Suboptimal control on metformin and sulfonylurea: what next?

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The epidemic of type 2 diabetes (T2D) is a major global health and economic burden. The number of people with diabetes is predicted to rise by more than 50 per cent in the next decade. The increasing incidence of T2D is largely attributable to changes in lifestyle and levels of obesity.

It is well established that the maintenance of good glycaemic control has been shown to reduce the risk of microvascular complications; the effect on macrovascular complications is less certain and is the subject of ongoing research.

T2D is a progressive disease, with insulin resistance thought to be the fundamental underlying metabolic abnormality. In the initial phase of the disease beta cells secrete higher than normal amounts of insulin in an attempt to maintain euglycaemia. Over time the number of beta cells and insulin secretory capacity decline, necessitating the use of further pharmacological therapies to maintain glycaemic control.

Most international guidelines, including NICE, place lifestyle-directed interventions along with metformin as first-line therapy in suitable patients. Sulfonylureas may be considered as an alternative first-line agent in some clinical scenarios.

If the HbA1c remains above the individualised target for the patient, a second oral agent should be added. This has traditionally been a sulfonylurea. Alternatively in situations where there is significant risk of hypoglycaemia or if a sulfonylurea is contraindicated or not tolerated, a thiazolidinedione (pioglitazone) is used. The use of thiazolidinediones has been declining with the withdrawal of rosiglitazone over cardiovascular concerns, and with pioglitazone being associated with bladder cancer, heart failure and insufficiency fractures.

With the emergence of novel therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogues, more treatment options for the individualisation of diabetes treatment prior to the use of subcutaneous insulin are now available.

This article will address the place of these therapies in the...
management of patients with T2D who remain over HbA1c target despite ‘standard’ first- and second-line treatment with metformin and a sulfonylurea.

The new agents

GLP-1 analogues

GLP-1 is an endogenous intestinal hormone whose secretion is dependent on the presence of nutrients in the small intestine. GLP-1 increases insulin and decreases glucagon secretion from the pancreas, inhibits gastric emptying and increases satiety in normal physiology. As its actions are dependent on the presence of glucose in the intestine it avoids causing hypoglycaemia during fasting periods.

The currently available GLP-1 analogues are exenatide and liraglutide (Victoza). These are structurally similar to endogenous GLP-1 and activate GLP-1 receptors in several organs. Exenatide is available as a twice-daily (Byetta) or once-weekly (Bydureon) preparation. Liraglutide is given once daily. Both may require some initial dose titration. They reduce HbA1c by approximately 0.5–1.5 per cent on average.

There are no head-to-head studies between exenatide and liraglutide comparing efficacy on glycaemic control or weight. Key similarities and differences are listed in Table 1.

The effect on weight loss is approximately 2–4kg, although the response does show significant interindividual variability. The lack of hypoglycaemia is also a major advantage.

However they are injectable drugs, and this in itself has negative connotations for some patients. The once-weekly exenatide preparation uses a bulkier and more complicated delivery device that can cause minor skin reactions.

Most common side-effects are gastrointestinal disturbances, particularly nausea. There may be an association with increased risk of pancreatitis, although this has not been proven.

DPP-4 inhibitors

DPP-4 inhibitors are oral compounds that competitively inhibit the enzyme DPP-4. This enzyme breaks down the incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP). Thus there is an increase in the secretion of insulin and suppression of the release of glucagon by the pancreas.

This is glucose dependent, so this class of drugs does not cause hypoglycaemia. They are weight neutral and are generally well tolerated. Typically they reduce HbA1c levels by 0.5–0.8 per cent. There are no head-to-head trials

<table>
<thead>
<tr>
<th>GLP-1 analogue</th>
<th>Exenatide (Byetta)</th>
<th>Exenatide (Bydureon)</th>
<th>Liraglutide (Victoza)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>sc injection twice daily</td>
<td>sc injection once weekly</td>
<td>sc injection once daily</td>
</tr>
<tr>
<td><strong>Side-effects</strong></td>
<td>Gl disturbance, weight loss, headaches, dizziness, fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dual-therapy licence</strong></td>
<td>metformin or sulfonylurea or pioglitazone</td>
<td>metformin or sulfonylurea</td>
<td></td>
</tr>
<tr>
<td><strong>Triple-therapy licence</strong></td>
<td>in combination with both metformin and a sulfonylurea, or with metformin and pioglitazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Licensed with insulin</strong></td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>ketoacidosis, severe GI disease, pancreatitis</td>
<td>ketoacidosis, inflammatory bowel disease, diabetic gastroparesis, pancreatitis</td>
<td></td>
</tr>
<tr>
<td><strong>Device</strong></td>
<td>simple sc injection</td>
<td>sc device (requires reconstitution)</td>
<td>simple sc injection</td>
</tr>
<tr>
<td><strong>Renal precautions</strong></td>
<td>avoid if eGFR &lt;30ml/min/1.73m²</td>
<td>avoid if eGFR &lt;50ml/min/1.73m²</td>
<td>avoid if eGFR &lt;60/ml/min/1.73m²</td>
</tr>
<tr>
<td><strong>Pregnancy/breast-feeding</strong></td>
<td>avoid</td>
<td>avoid</td>
<td>avoid</td>
</tr>
</tbody>
</table>

Table 1. Properties of currently available GLP-1 analogues (green = preferred feature)
comparing efficacy of DPP-4 inhibitors, so the choice of a particular DPP-4 inhibitor is based on nonglycaemic factors.

Table 2 gives properties of the various DPP-4 inhibitors currently available.

The long-term safety of both GLP-1 analogues and DPP-4 inhibitors has yet to be established, and the impact of these drugs on cardiovascular disease is not currently known. Both classes of drugs may cause hypoglycaemia if used with sulfonylureas or insulin.

So how do we select the next line of therapy in a patient with T2D who is on maximal metformin and a sulfonylurea yet still has a suboptimal HbA1c?  

**Goals of treatment**

It is important to remember that the overall aim of glycaemic management in T2D is to minimise long-term complications while avoiding severe hypoglycaemia.

The multidisciplinary diabetes team has a vital role in ensuring the optimisation of lifestyle factors and drug treatment to suit the patient’s individual circumstances. This involves setting individualised glycaemic targets for the patient. These should take into account a number of factors including psychosocial (motivation, knowledge level, self-care ability) along with age, likely impact of hypoglycaemia, renal function, body mass index, duration of T2D, presence of micro- and macrovascular complications, other comorbidities, occupation and patient preference.

Whenever possible, patients should be involved in the decision-making process regarding glycaemic targets and selection of therapies. Therefore the selection of the most appropriate third-line therapy will largely depend on the desired goals of treatment.

**Insulin**

Insulin is often the most appropriate third-line agent. In practical terms a patient with long-duration T2D on metformin and a sulfonylurea at maximal dose, who has good adherence with lifestyle measures and who has an HbA1c of 10 per cent (86mmol per mol),

<table>
<thead>
<tr>
<th>DPP-4 inhibitor</th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Vildagliptin</th>
<th>Linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side-effects</strong></td>
<td>Gl disturbances, peripheral oedema, sore throat, URTIs</td>
<td>vomiting, dyspepsia, gastritis, peripheral oedema, URTIs, UTIs</td>
<td>nausea, peripheral oedema, headache, tremor, asthenia, dizziness</td>
<td>cough, nasopharyngitis, reported pancreatitis</td>
</tr>
<tr>
<td><strong>Monotherapy licence</strong></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Dual-therapy licence</strong></td>
<td>with metformin or sulfonylurea or pioglitazone</td>
<td></td>
<td>with metformin</td>
<td></td>
</tr>
<tr>
<td><strong>Triple-therapy licence</strong></td>
<td>with metformin and sulfonylurea; with metformin and pioglitazone</td>
<td>no</td>
<td>with metformin and sulfonylurea</td>
<td>with metformin and sulfonylurea</td>
</tr>
<tr>
<td><strong>Licensed with insulin</strong></td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>discontinue if symptoms of pancreatitis</td>
<td>hepatic impairment</td>
<td>liver function monitoring required; moderate-severe heart failure</td>
<td>discontinue if symptoms of pancreatitis</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>ketoacidosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal impairment</strong></td>
<td>reduce dose</td>
<td></td>
<td></td>
<td>no dose adjustment required</td>
</tr>
<tr>
<td><strong>Pregnancy/breast-feeding</strong></td>
<td>avoid</td>
<td>avoid</td>
<td>avoid</td>
<td>avoid</td>
</tr>
</tbody>
</table>

*Table 2. Properties of currently available DPP-4 inhibitors (green = preferred feature)*
is unlikely to achieve glycaemic targets with the addition of further noninsulin therapies. This patient will probably need insulin as a consequence of the progression of the disease and the resulting impaired endogenous insulin secretion.

Initiation of a basal insulin (usually at night), alongside metformin and a sulfonylurea, is often used in this situation. This can reduce HbA1c levels by 1.5–2.0 per cent or more. Further titration of insulin, using either mixed insulins or rapid-acting insulin, may then become necessary over time. Hypoglycaemia and weight gain are the potential consequences of this approach.

**Noninsulin treatment**

Many patients are keen to avoid insulin due to occupational or personal reasons. In some patients the use of insulin may exacerbate problems with obesity, or the treating physician may be concerned about the impact of hypoglycaemia, or in patients with a history of alcohol excess, in elderly patients or those with significant ischaemic heart disease.

In someone with shorter-duration diabetes in whom insulin may not be desirable for the above reasons, the most commonly used third-line options are currently pioglitazone, DPP-4 inhibitors and GLP-1 analogues. There is no evidence to support any particular third-line agent over another in terms of efficacy, so the choice should be tailored to the patient circumstances. See Figure 2 for...
**Prescribing challenges**

**Key points**

- DPP-4 inhibitors and GLP-1 analogues are relatively new classes of drugs for the treatment of T2D that offer potential beneficial effects with regards to weight and hypoglycaemia compared to other current therapies
- they are particularly useful as third-line drugs for selected patients who may want to avoid insulin for medical or personal reasons
- where there are no contraindications, GLP-1 analogues are the preferred third-line agent in the overweight patient
- DPP-4 inhibitors are preferred in the overweight patient with significant CKD or where GLP-1 analogues are contraindicated
- there are significant cautions to the use of pioglitazone
- data regarding long-term safety, cardiovascular disease and effects on microvascular complications with these new classes of drugs are awaited
- the choice of third-line agent and level of glycaemic control needs to be individualised to the patient’s needs, taking into account both medical and psychosocial factors

simplification of this decision-making process.

In accordance with NICE guidance, in a patient who is overweight (BMI ≥35kg per m²) and has problems associated with weight, GLP-1 analogues would be the preferred third-line agent, assuming no contraindications. Even in patients with BMI <35kg per m² in whom insulin is unacceptable because of occupational implications or if weight loss would benefit other comorbidities, a GLP-1 analogue may be beneficial. The choice of agent would depend on patient preference and adherence.

HbA₁c reduction of ≥1.0 per cent (approx. 11mmol per mol) and ≥3 per cent loss of initial body weight at six months of use is necessary in order to comply with NICE guidance for continued usage of GLP-1 analogues.

In the overweight patient with significant chronic kidney disease (CKD) or in whom GLP-1 analogues are contraindicated for other reasons, the preferred third-line agent would be a DPP-4 inhibitor. DPP-4 inhibitor therapy should be continued only if there is a reduction of ≥0.5 per cent points in HbA₁c in six months. Linagliptin (Trajenta) is the only currently available DPP-4 inhibitor for which no dose reduction is required in CKD.

DPP-4 therapy is preferable to pioglitazone if further weight gain would cause significant problems or if there is contraindication to the use of pioglitazone.

However, pioglitazone should be used in preference if the patient has marked insulin insensitivity but is not overweight and/or the person had a poor response to DPP-4 inhibitors or DPP-4 inhibitors are contraindicated. There are, however, significant cautions to the use of pioglitazone as mentioned above.

In those patients who may be eligible for either DPP-4 inhibitor therapy or pioglitazone as the third-line agent, the choice should be based on patient preference after a full discussion of the benefits and risks.

In the event that HbA₁c remains above target despite the third-line agent, then insulin should be initiated in line with NICE guidance.

**Conclusion**

The management of T2D is a complex and rapidly evolving area. GLP-1 analogues and DPP-4 inhibitors are the newest classes of agents to reach the market, although their role in the treatment algorithms for T2D has not been clearly defined. In addition data on long-term safety and their effects on diabetic complications and cardiovascular disease are lacking.

Medications need to be tailored to the individual patient’s target HbA₁c, taking into account any comorbidity they may have such as obesity and CKD as well as their lifestyle and preferences.

In the near future more novel compounds, including sodium glucose co-transporter-2 (SGLT2) inhibitors, are expected to be licensed for use in the management of T2D; the first SGLT2 inhibitor, dapagliflozin (Forxiga), has recently become available. These advances, along with the burgeoning prevalence of T2D, will accentuate the need for more up-to-date, evidence-based pathways for the treatment of patients with T2D.

**Further reading**


Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 87. 2009.

**Declaration of interests**

None to declare.

Dr Othonos is an SpR in diabetes and Dr Abbas is a consultant diabetologist in the Centre for Diabetes and Endocrinology, Leeds Teaching Hospitals NHS Trust.