Management of type 1 and type 2 diabetes requiring insulin

DOROTHY ABIOLA, THOZHUKAT SATHYAPALAN, DAVID HEPBURN

Insulin is a required therapy for people with type 1 diabetes, and its use in the treatment of type 2 diabetes has been increasing in recent years. This article discusses the main types of insulin currently available, their properties and their role in the management of both type 1 and type 2 diabetes.

### Table 1. Diagnostic criteria for diabetes mellitus, based on the WHO's 2006 Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia and 2011 Use of Glycated Haemoglobin in the Diagnosis of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Symptomatic (ie polyuria, polydipsia, unexplained weight loss)</th>
<th>Asymptomatic</th>
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<tbody>
<tr>
<td>• Single fasting plasma glucose ≥7mmol/L</td>
<td>• A fasting plasma glucose ≥7mmol/L on two separate occasions OR</td>
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<tr>
<td>• Single random plasma glucose ≥11.1mmol/L</td>
<td>• A random plasma glucose ≥11.1mmol/L on two separate occasions OR</td>
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<td></td>
<td>• An HbA1c ≥48mmol/mol (6.5%) on two separate occasions OR</td>
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<td></td>
<td>• An HbA1c ≥48mmol/mol AND a single elevated plasma glucose (fasting ≥7mmol/L or random ≥11.1mmol/L)</td>
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**Note:**

- HbA1c cannot be used for type 1 diabetes diagnosis
- An HbA1c <48mmol/mol does not exclude type 2 diabetes

Diabetes mellitus is a common chronic condition characterised by absolute or relative insulin deficiency, and its prevalence is increasing across the Western world and developing countries. This is particularly true of type 2 diabetes mellitus (T2DM) and UK data from the Quality and Outcomes Framework (QOF), published in 2015, showed there to be almost 3.5 million people in the UK with a diagnosis of diabetes. Diabetes costs the NHS close to £10 billion annually, with the majority of this cost going towards the treatment of diabetes-related complications. Furthermore, it is suspected that there are at least 590,000 people in the UK with undiagnosed T2DM.

This review discusses the role of insulin therapy in type 1 diabetes mellitus (T1DM) and T2DM in the UK, including current guidelines and management options. Table 1 shows the current recommendations from the WHO for the diagnosis of diabetes mellitus.

**Type 1 diabetes mellitus**

T1DM makes up approximately 10 per cent of all cases of diabetes mellitus and reduces life expectancy by up to 13 years. T1DM can occur at any age, but is usually diagnosed in children and adolescents and its incidence has been rising steadily in developed countries since the 1950s. It is
General aims of management

The principal aim of diabetes management is to restore blood glucose to normal and thus reduce the incidence and progression of diabetes complications. Inadequately controlled blood glucose levels can cause both macrovascular and microvascular damage, and subsequently lead to nephropathy, retinopathy, neuropathy and cardiovascular diseases, all of which impact profoundly on patients’ mortality, morbidity and quality of life. Therefore, healthcare professionals aim to help people with diabetes to reach and maintain blood glucose control without increasing the incidence of hypoglycaemia, which is the greatest risk of insulin therapy.

Insulin therapy in T1DM

Treatment with insulin remains essential for the management of T1DM (see Figure 1) via either subcutaneous injections or continuous subcutaneous insulin infusion (CSII) using a pump worn 24 hours per day. The aim of exogenous insulin is to mimic as closely as possible the insulin profile of a person without diabetes; however, the main barrier to achieving optimal blood glucose control remains the risk of hypoglycaemia. The principal methods for assessing blood glucose control are measurement of glycated haemoglobin (HbA1c) and self-monitoring of capillary blood glucose (SMBG).

In the NICE guideline, updated in August 2015, the target HbA1c for people with T1DM is ≤48mmol/mol (normal range <42mmol/mol), alongside individualisation of the target based on patients’ daily activities, lifestyle, co-morbidities and likelihood of developing complications, but without causing problematic hypoglycaemia.

There are three broad types of pharmaceutically produced insulin preparations available:

- Animal insulins: extracted and purified from cows (bovine) or pigs (porcine) and now used by very few patients with diabetes
- Human insulin: genetically engineered with an identical amino acid sequence to endogenous human insulin
- Insulin analogues: genetically engineered insulins with a similar but modified amino acid sequence to endogenous human insulin and may be synthetically modified.

Insulins can also be grouped by their onset and duration of action, as categorised in the BNF:

- Short-acting
- Intermediate and long-acting.

**Short-acting insulins**

Short-acting insulins are used principally to control the rise in blood glucose that occurs following ingestion of carbohydrate, usually in a meal, and can be subdivided into soluble short-acting (human insulins) and rapid-acting (analogues of human insulin).

Human and animal insulins given by subcutaneous injection have an onset of action of about 30 minutes with a peak of action of between two and four hours and a duration of around

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**Table 2. Diagnosis of type 1 diabetes (in accordance with updated NICE guideline on type 1 diabetes in adults, published August 2015)**

- **On clinical grounds:**
  - ketosis
  - rapid weight loss
  - BMI <25kg/m²
  - age of onset <50 years
  - personal or family history of autoimmune disease (new recommendation)

- **Nevertheless, type 1 diabetes should not be ruled out in people >50 years and with a BMI >25kg/m² (new recommendation)**

- **Anyone of any age or any BMI who presents with polyuria and polydipsia, especially those with weight loss and nausea, should have their random glucose and blood/urinary ketones checked. Ketonuria or ketonaemia should raise suspicion of type 1 diabetes**

- **Diabetic ketoacidosis (ketonaemia ≥3mmol/L or 2+ ketonuria on test strip; venous bicarbonate <15mmol/L or venous pH <7.3; or a combination of them both) is a medical emergency**

- **Lesser degrees of ketosis with hyperglycaemia (>11mmol/L) will probably also require urgent administration of insulin**

- **Consider further investigation, eg measurement of C-peptide or diabetes-specific autoantibodies or both, if patient has atypical features ie age >50 years, BMI>25kg/m², slow evolution of hyperglycaemia and if there is a degree of uncertainty about what type of diabetes the patient has (new recommendation)**
T1DM be advised to inject their bolus dose of rapid-acting insulin aspart (NovoRapid) 10–15 minutes before their meal to ensure the best match between the action profile of the insulin and the postprandial rise in blood glucose. The dose of rapid-acting insulin is usually determined by the carbohydrate content of the meal using a method called carbohydrate counting, with a common dose being 1 unit of insulin for each 10 grams of ingested carbohydrate. Thus most people with T1DM using a basal-bolus regimen will take the rapid-acting insulin analogue three times daily with main meals and possibly at other times when there is any substantial ingestion of carbohydrate; the so-called bolus part of the basal-bolus regimen.

Rapid-acting insulin analogues available in the UK are:
- insulin aspart (NovoRapid)
- insulin glulisine (Apidra)
- insulin lispro (Humalog).

Intermediate and long-acting insulin
People with T1DM usually take either an intermediate or long-acting insulin in addition to their mealtime doses of rapid-acting insulin analogues, the so-called basal part of the basal-bolus regimen. These insulins are administered in an attempt to mimic the background secretion of insulin from the pancreas in the interprandial or fasting period. In the 2015 NICE guideline on T1DM in adults, it is recommended that insulin detemir (Levemir) is used twice daily as the basal insulin of first choice alongside a rapid-acting insulin analogue. Insulin detemir is an analogue insulin in which a fatty acid moiety has been bound to the lysine molecule at the B29 amino acid position resulting in it binding to albumin after injection. This results in a prolonged duration of action and a relatively flat action profile without much of a peak. Insulin glargine (Lantus), another long-acting insulin analogue, can be used as an alternative but is usually administered once daily due to its longer duration of action compared with insulin detemir.

Long-acting insulin analogues are now preferred over the intermediate-acting isophane insulins because their mode of action is more predictable. Compared with isophane insulins, long-acting insulin analogues provide marginally better blood glucose control with less potential weight gain. However, the most important factor is the achievement of optimal blood glucose control without problematic hypoglycaemia and thus NICE permits the use of other basal insulins if the person with T1DM can achieve these blood glucose goals, including the use of insulin detemir once daily.

In the updated NICE guideline for adults with T1DM, it is emphatically recommended that those newly diagnosed with T1DM should not be offered non-basal–bolus insulin regimens, e.g. twice daily mixed, basal only or bolus only. However not all people with T1DM can cope with a multiple daily injection regimen and thus may take a mixed human insulin. An example is Humulin M3, which is a mixture of soluble short-acting human insulin and an intermediate-acting human isophane insulin. Mixed human insulins are usually given twice daily, before breakfast and the evening meal. If hypoglycaemia becomes a problem then an alternative mixed insulin preparation incorporating a rapid-acting insulin analogue, such as NovoMix 30, can be used. These mixed insulins can be useful in allowing insulin to be given by district nurses to frail or elderly patients or to people with cognitive decline who also have T1DM.

People with T1DM should regularly self-monitor their capillary blood glucose and it is recommended that they do this at least four times a day, in order to permit adjustment of their insulin doses and to avoid hypoglycaemia. In some scenarios, more regular monitoring is needed and they can self-monitor up to 10 times a day if necessary. For example when:
- at increased risk of hypoglycaemia
- about to drive, as advised by DVLA fitness to drive regulations
- they have not reached their target HbA1c
- experiencing periods of illness
- planning to become pregnant or are already pregnant
- before and after exercise.
It is important that patients who need to monitor more frequently are identified by their GP and diabetes specialist so that they can be prescribed an adequate number of testing strips for their blood glucose meter. Many patients report anecdotally that they are not prescribed enough blood glucose testing strips to match their monitoring needs. A number of self-monitoring blood glucose meters can also be used to measure capillary blood ketones and these strips should also be prescribed.

NICE has also placed emphasis on structured education programmes for people with T1DM. Dose Adjustment for Normal Eating (DAFNE) is a programme that should be offered to every patient with T1DM, 6 to 12 months after initial diagnosis. This programme is led by specialist diabetes nurses and dieticians, and occurs over five days, during which patients are extensively educated in:

- carbohydrate counting
- accurate calculation of bolus insulin doses
- how to set up background (basal) insulin
- how to correct deranged glucose levels (including sick day rules).

An economic report by the York Health Economics Consortium has suggested that DAFNE could potentially save about £2237 per patient over a 10-year period, as a result of a reduction in diabetes complications, after deducting the cost to run the programme.

People with T1DM who do not achieve optimal glycaemic control as determined by an HbA1c level >69mmol/mol on a multiple daily injection (basal-bolus) regimen can also be

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**Figure 1. Insulin regimens for adults with type 1 diabetes**

<table>
<thead>
<tr>
<th>Continuous subcutaneous insulin infusion</th>
<th>Mixed insulin</th>
<th>Basal-bolus regimen (first-line)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended in individuals ≥12 years when:</td>
<td>• Human mixed insulin twice daily should only be given if basal-bolus regimen is not possible</td>
<td>Long-acting insulin (twice daily) plus rapid-acting insulin (before each meal)</td>
</tr>
<tr>
<td>• Attempts to achieve target HbA1c with multiple daily injections (MDI) result in the person experiencing disabling hypoglycaemia</td>
<td>• Try a mixed analogue if human insulin leads to hypoglycaemia that affects the patient’s quality of life</td>
<td></td>
</tr>
<tr>
<td>• HbA1c has remained high on MDI therapy &gt;69mmol/mol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Must be initiated by a trained specialist team and should only be continued if it results in a sustained improvement</td>
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- **Insulin regimen options for adults with type 1 diabetes**

- **Continuous subcutaneous insulin infusion**
  - Recommended in individuals ≥12 years when:
    - Attempts to achieve target HbA1c with multiple daily injections (MDI) result in the person experiencing disabling hypoglycaemia
    - HbA1c has remained high on MDI therapy >69mmol/mol
  - Must be initiated by a trained specialist team and should only be continued if it results in a sustained improvement

- **Mixed insulin**
  - Human mixed insulin twice daily should only be given if basal-bolus regimen is not possible
  - Try a mixed analogue if human insulin leads to hypoglycaemia that affects the patient’s quality of life

- **Basal-bolus regimen (first-line)**
  - Long-acting insulin (twice daily) plus rapid-acting insulin (before each meal)

- **Long-acting insulin**
  - First-line: insulin detemir twice daily
  - Consider an alternative when:
    - A person is achieving their agreed targets using an existing insulin regimen
    - Twice-daily detemir is not tolerated; instead offer once-daily insulin glargine or detemir
    - Detemir is not tolerated; offer once-daily insulin glargine

- **Rapid-acting insulin**
  - Offer rapid-acting insulin analogues before meals, ie
    - Insulin aspart (NovoRapid)
    - Insulin lispro (Humalog)
    - Insulin glulisine (Apidra)
  - If an adult with type 1 diabetes has a strong preference for alternative mealtime insulin, respect their wishes and offer the preferred insulin
referred to a specialist diabetes team for consideration of continuous subcutaneous insulin infusion therapy (CSII) provided by an insulin pump.6 This type of treatment can also be considered if target HbA1c levels cannot be achieved without the person suffering disabling hypoglycaemia. Generally, a rapid-acting insulin analogue is used in the CSII pump. It is usual for patients to have been DAFNE trained before commencing a CSII regimen6 and for them to be seen in a specialist ‘pump clinic’ with access to continuous subcutaneous glucose monitoring facilities. NICE states that CSII therapy should only be offered to adults and children 12 years and older, although there is increasing use of CSII in younger children attending paediatric diabetes clinics and it is widely used in younger children throughout Europe. NICE also advises that CSII should only be continued if the therapy leads to a sustained improvement in glycaemic control, shown by a fall in HbA1c or a sustained drop in the number of hypoglycaemic episodes.18

**Insulin therapy in adolescence**

It is well documented that many adolescents with T1DM often struggle to comply with their insulin regimens, increasing the risk of diabetic ketoacidosis.19 It is important that clinicians explore the reasons why patients in this age group are not complying, eg fear of isolation from friends, weight loss, inconvenience when socialising, and ultimately remind the patient why it is important to comply. In a case where the patient is not complying, it may be necessary to readress their insulin regimen and adjust to a more feasible option for the patient. These problems can be compounded by physiological insulin resistance, which is a feature of the adolescent period, meaning that adolescents often need higher doses of insulin during this time to maintain adequate glycaemic control.19 In an attempt to support people with T1DM during this difficult period in their lives, many diabetes services have set up transition clinics to facilitate the move from paediatric to adult diabetes services. Additionally, most transition or young adult diabetes clinics are supported by clinical psychology services in a similar fashion to paediatric clinics.

**Insulin therapy in pregnancy**

Pregnancy is also a challenging time for women with T1DM and there are often changes in insulin sensitivity during the different trimesters of pregnancy. Hypoglycaemia is most common in the early phase of pregnancy, often compounded

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**Table: Management of type 2 diabetes with insulin**

<table>
<thead>
<tr>
<th>For basal dose, offer isophane insulin for injection at bedtime or twice daily</th>
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<tbody>
<tr>
<td>Consider long-acting analogue (insulin detemir) if:</td>
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<tr>
<td>• The person needs assistance from a carer or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily</td>
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<tr>
<td>• The person’s lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes</td>
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<tr>
<td>• The person would otherwise need twice-daily isophane insulin injections in combination with oral glucose-lowering drugs</td>
</tr>
<tr>
<td>• The person cannot use the device to inject isophane insulin</td>
</tr>
<tr>
<td>Consider starting insulin therapy in type 2 diabetes patients who:</td>
</tr>
<tr>
<td>• Have not achieved a controlled HbA1c using three oral hypoglycaemic drugs</td>
</tr>
<tr>
<td>When starting insulin, continue with standard-release metformin if there are no contraindications or intolerance</td>
</tr>
<tr>
<td>Consider premixed preparations that include rapid-acting insulin analogues, rather than premixed preparations that include short-acting human insulin, if:</td>
</tr>
<tr>
<td>• A person prefers injecting insulin immediately before a meal</td>
</tr>
<tr>
<td>• Hypoglycaemia is a problem</td>
</tr>
<tr>
<td>• Blood glucose levels rise markedly after meals</td>
</tr>
<tr>
<td>Consider twice-daily premixed (biphasic) human insulin, particularly if:</td>
</tr>
<tr>
<td>• HbA1c is 75mmol/mol (9.0%) or higher</td>
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<tr>
<td>A once-daily regimen may also be an option</td>
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**Figure 2. Management of type 2 diabetes with insulin**
by the maintenance of excellent blood glucose control, which had been started before conception in most patients. In planned pregnancies, there is an emphasis on preconception counselling and optimisation of blood glucose control in an attempt to reduce the risk of congenital malformations. This emphasis on excellent control should persist during the pregnancy to prevent macrosomia and early placental failure as much as possible, which can occur in some diabetes pregnancies.

**Insulin therapy in T2DM**

Insulin therapy is not the first-line treatment for T2DM and usually follows on from failure of standard oral agents or other injectable therapies (see Figure 2). Due to the progressive nature of T2DM, characterised by beta cell dysfunction and impairment, over time most patients with T2DM fail to reach their individualised HbA1c targets. Thus many people with T2DM need to include insulin in their treatment to maintain glucose control and slow down the progression of diabetes complications.20

A number of studies have supported the initiation of insulin in patients with T2DM early in the course of the disease.20 The UK Prospective Diabetes Study (UKPDS) in 2008 suggested that early insulin treatment in T2DM reduces the risk of macrovascular and microvascular complications.21 However, insulin therapy in people with T2DM also carries some risks, not least hypoglycaemia, as well as weight gain, which is often seen as a major disadvantage by patients.20 A recent retrospective cohort study22 controversially reported that the use of insulin therapy in T2DM was associated with an increased mortality rate in comparison with patients who were just on oral hypoglycaemic agents. However, this was not a randomised controlled trial and was likely to have been influenced by the fact that patients with poorer blood glucose control are treated with insulin. Therefore, the association in this study between insulin therapy and mortality is unlikely to be causal.

There has been an increase in the addition of insulin to T2DM management over the last 20 years.22 However, the correct point at which to commence insulin therapy in T2DM and where it stands in relation to newer hypoglycaemic therapies such as glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors, such as canagliflozin, has been controversial.22 The most recent NICE guideline for management of T2DM in adults, published in December 2015, recommends initiating insulin either at the point of failure of two oral agents (HbA1c >58mmol/mol) or alternatively adding a third oral agent instead of insulin.23 Insulin therapy combined with a GLP-1 agonist is recommended to be used only on the advice of diabetes specialists.

When initiating insulin therapy in T2DM, the patient should remain on metformin23 unless there is a contraindication or intolerance to the metformin. A recently published retrospective cohort study in people with T2DM has suggested an association between using insulin plus metformin and reduced risk of death and major cardiovascular outcomes compared with those treated with insulin alone.24

Patients with T2DM should be commenced initially on an isophane insulin23 once daily, injected before bedtime, or twice daily, before breakfast and then either at evening mealtime or at bedtime. If given at bedtime, this helps to avoid a peak of action at around 2am to 3am, so reducing the risk of nocturnal hypoglycaemia and instead providing a peak at dawn when insulin resistance is at its greatest.25 The main advantage of using isophane insulins over long-acting insulin analogues is the fact that they are less expensive. NICE only suggests the use of long-acting insulin analogues such as insulin detemir and insulin glargine should hypoglycaemia prove a problem with isophane insulins. Another scenario is when once-daily administration is needed, for example facilitating a district nurse to administer insulin glargine in the morning to a housebound patient who is unable to inject their own insulin.

The recently updated NICE guideline on T2DM in adults also recommends considering the use of premixed biphasic human insulin twice daily if HbA1c is >75mmol/mol,23 eg Humulin M3, although in our experience it is much easier to provide instructions for patients to self-adjust once- or twice-daily intermediate or long-acting insulin than a premixed biphasic insulin. If the patient will be injecting immediately before a meal and hypoglycaemia is a problem, or if the patient is markedly hyperglycaemic in the preprandial period, then the premixed preparations for these patients should include short-acting insulin analogues rather than short-acting human preparations,23 eg Novo Mix 30.

**Insulin and driving**

Hypoglycaemia may be less frequent in people with insulin-treated T2DM than in those with T1DM, but it remains the most common adverse effect of insulin therapy, and is particularly worrying in people who have impaired hypoglycaemia awareness. To be able to drive a car or motorcycle (Group 1), people treated with insulin must notify the DVLA and meet the following criteria:

- Have adequate awareness of hypoglycaemia
- Have had no more than one episode of severe hypoglycaemia in the preceding 12 months
- Undertake appropriate blood glucose monitoring (test blood glucose no more than two hours before the start of a journey and every two hours while driving)
- Not be regarded as a likely risk to the public while driving
- Meet the visual standards for acuity and visual fields.

For insulin-treated people to be able to drive a bus or lorry (Group 2), the DVLA stipulates that they must:

- Have full awareness of hypoglycaemia
- Have not had any severe hypoglycaemia in the preceding 12 months
- Undertake appropriate blood glucose monitoring (test blood glucose at least twice daily including on days when not driving, test blood glucose no more than two hours before the start of a journey and every two hours while driving)
- Use a glucose meter with sufficient memory to store three months of readings
• Be able to demonstrate an understanding of the risks of hypoglycaemia
• Have no disqualifying complications of diabetes.

The DVLA advises people who are insulin treated to take fast-acting carbohydrate before driving if their blood glucose is less than 5mmol/L and not to drive if their blood glucose is less than 4mmol/L; in this case they should take fast-acting carbohydrate, wait and then retest before driving. If hypoglycaemia occurs, they should not drive until 45 minutes after their blood glucose has returned to normal as subtle cognitive impairment can persist for a short period after blood glucose returns to within the normal range and the person feels better. Further details can be found on www.gov.uk in the document Assessing Fitness to Drive – A Guide for Medical Professionals.

New developments

New longer acting insulin analogue formulations are being developed in the hope of further reducing the chances of nocturnal hypoglycaemia. Insulin degludec (Tresiba), which has recently been licensed by the European Medicines Agency, has a metabolic effect that is still present 42 hours postinjection. Insulin degludec is also available at a higher strength (200units/ml) than the European-wide standard of 100units/ml, which could be an advantage in the more insulin-resistant T2DM patient. When prescribing insulin degludec, it is important to be aware of the strength prescribed as the 100units/ml prefilled pen allows one-unit dose adjustments, whereas the 200units/ml prefilled pen allows two-unit dose adjustments. The use of prefilled pens has reduced the risk of dosing errors but it is important that the patient using the pen is aware of the strength and the value of the dose adjustment. The number of units being injected, irrespective of the strength used, is provided in a dose counter window on the pen every time the patient dials up a dose.

Some diabetologists have been using insulin degludec 200units/ml in very insulin-resistant diabetes patients in place of unlicensed Humulmin R 500units/ml, which needs to be obtained on a named-patient basis.

Insulin glargine is also now available in a higher strength of 300units/ml in the form of Toujeo and it is also available in a prefilled pen. Insulin degludec and Toujeo are not specifically mentioned in the 2015 NICE guideline on T2DM in adults, although there is a comment about the use of any current or future biosimilar product(s) of insulin glargine within the same marketing authorisation and indication, and this could be interpreted to permit the use of Toujeo. It will also sanction the use of the first truly biosimilar insulin to be launched in the UK, Abasaglar, a biosimilar version of insulin glargine. Biosimilars are the equivalent of generic drugs, but for biological molecules, and could potentially reduce the cost of medication.

Toujeo has been assessed by the Scottish Medicines Consortium, which has recommended that its use should be targeted to patients with T1DM who are at risk of, or experience, frequent or severe night-time hypoglycaemia. It can also be considered an option as a once-daily therapy for patients who require carer administration of their insulin, and in T2DM patients who suffer from recurrent episodes of hypoglycaemia or need assistance with their insulin injections.

Another development that was not included in the NICE guideline on T2DM for adults is Xultophy, which is a combination of liraglutide (a GLP-1 agonist) with insulin degludec in a fixed-dose combination, delivered by prefilled pen device. Many diabetologists have been using combined therapy with GLP-1 agonists and usually long-acting insulins with success in obtaining improved blood glucose control without the weight gain seen with insulin therapy alone. However, as GLP-1 agonists are also administered by subcutaneous injection, this requires at least two injections a day and the advent of Xultophy, which is administered as a single injection once daily, should make dosing easier for patients and aid adherence.

Moreover, this may not be the only benefit and recent clinical trials have supported the use of a fixed-dose combination of a GLP-1 agonist and a long-acting insulin in achieving better glycaemic control than either component given alone. More importantly, top-line results presented at the American Diabetes Association meeting in June 2016 showed that liraglutide significantly reduced the risk of major adverse cardiovascular events compared with placebo but in addition to standard treatment for diabetes. Other GLP-1 agonist-insulin combinations are also in development and their exact position in the management of T2DM is yet to be fully determined, but they could be used either at the point of oral agent failure or as the next step in intensification in people already using either a GLP-1 or a long-acting insulin alone.

References
12. McCall AL, Farhy LS. Treating type 1 diabetes: from strategies...
Opioid analgesia hard to tolerate and not effective for chronic low back pain

Clinical question:
Is opioid analgesic treatment effective in patients with low back pain?

Reference:

Bottom line:
Effective pain control in patients with low back pain (LBP) is still elusive. Approximately half of all patients with LBP who take an opioid analgesic will stop treatment because of ineffectiveness or adverse effects. Patients staying the course will experience, on average, a small decrease in pain relative to patients who take placebo and will not have improved function. (LOE = 1a)

Study design: Meta-analysis (RCT).
Funding source: Government.
Setting: Various (meta-analysis).

Synopsis:
To identify randomised controlled trials that enrolled patients with non-specific LBP and evaluated an opioid analgesic, the researchers searched five databases including Cochrane CENTRAL, as well as reference lists of identified studies. They retrieved 20 studies with an enrolment of 7295 patients; all but one study enrolled patients with chronic LBP. The length of studies was 12 weeks or less. Based on 13 studies with moderate-quality evidence, opioids reduced pain in the short term, though the mean difference in pain scores was minimal (mean difference: 10.1 on a scale of 0–100). This effect size is similar to that for NSAIDs versus placebo for LBP in a prior Cochrane review. Overall, opioid treatment did not produce clinically important pain relief compared with placebo, ie a mean difference in pain scores of at least 20, even with doses as high as 240 mg morphine daily. Half of the studies had more than 50 per cent of the enrolled patients drop out, either because of adverse effects or lack of effectiveness.