

New NICE guidelines for type II diabetes treatment

Guidelines on the drug treatment of patients with type II diabetes were published last month by NICE. They clarify the place of the newer anti-hyperglycaemic drugs and expand the indications for insulin analogues. Natasha Jacques summarises the key changes.

New guidelines on the management of type II diabetes mellitus were published last month by the National Institute for Health and Clinical Excellence, replacing guidance issued last year. The new guidelines clarify the place of the recently licensed anti-hyperglycaemic drugs (the dipeptidyl peptidase-4 [DPP-4] inhibitors and exenatide) in therapy. Many diabetes teams have been waiting for these guidelines, to help formulary development.

The new guidelines form a relatively extensive document, but changes only relate to the section on blood glucose-lowering therapy.

DPP-4 inhibitors

The new guidelines state that the DPP-4 inhibitors sitagliptin (Januvia; MSD) and vildagliptin (Galvus; Novartis) should be considered at the third stage of the blood glucose algorithm. At this stage a patient would have tried lifestyle changes and would be taking, or would have tried, metformin and a sulphonylurea (see Figure 1, p168). The new guideline recommends that a DPP-4 inhibitor or a thiazolidinedione (e.g. pioglitazone or rosiglitazone) should be substituted for the

sulphonylurea if there is a significant risk of hypoglycaemia (or its consequences) or if a sulphonylurea is contraindicated or not tolerated.

DPP-4 inhibitors or a thiazolidinedione (TZD) have also been added earlier on in treatment (i.e. at the second stage) for patients in whom metformin is contraindicated or was not tolerated.

Examples of oral anti-diabetes drug regimens following the new guidelines (and subject to the fulfilling the above criteria) would therefore be:

- Metformin *plus* a sulphonylurea *or* DPP-4 inhibitor *or* TZD
- Sulphonylurea *plus* a DPP-4 inhibitor *or* TZD

At the next stage of the algorithm, if the HbA1c level remains high or has deteriorated to $\geq 7.5\%$ despite the above combinations of oral diabetes drugs, the previous guidelines recommended adding insulin or a TZD. The new guidelines recommend adding in sitagliptin or a TZD if insulin is unacceptable (because of employment, social, recreational or other personal issues, or obesity). It is important to note that this stage of the guideline only

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refers to sitagliptin and not to all DPP-4 inhibitors, since sitagliptin is the only DPP-4 inhibitor currently licensed for triple oral therapy.

Exenatide

Recommendations for the use of the incretin mimetic exenatide (Byetta; Lilly) are simplified in the new guidelines. Exenatide is now recommended as an addition to metformin and a sulphonylurea as a third line option in patients:

- With a BMI $\geq 35\text{kg/m}^2$ (if of European descent; adjustments required for other ethnic groups) and problems associated with being overweight
- With a BMI $< 35\text{kg/m}^2$ in whom insulin is unacceptable because of occupational implications, or in whom weight loss would benefit other co-morbidities

Additional restrictions are now placed on the continuation of treatment with exenatide. It should only be continued

At a glance...

The key changes to the NICE guidelines on the management of type II diabetes are:

- Inclusion of DPP-4 inhibitors as an alternative or additional oral hypoglycaemic drug as second or third line therapy
- Recommendations that DPP-4 inhibitors or thiazolidinediones should only be continued if there is a reduction in HbA1c of $\geq 0.5\%$ after six months
- A recommendation that exenatide should only be continued if body weight is reduced by $\geq 3\%$ after six months and HbA1c is reduced by $\geq 1\%$.
- Expansion of the indications to switch to an analogue insulin from a NPH human insulin
- The inclusion of insulin detemir as an option for a long-acting insulin analogue

if the patient has a reduction in HbA1c of $\geq 1\%$ (as in prior guidance) plus $\geq 3\%$ weight loss at six months (the previous guideline required a weight loss of $\geq 5\%$ after one year for continuation of the drug). This part of the guideline could be considered controversial, see Box 1 (below) for an example.

At this stage a patient could therefore be on any of the following regimens (subject to fulfilling the above criteria):

- Insulin *plus* metformin *plus* a sulphonylurea
- Metformin *plus* a sulphonylurea *plus* sitagliptin or a TZD
- Metformin *plus* a sulphonylurea *plus* exenatide

Starting and stopping therapy

Before starting TZD or DPP-4 inhibitor therapy, the new guidelines recommend that the benefits and risks of both therapies are discussed with the patient. A TZD might be preferable to a DPP-4 inhibitor if a person has marked insulin insensitivity, has had a previous poor response with or is intolerant to DPP-4 inhibitor therapy, or if a DPP-4 inhibitor is contraindicated. Similarly, a DPP-4 inhibitor might be preferable to a TZD if further weight gain would cause significant problems, the person has had a poor response to or is intolerant of TZDs, or a TZD is contraindicated.

The previous guidelines did not make any recommendation on stopping TZDs, apart from warning that pioglitazone (when added to insulin) should be discontinued if clinically significant fluid

A patient with diabetes and a BMI $>35\text{kg/m}^2$ has been initiated on exenatide. After six months he has lost 2% of his body weight and his HbA1c has fallen by 1.1% to a level of 7.3%. Following the new NICE guidelines, exenatide should now be stopped because the patient has not achieved a weight loss of 3%. However, a response of this magnitude, particularly in terms of the reduction in HbA1c and accompanied weight loss would be considered to be a successful result by many diabetologists.

Box 1: An example of a case in which the new guidelines may cause controversy

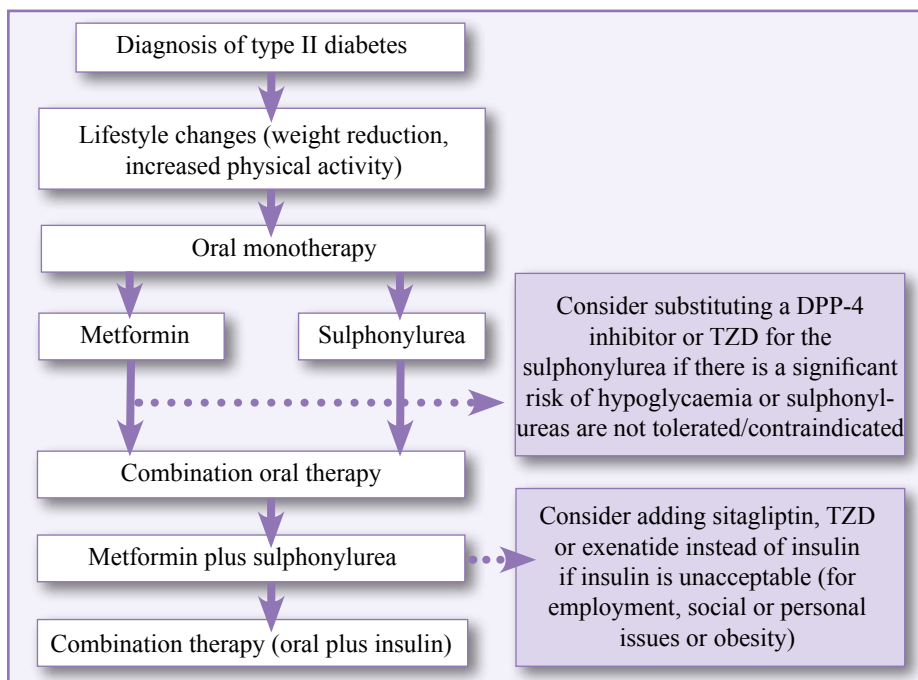


Figure 1: A type II diabetes treatment algorithm showing the place of newer treatments

retention occurs. The new guidelines recommend continuing TZD therapy or DPP-4 therapy only if there is a reduction of in HbA1c $\geq 0.5\%$ after six months.

Insulin recommendations

Insulin initiation The main change to the recommendations for insulin therapy is the advice about the initiation of analogue insulins (insulin glargine and insulin detemir). Insulin detemir (Levemir; Novo Nordisk) is newly included in this guidance. The guideline continues its recommendation that a patient should be switched from human NPH insulin to a long-acting analogue if their lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or if they would otherwise need twice daily basal insulin injections plus oral glucose-lowering drugs. It adds that the switch should be made if the person needs help with injecting insulin, if a long-acting insulin analogue would reduce injections from twice to once daily, or if the person cannot use the device to inject NPH insulin.

The new guidelines add that pre-mixed insulin analogues (including short-acting insulin analogues) rather than pre-mixed human insulin preparations, can be considered if immediate injection before a meal is preferred, hypoglycaemia is a problem, or a patient's blood glucose levels rise markedly after meals.

Insulin switching Another new recommendation is that NPH insulin should be switched to a long-acting insulin analogue if the person:

- Does not reach their target HbA1c level because of hypoglycaemia
 - Has significant hypoglycaemia with NPH insulin irrespective of their HbA1c level
 - Cannot use the delivery device for NPH insulin but could administer a long acting analogue
- Or
- Needs help to inject insulin and a long-acting analogue could reduce the number of injections.

Summary

The new NICE guidelines have made a good attempt to place the new anti-hyperglycaemic therapies into the glucose treatment algorithm. This will help with the development of local formularies and protocols to reflect not only when these drugs should be included, but also when they should be stopped.

In terms of insulin initiation and switching to analogue insulins, the new guidelines reflect current practice more closely than the previous guidelines.

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