Diabetes requiring insulin – recent developments in management

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Choice of insulin in the treatment of diabetes should be based on patient preference, lifestyle, blood glucose profile and risk of hypoglycaemia. Our Drug review focuses on key points and recent advances in the management of diabetes requiring insulin, followed by sources of further information and a review of the prescription data.

Diabetes is a metabolic disease characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. It is a chronic, multisystem disorder affecting 4.5 per cent of the UK population and is associated with reduced life expectancy, significant morbidity due to specific diabetes-related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease) and diminished quality of life.

Classification and diagnosis
Diabetes is broadly subdivided into type 1, type 2, gestational and other forms. Type 1 diabetes results from pancreatic beta-cell destruction leading to an absolute insulin deficiency. Type 2 diabetes results from insulin resistance in combination with a varying degree of relative insulin deficiency.

Other forms include diabetes secondary to diseases of the exocrine pancreas, endocrinopathies and inherited forms of the condition. Diabetes secondary to diseases of the exocrine pancreas, including pancreatitis, cystic fibrosis and cancer of the pancreas, almost always requires insulin therapy.

The occurrence of diabetes-specific complications (in particular the incidence and prevalence of retinopathy across a range of plasma blood glucose levels) has been used to derive diagnostic cut-off points for diabetes. Traditionally, the WHO diagnostic criteria were as follows:

- fasting plasma glucose level ≥7.0mmol per litre or two-hour plasma glucose ≥11.1mmol per litre following ingestion of a 75g oral glucose load
- in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥11.1mmol per litre
- in the absence of unequivocal hyperglycaemia or symptoms, repeat testing should be carried out four to six weeks later.

More recently, WHO has recommended incorporating HbA1c into the current diagnostic criteria. An HbA1c of 48mmol per
mol indicates diabetes. Individuals with an HbA1c of 42–47mmol per mol should be considered at high risk of progression to diabetes.3

**Current guidance on insulin use**

In all patients, insulin initiation and choice of regimen should be based on patient preference, lifestyle, blood glucose profile and risk of hypoglycaemia. Glycaemic control targets should be individualised after discussion between the patient and physician. Education and ongoing multidisciplinary team support are essential to optimise glycaemic control and outcomes.

Properties of commonly used insulin preparations in the UK are shown in Table 1.

**Insulin use in type 1 diabetes**

Insulin treatment is essential in all individuals with type 1 diabetes. NICE states that all patients with type 1 diabetes should have access to the types of insulin that they find offer them optimal well-being and highlights the importance of considering cultural preferences when choosing insulin regimens.

NICE suggests an HbA1c target of 58mmol per mol (7.5 per cent) for prevention of microvascular complications, but stricter targets – 48mmol per mol (6.5 per cent) – in those with increased risk of arterial disease.

Figure 1 summarises commonly used insulin regimens in type 1 diabetes.4

Use of continuous subcutaneous insulin infusion (CSII) is becoming more common and it is currently estimated that 7 per cent of patients with type 1 diabetes in the UK use an insulin pump. However, the UK currently lags behind other European countries where over 15 per cent receive CSII therapy.5

A Cochrane review concluded that CSII improved HbA1c by 0.3 per cent and reduced the risk of severe hypoglycaemic episodes when compared to a multiple daily injection (MDI) regimen in type 1 diabetes. They also concluded that CSII was associated with an improved quality of life and a statistically significant reduction in daily insulin requirement,6 and in clinical
practice the use of CSII in appropriately selected and educated patients is proving to be cost-effective.

Successful insulin pump therapy depends heavily upon patient motivation, robust structured education and use of carbohydrate counting to ensure accurate meal-related insulin adjustment. Carbohydrate counting is also increasingly being used to optimise glycaemic control in patients with type 1 diabetes on a basal bolus regimen.

**Insulin use in type 2 diabetes**

Insulin therapy should be considered in patients with type 2 diabetes when oral hypoglycaemic agents (OHAs) fail to achieve satisfactory glycaemic control. In most cases, an HbA₁c of 58mmol per mol (7.5 per cent) is considered to be the threshold for intensification of treatment. Education is an integral part of the management of type 2 diabetes, and the need for lifestyle change to be optimised must be reiterated at the point at which insulin is initiated.

A pathway for insulin use in type 2 diabetes based on current national and international guidance is shown in Figure 2. NPH (neutral protamine Hagedorn) insulin is recommended as first-line basal insulin in type 2 diabetes due to its cost effectiveness and is often commenced in addition to existing OHAs in the first instance. Use of NPH insulin has become more user friendly in recent years due to improvement in available delivery devices.
In the majority of cases, adding a basal insulin to existing oral agents is the most convenient strategy, but when the \( \text{HbA}_1c \) is greater than 75mmol per mol (9 per cent) a twice-daily pre-mixed insulin could be considered.

NICE does not support the use of CSII therapy in type 2 diabetes.\(^7\)

**Recent evidence for insulin use in diabetes during pregnancy**

Newer insulin analogues have limited evidence in pregnancy. Insulin detemir (Levemir) was shown to be safe in pregnancy in a group of women with type 1 diabetes in a recent study. It also showed a lower fasting plasma glucose and \( \text{HbA}_1c \) level compared to NPH insulin with no increase in the incidence of hypoglycaemia.\(^10\)

A Cochrane review on the use of CSII treatment in diabetes during pregnancy that included women with pre-existing type 1 or 2 diabetes and gestational diabetes failed to show a benefit compared to MDI. There was no difference in the incidence of macrosomia, the need for operative delivery, perinatal mortality or the incidence of fetal anomalies between the two groups. The birth weight was marginally higher in the CSII group but this was not thought to be clinically significant.\(^11\)

A more recent study found that in a group of women with type 1 diabetes, CSII use improved \( \text{HbA}_1c \) and was associated with a reduction in insulin requirement. However, there was no difference in perinatal outcomes.\(^12\)

**New treatments and emerging trends**

**Intensive insulin treatment in newly diagnosed type 2 diabetes**

Over and above the benefits of appropriate, intensive control of type 2 diabetes using insulin therapy following treatment failure with oral agents, as demonstrated in various treat-to-target studies, there is emerging evidence that early intensive treatment with insulin in newly diagnosed patients improves beta-cell function by reducing visceral adipose tissue and brings about sustained euglycaemia.\(^13,14\)

**Insulin degludec**

Insulin degludec (Tresiba) is the latest basal insulin to become available in the UK. It has advantages over existing basal insulin.

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**Figure 1.** Insulin use in type 1 diabetes in adults in accordance with NICE guidance
analogue including a very long half-life of 25 hours and lower risk of hypoglycaemia. Initial trials have shown it to be as efficacious as insulin glargine (Lantus) in HbA1c reduction with a 25 per cent reduction in nocturnal hypoglycaemia in both type 1 and type 2 diabetes when used in a basal bolus regimen. When used as a basal insulin in type 2 diabetes, nocturnal hypoglycaemia rates were reduced by 36 per cent.

Insulin degludec allows for a greater degree of flexibility as the clinical effect of day-to-day variation of the timing of insulin injection is minimal due to the very long half-life. It is the first long-acting insulin analogue to be available as a premixed formulation with a short-acting insulin analogue.\(^{15}\)

One trial demonstrated that it could be successfully used three times a week in patients with type 2 diabetes in combination with metformin, and it was shown to achieve similar HbA1c reduction when compared to once-daily insulin glargine.\(^{16}\)

**Inhaled insulin**

An inhaled insulin (Exubera) was first marketed in 2006 for use in patients with both type 1 and type 2 diabetes. This was withdrawn in 2007 with pharmaceutical company Pfizer citing poor sales.\(^{17}\) However, interest in alternative delivery systems continues and other inhaled insulin therapies are in development. In early 2011, the US Food and Drug Administration (FDA) declined to approve Afrezza, an ultra rapid-acting mealtime insulin that is inhaled through a small inhalation device. The FDA requested additional clinical trials to investigate efficacy of its next-generation inhaler and up-to-date safety information.\(^{18}\)

Inhaled insulin is thought to be equally effective, but not superior to, injected short-acting insulin. However, this therapy is expensive and a systematic review concluded that it is unlikely to be cost effective.\(^{19}\)

**Combination of insulin and GLP-1 agonists**

Liraglutide (Victoza) and exenatide are glucagon-like peptide-1 (GLP-1) agonists used in the treatment of type 2 diabetes and were previously licensed only for use with OHAs. Despite this, the combination of insulin and GLP-1 therapy has been widely used in clinical practice.

The European Medicines Agency (EMA) approved the addition of insulin detemir to liraglutide in 2011. It has also
recently granted marketing authorisation to exenatide as an adjunctive therapy to basal insulin, with or without metformin and/or pioglitazone, for type 2 diabetes treatment in adults who have failed to achieve adequate glycaemic control with these agents alone.

GLP-1 agonists stimulate insulin production and secretion, suppress glucagon secretion, enhance satiety and delay gastric emptying. It is hypothesised that in insulin-treated patients, due to their mode of action, GLP-1 agonists would reduce calorie intake, cause less pronounced postprandial blood glucose increase and possibly also reduce the need for exogenous insulin.

This has been demonstrated in a small number of prospective trials. Addition of exenatide in patients with type 2 diabetes treated with insulin glargine resulted in an HbA1c reduction of 0.69 per cent, an average weight difference of 2.7 kg favouring

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**Figure 2. A pathway for insulin initiation and intensification in type 2 diabetes**

<table>
<thead>
<tr>
<th>Patient with type 2 diabetes on 3 oral hypoglycaemics and glycaemic target not met (usually HbA1c &gt;7.5) or markedly hyperglycaemic on 2 agents</th>
</tr>
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<tbody>
<tr>
<td>Consider if HbA1c &gt;75mmol/mol (9%)</td>
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<table>
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<tr>
<th>Commence basal insulin* (0.1–0.2 units/kg/day)</th>
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<tbody>
<tr>
<td>Uptitrate dose by 5–10% once or twice weekly until preprandial targets** are met</td>
</tr>
<tr>
<td>Check HbA1c after 3 months</td>
</tr>
<tr>
<td>If HbA1c within target continue with current regimen</td>
</tr>
<tr>
<td>If HbA1c remains above target</td>
</tr>
<tr>
<td>Add prandial insulin for the meal with largest glucose excursion</td>
</tr>
<tr>
<td>If HbA1c targets not met, consider sequentially adding prandial insulin with all meals (basal bolus regimen)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Commence premix insulin twice/day (0.1–0.2 units/kg/day)</th>
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</thead>
<tbody>
<tr>
<td>Uptitrate dose 5-10% once or twice weekly until preprandial targets** are met</td>
</tr>
<tr>
<td>Check HbA1c after 3 months</td>
</tr>
<tr>
<td>If HbA1c within target continue with current regimen</td>
</tr>
<tr>
<td>If HbA1c remains above target</td>
</tr>
<tr>
<td>Consider conversion to basal bolus regimen</td>
</tr>
</tbody>
</table>

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*NICE recommends use of NPH insulin as first-line basal insulin in type 2 diabetes consider long-acting insulin analogue if:
- recurrent hypoglycaemic episodes
- requiring twice-daily NPH insulin
- a carer is needed to administer insulin and frequency could be reduced to once daily with insulin analogues

**suggested preprandial targets: capillary blood glucose 4–6mmol/l; however, targets should be individualised
exenatide, and a slight reduction in insulin requirement. In this study, 60 per cent of the exenatide group achieved a target HbA1c of 7 per cent compared to only 35 per cent of the control group.

The Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit showed that a third of all patients on GLP-1 agonists were on insulin as well. Although exenatide was less effective in lowering HbA1c among insulin-treated patients, a significant number of these insulin-treated patients still achieved significant reductions in HbA1c weight and insulin doses.

There is extremely limited evidence for the use of GLP-1 agonists along with insulin in long-standing type 1 diabetes and this is currently not licensed. One small trial of 11 patients on CSII treatment showed a weight loss of 4.2 per cent and a reduction in insulin requirement of 19.2 per cent when liraglutide was added. HbA1c improved by 0.7 per cent with no significant increase in hypoglycaemia.

**Combination of insulin and DPP-4 inhibitors**

Dipeptidylpeptidase-4 (DPP-4) inhibitors inhibit the degradation of the incretins, GLP-1 and glucose-dependent insulinotropic peptide (GIP). Available preparations include sitagliptin (Januvia), vildaglaptin (Galvus), saxagliptin (Onglyza) and linagliptin (Trajenta). Studies have demonstrated an HbA1c reduction following the addition of DPP-4 inhibitors to insulin therapy in type 2 diabetes with no increase in weight or incidence of hypoglycaemia.

**Combination of insulin and dapagliflozin**

Dapagliflozin (Forxega) is a highly selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that reduces renal glucose reabsorption, increases renal glucose excretion and reduces hyperglycaemia in a dose-dependent manner. When added to existing insulin therapy, studies have demonstrated an HbA1c reduction and significant and sustained weight loss. Use of dapagliflozin was also found to reduce the need for insulin dose escalation. Side-effects of treatment include increased rates of urinary and genital tract infections that may limit its use. The EMA approved the use of dapagliflozin in April 2012.

**Conclusion**

Diabetes is a complex multisystem condition requiring multidisciplinary team input. Treatment options depend on the classification of diabetes, patient lifestyle and choice. Clinical guidelines are available to aid therapy decisions with the aim of optimising glycaemic control and minimising diabetic complications.

Insulin is currently only available for administration in injectable form, but other delivery devices are in development. Newer, longer-acting basal insulins could improve flexibility in insulin regimens and reduce incidence of hypoglycaemia.

Diabetes is a condition that is predominantly self-managed by patients and/or their carers on a day-to-day basis. Therefore, to be successful, both existing and newer agents need to be easy to administer and have an acceptable side-effect profile, as well demonstrating improvement in glycaemic control and cost-effectiveness.

**References**


**Declaration of interests**

Dr Bennett: none to declare; Dr Joseph has received honoraria from Novo Nordisk, Eli Lilly, Sanofi Aventis, Boehringer Ingelheim and MSD, and his department has received research grants from Sanofi Aventis and Eli Lilly.

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**Prescription review**

In 2012, GPs in England wrote 4.3 million prescriptions for intermediate and long-acting insulins at a total cost of £229 million – almost the same as the previous year.

Since 2007 there has been a 10 per cent increase in prescribing volume for this category of insulins overall, though prescribing of biphasic isophane insulin had declined by about half up to 2011. Trends in costs mirrored the changes in prescribing, increasing spending by 11 per cent over the five-year period.

The newer insulins dominated prescribing. Insulin glargine accounted for 31 per cent of all scrips and 34 per cent of costs, followed by biphasic insulin aspart (25 and 24 per cent) and insulin detemir (16 and 18 per cent), though only 8 per cent of scrips and spending was on insulin lispro. The older isophane insulin (9 and 6 per cent) and biphasic isophane insulin (11 and 9 per cent) accounted for most of the remainder.

![Figure 3. Usage of intermediate- and long-acting insulins in general practice in England by quarter, 2007–12](image1)

![Figure 4. Cost of intermediate- and long-acting insulins prescribed in general practice in England by quarter, 2007–12](image2)
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Resources

Groups and organisations
Primary Care Diabetes Society. Tel: 020 7627 1510; website: www.pcdsociety.org. Promotes diabetes care within general practice.

Diabetes UK, 10 Parkway, London NW1 7AA. Tel: 020 7424 1000; website: www.diabetes.org.uk. A charity for people with diabetes providing useful links for both patients and healthcare professionals in the UK.

Guidelines


CPD: Treatment with insulin

Answer these questions online at Prescriber.co.uk and receive a certificate of completion for your CPD portfolio. Utilise the Learning into Practice form to record how your learning has contributed to your professional development.

1. Which one of these questions about the diagnosis and classification of diabetes is false?
   a. Diabetes secondary to diseases of the exocrine pancreas, including pancreatitis, cystic fibrosis and cancer of the pancreas, almost always requires insulin therapy.
   b. In a person suspected of having diabetes, an HbA1c ≥48mmol per mol (6.5 per cent) indicates diabetes.
   c. One of the WHO diagnostic thresholds for diabetes is a two-hour plasma glucose ≥7.0mmol per litre after a 75g oral glucose load.
   d. Individuals with an HbA1c of 42–47mmol per mol should be considered at high risk of progression to diabetes.

2. Which one of these statements is false?
   a. The duration of action of insulin aspart is three to five hours.
   b. Humulin 1 is an isophane insulin.
   c. Insulin glargine and insulin detemir both have a duration of action of approximately 24 hours.
   d. Analogue premixed insulins have a duration of action of 8–10 hours.

3. One of the following is not among the factors that should be considered for insulin initiation and choice of regimen – which is it?
   a. duration of symptoms
   b. lifestyle
   c. blood glucose profile
   d. risk of hypoglycaemia

4. One of these statements is false – which one?
   a. Glycaemic control targets should be individualised after discussion between the patient and physician.
   b. NICE states that all patients with type 1 diabetes should have access to the types of insulin that they find offer them optimal well-being.
   c. NICE suggests an HbA1c target of 58mmol per mol (7.5 per cent) for patients at increased risk of arterial disease.
   d. Cultural preferences are important when considering the choice of an insulin.

5. Which one of these statements is false?
   a. Successful insulin pump therapy depends on patient motivation, robust structured education and use of carbohydrate counting.
   b. In most patients with type 2 diabetes, an HbA1c of 75mmol per mol (9.0 per cent) is considered to be the threshold for intensification of treatment by starting insulin.
   c. NPH insulin is recommended as first-line basal insulin in type 2 diabetes due to its cost effectiveness.
   d. A Cochrane review failed to show a benefit with insulin pump therapy compared with multiple daily injections in the treatment of diabetes during pregnancy in women with type 1 or 2 diabetes and gestational diabetes.

6. One of these statements is false – which is it?
   a. Insulin degludec is associated with a lower risk of hypoglycaemia than older analogue basal insulins.
   b. Adding exenatide to treatment with insulin reduces insulin requirement slightly.
   c. The Association of British Clinical Diabetologists nationwide exenatide audit showed that a third of all patients on GLP-1 agonists were on insulin as well.
   d. Adding a DPP-4 inhibitor to treatment with insulin improves glycaemic control but causes weight gain.