The aim of type 2 diabetes treatment is to maintain a patient’s HbA1c level below 6.5%. To ensure there is a range of treatment options, NICE has updated its guidance to include newer medicines

**Type 2 diabetes management**

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In May 2009, the National Institute for Health and Clinical Excellence published new guidance on the management of type 2 diabetes. The guidance offered a blueprint for when, and to which patients, newer antidiabetic medicines (eg, incretin mimetics, thiazolidinediones) should be offered. The Scottish Intercollegiate Guideline Network published guidelines on the management of diabetes in 2001 but these do not offer detailed recommendations for type 2 diabetes treatment or on glycaemic control and are not recent enough to include some of the newer medicines.

This article summarises the available pharmacological treatments for people with type 2 diabetes, in the context of the recent NICE recommendations (although insulin treatment is not discussed in great detail).

**Lifestyle advice**

After being diagnosed with type 2 diabetes, patients should first be offered lifestyle advice — such as information on healthy eating and physical activity. This should incorporate recommendations to:

- Include high-fibre, low-glycaemic-index sources of carbohydrate (eg, beans, wholegrain breads)
- Include low-fat dairy products and oily fish
- Limit intake of foods containing saturated fats and trans fatty acids (eg, butter, cheese)

The aims are to help the patient achieve and maintain a HbA1c target of <6.5% (<48mmol/mol; see Box 1, p480) and, if he or she is overweight, lose 5–10% of body weight. Each patient should be offered therapy (lifestyle and medicines) to help achieve and maintain the HbA1c target level.

**Metformin**

Metformin is generally considered the gold standard treatment for type 2 diabetes. It has several pharmacological actions, which include:

- Reducing hepatic glucose production
- Inhibiting intestinal absorption of glucose
- Increasing glucose utilisation by enhancing the action of insulin at peripheral receptors
- Increasing glucose uptake by muscles

Because metformin has no effect on insulin release it is unlikely to cause hypoglycaemia. The starting dose of metformin is usually 500mg daily, which is increased to a usual maximum of 1g twice a day (or 850mg three times a day). The dose is often limited by gastrointestinal side effects, such as diarrhoea, although these are often overcome by titrating the dose up slowly or switching to a modified-release formulation.

Advantages of metformin over other oral antidiabetic medicines include: it does not cause weight gain; and there is strong evidence to confirm that it reduces the risk of myocardial infarction and death among diabetic patients.

According to NICE, metformin should be used as first-line treatment for patients with type 2 diabetes who are overweight. For those who are not overweight, or for whom the use of metformin is contraindicated, a sulphonylurea should be considered as an alternative.

**SUMMARY**

Patients diagnosed with type 2 diabetes should first be offered healthy lifestyle advice, with the aim of maintaining a HbA1c target of under 6.5% (48mmol/mol). Treatment with oral hypoglycaemic medicines (for example, metformin, sulphonylureas) is usually the next option. The choice of medicine will depend on the characteristics of the individual patient.

If the HbA1c remains above 7.5% (59mmol/mol) despite treatment with metformin and a sulphonylurea, the patient should be offered insulin.

Third-line alternatives include thiazolidinediones and the newer dipeptidylpeptidase-4 inhibitors and incretin mimetics (restricted to certain patient groups).
Renal failure Metformin is excreted renally; therefore, pharmacists should review the kidney function of all patients for whom it is prescribed. Metformin should be stopped if a patient’s estimated glomerular filtration rate falls below 30ml/min/1.73m² or if the patient experiences a sudden deterioration in kidney function.

Sulphonylureas
Sulphonylureas augment the body’s residual insulin function by enhancing the release of insulin from pancreatic islet beta cells and increasing tissue sensitivity to insulin. Sulphonylureas might also increase the number of insulin receptors on cells. It is common for sulphonylureas to cause hypoglycaemia.

When choosing a sulphonylurea the duration of action should be taken into account. A short-acting sulphonylurea (eg, gliclazide) is an appropriate choice, particularly if the patient is elderly or has compromised kidney function, since both of these groups are at increased risk of developing hypoglycaemia. All patients who start sulphonylurea treatment should be counselled on the risk of hypoglycaemia and its management (see Box 2). They need to be able to recognise a “hypo” and treat it quickly and effectively.

Sulphonylureas can cause weight gain. This is a particular issue for patients with type 2 diabetes, most of whom are already overweight. According to NICE, sulphonylureas can be considered first-line for patients who are not overweight. Otherwise, they can be added to metformin if a patient’s HbA₁c fails to drop below 6.5% (48mmol/mol) after proactive dose titration of metformin monotherapy. NICE recommends selecting a sulphonylurea with a low cost, although the use of glibenclamide is not recommended because of its long duration of action and hence increased risk of hypoglycaemia.

Meglitinides
Also known as insulin secretagogues or postprandial regulators, meglitinides (eg, repaglinide, nateglinide) have a pharmacologically distinct mechanism of action from that of the sulphonylureas.

They stimulate insulin release by, in the presence of glucose, closing the K⁺-ATP channels found on the surface of pancreatic beta cells. This enables a postprandial glycaemic response so, to work effectively, the medicines must be taken less than 30 minutes before eating a meal. They are particularly useful for people with erratic lifestyles who do not eat regularly because they allow patients to omit a dose if they miss a meal.

NICE recommends that meglitinides are used in place of sulphonylureas for such patients.

Acarbose
Alpha glucosidase inhibitor acarbose works by preventing the breakdown of carbohydrate in the gastrointestinal tract. This delays the digestion and absorption of glucose and therefore reduces postprandial blood glucose levels.

Acarbose is rarely used because of its limited effect on reducing HbA₁c and its unpleasant gastrointestinal side effects (eg, diarrhoea, abdominal pain, bloating). NICE
recommends that acarbose be considered as an option for patients with type 2 diabetes who are unable to use other oral treatments.

Those prescribed acarbose must be made aware that the drug interferes with the absorption of sucrose (and other polysaccharide sugars). Therefore, patients at risk of hypoglycaemia (eg, those also prescribed sulphonylureas or insulin) should use glucose, not sucrose, to treat a hypo.

Insulin

In patients whose HbA1c remains above 7.5% (59mmol/mol) despite being treated with metformin and a sulphonylurea, NICE recommends adding insulin.

The institute advises starting treatment with a human isophane (NPH) insulin, administered at bedtime or twice daily. Alternatively, a once-daily long-acting insulin analogue (eg, insulin detemir or glargine) can be considered for patients:

- Who require assistance with injecting insulin
- Whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia
- Who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic medicines
- Who cannot use the device needed to inject isophane insulin

In practice, if the decision to start insulin is made it is usual to start once-daily insulin injections and continue metformin at the same dose while reducing the dose of sulphonylurea. Intensifying insulin regimens is beyond the scope of this article.

If insulin use is not appropriate (eg, because of the patient’s employment, social, recreational or other personal circumstances, or because he or she is obese), other treatments (below) can be considered for use instead.

Thiazolidinediones

The thiazolidinediones rosiglitazone and pioglitazone are agonists of a nuclear receptor called PPAR-gamma (peroxisomal proliferator activated receptor gamma). They enhance the action of insulin on liver, fat and skeletal muscle cells by:

- Increasing tissue sensitivity to insulin
- Slowing gastric emptying
- Suppressing glucagon secretion
- Stimulating glucose-dependent insulin secretion
- Reducing hepatic glucose production
- Decreasing insulin resistance
- Increasing glucose uptake into muscle cells

It should be noted that thiazolidinediones have no effect on insulin secretion and if used as monotherapy could be less likely to cause hypoglycaemia.

Safety concerns

There is consistent evidence that rosiglitazone and pioglitazone can cause weight gain and fluid retention, which can lead to new or worsening heart failure that can be fatal. There is also evidence that rosiglitazone might increase the risk of cardiac ischaemia, particularly when used with insulin, and that pioglitazone and rosiglitazone might increase patients’ risk of fracture.4

According to the Medicines and Healthcare products Regulatory Agency, neither pioglitazone nor rosiglitazone should be prescribed for patients with a history of heart failure or who are at increased risk of fractures. In addition, rosiglitazone should be used with caution for patients with previous or current ischaemic heart disease.

Place in therapy

According to NICE, these medicines should be used third-line, behind lifestyle modifications and metformin/sulphonylurea monotherapy. Therefore, if glycaemic control is inadequate, thiazolidinediones could be added to:

- Metformin (if treatment with a sulphonylurea is unsuitable)
- A sulphonylurea (if treatment with metformin is unsuitable)
- Metformin and a sulphonylurea (if insulin is unsuitable)

Treatment should only be continued if HbA1c reduces by more than 0.5 percentage points over six months of treatment. The benefits and risks of thiazolidinediones should be discussed with patients before these medicines are prescribed.

Newer treatments

Incretins such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are proteins secreted by intestinal endocrine cells in response to intake of nutrients. They influence glucose homeostasis by:

- Stimulating glucose-dependent insulin secretion
- Suppressing glucagon secretion
- Slowing gastric emptying
- Increasing tissue sensitivity to insulin

It was noted in 1986 that people with type 2 diabetes have diminished secretion of GLP-1.5 If used
therapeutically, GLP-1 would need to be administered intravenously to prevent its rapid degradation by an enzyme called dipeptidylpeptidase-4 (DPP-4). Intravenous administration is not suitable for treating chronic conditions like diabetes.

Knowledge of the role of incretins in diabetic patients led to the development of incretin enhancers (ie, DPP-4 inhibitors sitagliptin, vildagliptin, saxagliptin) and incretin mimetics (exenatide, liraglutide). These treatments have been shown to improve glycaemic control in type 2 diabetes.

DPP-4 inhibitors The first DPP-4 inhibitor to be licensed in the UK was sitagliptin, followed by vildagliptin and, more recently, saxagliptin. DPP-4 inhibitors are generally well tolerated, have a low risk of causing hypoglycaemia and are weight neutral. They are all licensed for use as dual therapy with metformin, a sulphonylurea or a thiazolidinedione. Sitagliptin is also licensed as monotherapy and as triple therapy with metformin and a sulphonylurea/thiazolidinedione.

Incretin mimetics In 2006, exenatide became the first incretin mimetic to be licensed in the UK to treat type 2 diabetes. Liraglutide was launched in the UK in 2009 (Clinical Pharmacist 2009;1:301). Both medicines are administered by subcutaneous injection.

Exenatide Exenatide is injected twice daily up to 60 minutes before breakfast and the evening meal. It works by mimicking the action of GLP-1 and is licensed for use with metformin and/or a sulphonylurea. In some specialist diabetes centres, it is also being used out of licence with insulin.

One of the main side effects of exenatide is nausea, which has been reported by 40–50% of patients. Most episodes of nausea are mild to moderate in severity and dose-dependent, and tend to decrease in frequency and severity over time.

A major advantage for exenatide is that it causes weight loss — an effect seen irrespective of the occurrence of nausea. According to the manufacturer, the reduction is dose-dependent, and tend to decrease in frequency and severity over time.

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Liraglutide Unlike exenatide, liraglutide is injected subcutaneously once a day. It has a similar licence to exenatide but, in addition, can be used in combination with metformin and a thiazolidinedione.

In an open-label trial published earlier this year, type 2 diabetic patients treated with liraglutide achieved better glycaemic control than those treated with exenatide. Weight loss was similar for the two treatments.

Place in therapy According to NICE, exenatide can be added to metformin and a sulphonylurea as a third-line treatment option (ie, as an alternative to insulin, thiazolidinediones or DPP-4 inhibitors) for patients who satisfy the following criteria:

- They have a body mass index ≥35kg/m², are of European descent (adjustments to this BMI threshold should be made for ethnic groups at greater risk of cardiovascular disease) and have medical problems associated with high body weight.
- They have a BMI <35kg/m² but are not able to take insulin (ie, for occupational reasons) or have comorbidities that would benefit from weight loss.

The NICE guideline states that exenatide should only be continued in patients who experience at least a 1 percentage point reduction in HbA1C, and who lose at least 3% of their initial body weight after six months. The guideline does not mention liraglutide because the medicine was not available at the time of publication. NICE is expected to publish a single technology appraisal for liraglutide in 2010. In the meantime, the institute’s guidance for exenatide is likely to be applied to the use of liraglutide.

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According to NICE, exenatide can be added to metformin and a sulphonylurea as a third-line treatment option.

References

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