifts,

Page points

1. The NICE update on newer therapies for blood glucose lowering in type 2 diabetes positioned insulin as a third-line therapy option.
2. In practice, the degree of hyperglycaemic symptoms, especially unintentional weight loss, and level of HbA_{1c} will influence how quickly insulin is introduced in a person with type 2 diabetes.
3. NICE has provided guidance on how to initiate insulin therapy and some direction on subsequent intensification.

Table 2. Comparison of some type 2 diabetes insulin regimens in use in the UK, based on clinical experience.

Insulin regimen	Advantages	Disadvantages
Basal only	Simple to use Easy to titrate May involve only one daily injection Less requirement to self-monitor blood glucose levels compared with some other regimens A once-daily regimen is useful if a district nurse or other third party is required to administer injections Often a useful starting point Lower risk of hypoglycaemia and weight gain compared with other initial regimens (Holman et al, 2009; Bretzel et al, 2008)	Unlikely to enable good glycaemic control in the long term as postprandial hyperglycaemia is not addressed, and thus intensification of the regimen will be required
Twice-daily pre-mixed	Offers postprandial coverage while being relatively simple to use Offers possibility of injecting different amounts of insulin in the day and night to achieve better glycaemic control Requires only two daily injections Can be intensified to a thrice-daily regimen if required, which for some people may be more suitable than a basal–bolus regimen	Insulin needs to be resuspended thoroughly at every injection time Requires fixed mealtimes and relatively stable carbohydrate intake
Basal-plus (intermediate- or long-acting basal insulin with a short- or rapid-acting insulin with the main meal)	Potential for only two daily injections Can vary mealtime injection to suit time of the main meal May form an interim step to a basal–bolus regimen, which may ultimately be required	Higher risk of weight gain than a basal-only regimen
Basal–bolus (intermediate- or long-acting basal insulin with short- or rapid-acting insulin with each meal)	Offers greatest flexibility with timing of meals and portion sizes Achievement of HbA_{1c} targets more likely than with other regimens	Four or more injections required daily Frequent self-monitoring of blood glucose required Not suitable for some people due to the level of motivation and understanding required to alter insulin doses in response to self-monitoring of blood glucose levels.

travel, eating habits, dependence on others for injections, age, life expectancy, visual or manual dexterity issues, the HbA_{1c} target to be achieved, complications, other comorbidities, cognitive function, weight and hypoglycaemia risk (especially in older people).

A once-daily basal insulin regimen added to OADs is a simple starting point but, with the progression of type 2 diabetes, is unlikely to be sufficient in the long term. A basal insulin regimen addresses fasting hyperglycaemia in particular, but the lower the HbA_{1c} level to be achieved, the more significant the management of postprandial hyperglycaemia becomes if the target is to be reached. For example, at an HbA_{1c} level of 56 mmol/mol (7.3%), postprandial hyperglycaemia accounts for about 70% of overall hyperglycaemia and fasting hyperglycaemia accounts for around 30%

(Monnier et al, 2003). In contrast, if HbA_{1c} is >88 mmol/mol (>10.2%), these percentages are reversed. As a result, postprandial hyperglycaemia will need to be addressed – either in the form of short-acting or biphasic insulin with one or more meals – to achieve tighter HbA_{1c} targets, and particularly over time as endogenous insulin secretion diminishes (Barnett et al, 2003).

Given that initial insulin regimens will require intensification, the author recommends that practitioners "think ahead" when insulin therapy is initiated. For example, some older people may struggle to self-care if prescribed a basal–bolus regimen, and in such cases intensifying a basal-only regimen by adding short-acting insulin at mealtimes would not be the most sensible long-term strategy. A consensus statement from 2008 offers some sensible and practical suggestions in this area (Barnett et al, 2008). *Boxes 3* and *4* provide case examples that highlight some of the practical considerations related to insulin therapy in type 2 diabetes.

Starting and adjusting insulin

Start doses

Guidance from the Royal College of Nursing (2006) on "Starting insulin treatment in adults with Type 2 diabetes" makes the following comment concerning start doses:

> *"Once-daily regimens often start with 10 units. Most twice-daily regimens start with 6–10 units twice daily, depending upon the person's build. There is no such thing as a 'correct' dose: starting low and working up will build the person's confidence and your own."*

Adjustment

In the author's view people with type 2 diabetes should ideally be encouraged to self-titrate their insulin dose to achieve target blood glucose levels without unacceptable hypoglycaemia. Indeed, the results of the ATLANTUS study demonstrated that self-titration can be more effective than titration advised by healthcare professionals (Davies et al, 2005).

People with diabetes should be encouraged to look for patterns in their blood glucose readings, and to not alter insulin doses on the basis of a single result. They should be able to identify what the problem is (i.e. readings are above or below target), when the problem is occurring (e.g. during the night) and which insulin or insulins are active when it occurs (e.g. basal or prandial). Before making an adjustment to the insulin dose, however, other potential causes should be excluded, such as

Box 2. Abbreviated NICE recommendations for insulin therapy in type 2 diabetes (NICE, 2009).

- Begin with human neutral protamine Hagedorn (NPH) insulin injected at bedtime or twice daily according to need.
- Consider, as an alternative, using a long-acting insulin analogue if:
  - ❒ The person needs assistance to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily; *or*
  - ❒ The person's lifestyle is restricted by recurrent symptomatic hypoglycaemia; *or*
  - ❒ The person would otherwise need twice-daily NPH insulin injections in combination with OADs.
  - ❒ The person cannot use the device to inject NPH insulin.
- Consider twice-daily pre-mixed human insulin (particularly if HbA_{1c} ≥75 mmol/mol [≥9.0%]). A once-daily regimen may be an option.
- Consider pre-mixed preparations that include short-acting insulin analogues, rather than pre-mixed preparations that include short-acting human insulin preparations, if:
  - ❒ Insulin injection immediately before a meal is preferred; *or*
  - ❒ Hypoglycaemia is a problem; *or*
  - ❒ Blood glucose levels rise markedly after meals.
- Consider switching to a long-acting insulin analogue from NPH insulin in people:
  - ❒ Who do not reach their target HbA_{1c} because of significant hypoglycaemia; *or*
  - ❒ Who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA_{1c} reached; *or*
  - ❒ Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made; *or*
  - ❒ Who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.
- Monitor a person on a basal insulin regimen for the need for short-acting insulin before meals (or a pre-mixed insulin preparation).
- Monitor a person who is using pre-mixed insulin once or twice daily for the need for a further injection of short-acting insulin before meals or for a change to a regimen of mealtime plus basal insulin, based on NPH insulin or long-acting insulin analogues, if blood glucose control remains inadequate.

poor injection technique, use of inappropriate injection sites, lipohypertrophy, exercise, dietary indiscretions and inaccurate blood glucose monitoring.

Blood glucose monitoring readings generally inform on the effect of the last insulin injection, and therefore it is this injection that should be adjusted. The paragraphs that follow give some simple advice, which is adapted from the Tayside Diabetes Handbook (NHS Tayside Diabetes MCN, 2009):

- **Once-daily basal regimen.** Increase or decrease the dose if pre-breakfast readings are above or below target, respectively.
- **Twice-daily pre-mixed insulin regimen.** Increase or decrease the morning dose if the pre-lunch and pre-evening meal readings are above or below target, respectively. Increase or decrease the evening dose if the pre-bedtime and pre-breakfast readings are above or below target, respectively.
- **Basal–bolus regimen.** Increase or decrease the basal insulin dose if pre-breakfast readings are above or below target, respectively. Increase or decrease the breakfast bolus dose if pre-lunch readings are above or below target, respectively. Increase or decrease the lunch bolus dose if pre-evening meal readings are above or below target, respectively. Increase or decrease the evening bolus dose if pre-bedtime readings are above or below target, respectively.

The amount by which the dose is adjusted can vary. The experience of the clinician, symptoms, concern about hypoglycaemia, the level of involvement of the person with diabetes and existence of complications are some of the factors that will determine how quickly and by how much insulin doses are adjusted.

Box 3. Case example 1.

Narrative

Mrs R is an 82-year-old white Caucasian woman who has had type 2 diabetes for 9 years. She lives alone but likes to go out regularly and also has a daughter living near by who visits her a couple of times a week. Her HbA_{1c} level has been gradually increasing over the past 2 years and is now 72 mmol/mol (8.7%). Her BMI is 26 kg/m^2 and stable. She takes metformin 1 g twice daily, gliclazide 160 mg (morning) and 80 mg (evening) and pioglitazone 45 mg daily. She checks her own blood glucose level several times a week. On questioning, Mrs R admits to feeling more tired recently and needs to get up at least twice a night to pass urine. Her daughter commented that her mum does not go out as often as she used to and is always asleep in the chair when the daughter visits.

Discussion

Mrs R has had type 2 diabetes for at least 9 years. The results of the UKPDS (UK Prospective Diabetes Study) demonstrate that the condition is progressive and eventually most people will require insulin to keep good glycaemic control. NICE guidelines for management of type 2 diabetes recommend that the target HbA_{1c} for this woman should be 58 mmol/mol (7.5%) but concerns about her age, living alone and risk of hypoglycaemia need to be taken into consideration.

She is on triple oral therapy, and maximising the dose of gliclazide is unlikely to reduce her HbA_{1c} level by the required amount. Checking her concordance with her medication is important. Her BMI is reasonable and stable, so her diet is unlikely to be the reason for her deteriorating HbA_{1c}.

Although concerns about her age and circumstances may be a reason to avoid insulin, she is symptomatic and this is affecting the quality of her life. A daily injection of a basal insulin will be relatively easy for Mrs R to administer (she is able to use a blood glucose meter), can be titrated to relieve symptoms without significantly increasing the risk of hypoglycaemia, and will be easier for a carer or district nurse to administer should Mrs R be unable to inject herself. Showing her a range of insulin devices will help to find a pen that overcomes any manual dexterity or reduced vision problems she may have.

The pioglitazone can be stopped and the gliclazide dose may also be reduced as the insulin dose is titrated.

Insulin delivery devices

Most insulins are available in a 10 mL vial for use with a syringe (especially useful if insulin is being given by someone else to reduce risk of stick injury), 3 mL cartridges for use in durable pens, or in 3 mL disposable pens. Insulin manufacturers generally produce insulin pen devices compatible with cartridges containing their own insulin, which are not interchangeable. Needles are available in a variety of lengths, from 4 mm to 12.7 mm, and should be used once only and disposed of according to local sharps policy.

Although insulin pump therapy is used in the USA for people with type 2 diabetes, this is not recommended by NICE (2008).

Care planning and education

All people starting insulin therapy should have a care plan agreed with their healthcare professional and a programme of education to enable them to build up their skills in self-management. The latter was recommended by NICE in its 2009 guidance on type 2 diabetes (NICE, 2009). Such a programme will include advice on injection technique,

suitable injection sites, disposal of needles, identification, treatment and avoidance of hypoglycaemia, management of insulin during illness, diet (weight management and carbohydrate load) and insulin adjustment to achieve target HbA_{1c} levels. Knowledge should be checked at the annual diabetes review, including inspection of injection sites for signs of lipohypertrophy.

Safety-related issues

In addition to the well-established issues of hypoglycaemia and weight gain, both of which were discussed earlier in the module, themes concerning other aspects of insulin's safety and the need to minimise errors have risen to prominence in the past few years.

"Safe Use of Insulin" e-learning module

A report by the NHS's National Patient Safety Agency (NPSA) revealed that there had been over 16 000 medication incident reports involving insulin between 1 November 2003 and 1 November 2009 (NPSA, 2010; 2011). These included errors resulting from abbreviating "units" to "u" or "iu", as well as many mistakes relating to people being given the wrong insulin owing to the names of several insulins being similar. As part of the response, an e-learning module on the safe use of insulin was released by NHS Diabetes (2010).

Insulin passports

A subsequent report from the NPSA (2011) has made it compulsory for adults with type 2 diabetes on insulin therapy to receive, by the end of August 2012, an insulin passport and a patient information booklet, in order to "help provide accurate identification of their current insulin products and provide essential information across healthcare sector." The NPSA has produced a double-sided A4 template for the insulin passport, which is designed to fold down to the size of a credit card (NPSA, 2011).

Insulin safety cards have been produced by the insulin companies and a short patient information booklet is also available on the websites for the NPSA (http://www.npsa.nhs.uk/) and NHS Diabetes (http://www.diabetes.nhs.uk/), which may be more helpful for some people with diabetes. If using these, instead of the NPSA tools, this should be recorded on the organisation's risk register to comply with the NPSA alert action.

Driving legislation

Recent changes to the Driver and Vehicle Licensing Agency (DVLA) medical standards potentially have a significant bearing on drivers with diabetes who are treated with insulin (Diabetes UK, 2012). People using insulin

Box 4. Case example 2.

Narrative

Mr D is a 58-year-old man of South Asian origin who has had type 2 diabetes for about 5 years. He started a daily basal insulin 8 months ago, initially at 10 units at bedtime and has been titrating the dose by 2 units regularly to achieve a fasting blood glucose target between 4 and 6 mmol/L. He is now injecting 68 units but his pre-breakfast readings remain stubbornly at about 7 to 9 mmol/L, his weight is increasing and he feels hungry all the time. He has tested his blood glucose before bed occasionally and found it to range from 14 to 20 mmol/L.

Discussion

Although a daily basal injection is a simple starting point when initiating insulin, and seems more acceptable to people who are reluctant to use insulin, this regimen is less likely to achieve an HbA_{1c} level of 58 mmol/mol (7.5%) than more intensive insulin regimens. The titration algorithm Mr D is using, based on regular dose increases related to fasting blood glucose levels, has been demonstrated to be an effective way for people to titrate insulin doses themselves, without requiring regular clinic visits or telephone calls (Davies et al, 2005).

However, insulin users do need to vary the timing of their blood glucose tests once the pre-breakfast readings are within target or stable. If the blood glucose level is high at another time of day (commonly before bed after the main evening meal as Mr D has found) it will impact on the fasting reading. The insulin needs to be focused on the period of hyperglycaemia. Increasing the basal insulin will increase insulin levels over the whole 24-hour period, increasing the risk of hypoglycaemia at other times, increasing hunger and causing weight gain.

Mr D has several choices:

- Reduce the amount of carbohydrate he is consuming with his evening meal (or snacks while watching the television?). Although formal carbohydrate counting is not commonly used in people with type 2 diabetes, identifying these foods and recognising that large quantities will cause hyperglycaemia is important.
- Add a short-acting insulin with his evening meal (i.e. change to a basal-plus regimen). He is likely to need a reduction in his basal insulin dose as he improves his bedtime blood glucose levels.
- Change his daily basal insulin to a pre-mixed insulin and inject this before his evening meal, to give him insulin cover for the carbohydrates consumed as well as some basal cover during the night.
- Change to a twice-daily pre-mixed insulin regimen so he can have more insulin in the evening and overnight (when he has hyperglycaemia) and a smaller dose in the morning.

CPD module

Page points

1. Recent changes to the Driver and Vehicle Licensing Agency medical standards potentially have a significant bearing on drivers with diabetes who are treated with insulin.
2. The cost-effectiveness of insulin analogues compared with human insulins has been the topic of debate in recent years.

have been advised to test their blood glucose level before driving Group 1 vehicles (cars and motorcycles). People with insulin-treated diabetes can now apply to hold a licence to drive Group 2 vehicles (large goods vehicles and passenger-carrying vehicles) as long as they meet specific safety criteria, which include:

- Monitoring blood glucose at least twice daily, and at times relevant to driving, using a meter with a memory function.
- Attending an annual examination by a diabetologist, at which they will need to have 3 months of glucose readings available for examination.
- Having good awareness of hypoglycaemia symptoms.

Any driver who has more than one episode of severe hypoglycaemia (i.e. that requiring the help of another person) in a year, even if unrelated to driving, must inform the DVLA and will lose his or her licence (Group 2 vehicle licence drivers must report any episode).

Cancer risk

A series of four studies published in *Diabetologia* in 2009 raised concerns that there might be a link between use of insulin glargine and cancer (Colhoun et al, 2009; Currie et al, 2009; Hemkens et al, 2009; Jonasson et al, 2009). However, a statement from the ADA noted that findings were "conflicting and inconclusive" and cautioned against "over-reaction until more information is available" (ADA, 2009). In a similar report, the EASD – the assocation for which *Diabetologia* is the official journal – emphasised that the studies were "far from conclusive," although noting that they did "indicate the need for further investigation" of the issue (EASD, 2009). Finally, a European Medicines Agency (2009) update observed that owing to methodological limitations the studies in question were found to be inconclusive and inconsistent, and they "did not allow a relationship between insulin glargine and cancer to be confirmed or excluded."

Subsequently, the debate has extended to include other treatments for the condition and broadened to cover further aspects of the potential association between diabetes and cancer, incuding possible biological links (Giovannucci et al, 2010).

The QIPP agenda

The cost-effectiveness of insulin analogues compared with human insulins has been the topic of debate in recent years. It has been argued that "for most people with type 2 diabetes the extra cost does not correspond to the equivalent extra benefit" (Cohen and Carter, 2010).

In line with this argument, QIPP (Quality, Innovation, Productivity and Prevention) – a transformational programme for the NHS in England aiming at improving quality of care while making up to £20 billion of efficiency savings by 2014–15 (the other UK nations are taking similar steps in response to cost constraints) – recommends that prescribing of long-acting insulin analogues in type 2 diabetes is reviewed and, where appropriate, revised "to ensure that it is in line with NICE guidance" (National Prescribing Centre, 2012). As described earlier, NICE (2009) recommends a starting regimen of NPH insulin injected at bedtime or twice daily according to need, although it acknowledges that there are circumstances in which long-acting insulin analogues are still appropriate.

Potential developments on the horizon

Advances in insulin

There are some newer insulin preparations on the horizon, with the first to market possibly being insulin degludec. This is a basal insulin that forms soluble multi-hexamer assemblies following subcutaneous injection, resulting in an ultra-long action profile (Heise et al, 2011). In addition to providing an alternative long-acting insulin for use in type 1 diabetes it has been proposed for use as a basal insulin in type 2 diabetes, with comparable glycaemic control to insulin glargine being reported, without additional adverse events, in one recent study (Zinman et al, 2011).

Delivery routes

A range of non-traditional insulin delivery routes are under investigation (Munro et al, 2011):

- The lung has a large absorptive area and offers an attractive alternative route of administration to subcutaneous injection, and inhaled insulin continues to be researched.
- Dermal absorption is another route being explored, and there are a number of insulin patch systems under development.
- Oral administration is a third delivery route being investigated, but degradation and diffusion are significant challenges to be overcome if insulin is to be delivered orally. Insulin polymers may provide a solution.
- Nasal, sublingual and buccal administration are also being explored.

Conclusion

Insulin therapy will ultimately be required by many people with type 2 diabetes. To minimise potential delay in changing the treatment regimen later, it is important that the eventual need for insulin is discussed early after diagnosis.

In type 2 diabetes insulin therapy is initially provided to supplement endogenous insulin secretion, and hence the regimen used is less intensive than that in type 1 diabetes, where insulin is used to mimic physiological insulin secretion. However, the progressive nature of the condition often necessitates intensification of the regimen. As such, there are a number of regimens in use, using the different properties of the various insulin preparations. ■

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"In type 2 diabetes, insulin therapy is initially provided to supplement endogenous insulin secretion, but the progressive nature of the condition often necessitates intensification of the regimen, taking into account the different properties of the various insulin preparations."

CPD module

Online CPD activity

Visit www.diabetesandprimarycare.co.uk/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learned in practice.

1. **Which is the single most appropriate initial aim of insulin therapy in people with type 2 diabetes? Select ONE option only.**
   A. To enhance the action of endogenous insulin.
   B. To inhibit the action of endogenous insulin.
   C. To reduce insulin resistance.
   D. To replace endogenous insulin.
   E. To supplement endogenous insulin.

2. **Which is the single most appropriate estimation of the expected long-term reduction in HbA_{1c} level after insulin therapy is initiated in people with type 2 diabetes? Select ONE option only.**
   A. 0 to 5 mmol/mol
   B. 6 to 10 mmol/mol
   C. 11 to 16 mmol/mol
   D. 17 to 38 mmol/mol
   E. 39 to 54 mmol/mol

3. **Which two reasons help best explain why, compared with people with type 1 diabetes, people with type 2 diabetes often require bigger doses of exogenous insulin? 1. Concomitant use of insulin and oral antidiabetic agents; 2. Family history of first-degree relatives with type 2 diabetes; 3. Increased hepatic metabolism; 4. Impaired absorption of insulin; 5. Insulin resistance ; 6. Obesity; 7. Rapid breakdown of insulin in the small intestine. Select ONE option only.**
   A. Options 1 and 2
   B. Options 3 and 6
   C. Options 5 and 6
   D. Options 7 and 4
   E. Options 1 and 5

4. **According to the UKPDS Group, which is the single most appropriate estimate of the number of people being treated with insulin who will suffer at least one severe hypoglycaemic episode per year? Select ONE option only.**
   A. <1%
   B. 2–3%
   C. 4–5%
   D. 6–10%
   E. >10%

5. **According to the UKPDS Group, which is the single most appropriate estimate of the average weight gain when people with type 2 diabetes are treated with insulin? Select ONE option only.**
   A. <1 kg
   B. 2 kg
   C. 4 kg
   D. 8 kg
   E. >10 kg

6. **Animal insulin in the UK can be produced from which two animal sources? Select ONE option only.**
   A. Beef and chicken
   B. Chicken and lamb
   C. Fish and beef
   D. Lamb and fish
   E. Pork and beef

7. **Which is the correct rank ordering of insulins by duration of action (shortest expected duration of action first, longest last)? Select ONE rank order only.**
   A. Actrapid, Insulatard, Humalog Mix50, Humulin S
   B. Humulin M3, Humulin I, Humulin S, Apidra
   C. Hypurin Bovine Lente, Insuman Rapid, Humalog, NovoMix 30
   D. Levemir, Actrapid, Humalog Mix25, Lantus
   E. NovoRapid, Actrapid, Insuman Comb 50, Lantus

8. **A 66-year-old woman has type 2 diabetes with poor long-term blood glucose control despite regularly taking her oral antidiabetes drugs and therefore accepts that she needs to start insulin. She has a BMI of 37 kg/m^2, chronic kidney disease stage 3 with persistent microalbuminuria and background diabetic retinopathy. Her medication is listed as follows:**
   - **Losartan: 100 mg once daily**
   - **Metformin: 1 g twice daily**
   - **Gliclazide: 160 mg twice daily**
   - **Simvastatin: 40 mg once daily**
   - **Pioglitazone: 30 mg once daily**

   Which of the following is the most appropriate insulin therapy regimen to recommend? Select ONE option only.
   A. Basal–bolus insulin plus metformin.
   B. Basal insulin plus metformin and sulphonylurea.
   C. Pre-mixed insulin plus metformin and sulphonylurea.
   D. Pre-mixed insulin plus pioglitazone.
   E. No single regimen is best.

9 **A 56-year-old man has type 2 diabetes with poor long-term control. He has been intolerant of metformin, sulphonylureas, pioglitazone and sitagliptin. His dietary habits are erratic due to the nature of his self-employed work and he feels unable to fix his mealtimes but is motivated to try insulin to improve his glycaemic control. Which of the following is the most appropriate insulin regimen to recommend long-term? Select ONE option only.**
   A. A basal insulin once daily and acarbose three times per day.
   B. A basal insulin dose once daily plus metformin once-daily.
   C. A basal insulin once daily.
   D. A basal insulin once daily plus a dose of rapid-acting insulin with each meal.
   E. A mixed insulin twice daily and a basal insulin once daily.

Please note: The usual journal style of using generic rather than brand names for medicines has not been applied in these questions to enhance readability. For a list of manufacturers of each insulin, please see *Figure 1*.

10. **A 49-year-old woman with type 2 diabetes was started on Humulin M3 twice daily 6 months ago. She has a good injection technique and eats regular meals. Her typical weekly blood sugars are shown (all readings in mmol/L). Which of the following is the most appropriate initial dose adjustment to make? Select ONE option only.**

    A. Decrease the morning dose.
    B. Increase the morning dose.
    C. Decrease the evening dose.
    D. Increase the evening dose.
    E. No adjustment needed.

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Before breakfast	10.2	13	8.9	9.4	13.1	12.4	12.2
Mid morning	6	7.1	7.3	5.7	6.3	6.8	9
Before evening meal	7.1	6.4	5.2	6.9	5.8	6.3	7.2
Before bedtime	8.8	7.2	7.3	8.6	9.9	7.7	7