

# Glucose-lowering medicines for type 2 diabetes



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## Background

There is an increasing array of medicines available to improve blood glucose control in type 2 diabetes. Finding the best combination for an individual patient requires an assessment of the patient's characteristics and understanding the mechanism of action for each drug.

## Objective

The aim of this article is to provide a rational approach for choosing between the various blood glucose-lowering medicines available for treatment of patients with type 2 diabetes mellitus.

## Discussion

Metformin is the first choice of glucose-lowering medicines for most patients with type 2 diabetes. Sulphonylureas have proven benefits in long-term trials. Insulin is required in patients with symptoms of insulin deficiency. Glucagon-like peptide 1 agonists and sodium-glucose co-transporter 2 inhibitors provide some assistance in weight loss as well as improving blood glucose control. Dipeptidyl peptidase 4 inhibitors provide an alternative to metformin and sulphonylureas, especially when side effects of those drugs limit their use. Re-assessing blood glucose control after an appropriate trial period before deciding on continuing use is appropriate.

In recent years, pharmacological options for treating type 2 diabetes have expanded substantially. The place of metformin as the drug of first choice is unquestioned. Sulphonylureas have a long history and their use is supported by outcome data from the UK Prospective Diabetes Study (UKPDS).<sup>1</sup> Choosing agents other than metformin or sulphonylureas is more difficult, apart from the use of insulin in patients who are clearly insulin-deficient.

Most pharmacological options will reduce glycosylated haemoglobin (HbA1c) by 0.5–1.0%, on average, either as monotherapy, compared to placebo, or in addition to metformin and or a sulphonylurea. Confidence intervals for the decline in HbA1c, however, are 0–2%. The newer agents have not been tested in head-to-head trials. The challenge is often to choose the option that best suits the patient and achieves a larger decline in HbA1c. It is likely that not all drugs will produce the same improvements in blood glucose control in all patients. Importantly, poor dietary adherence and inadequate physical activity can be major deterrents to achieving improved glucose control. Ideally, new agents should be instituted and, if ineffective, stopped and an alternative agent used.

This article discusses the use of glucose-lowering therapies. Monotherapy and combination therapies (including insulin) outside the Pharmaceutical Benefits Scheme (PBS) indications and non-PBS listed drugs are not considered. The Australian Diabetes Society has recently published a position statement on this topic.<sup>2</sup>

Tables 1 and 2 outline available drugs and suggested uses.

## Metformin

Metformin increases insulin sensitivity in peripheral tissues, predominantly muscle, and reduces hepatic glucose output. It has clear outcome data for microvascular and macrovascular events.<sup>3</sup> In a large survey of metformin prescribing it was

observed that contraindications to its use are commonly ignored<sup>4</sup> and its association with lactic acidosis is questionable.<sup>5</sup> It should be suspended for 24–48 hours at times of iodinated contrast administration in patients with impaired renal function.<sup>6</sup> It can probably be used at lower doses in patients with impaired renal function (eGFR to at least 40 mL/min, and with caution can be considered at even lower levels of renal function). The evidence does not support other contraindications such as heart failure.<sup>7</sup>

### Sulphonylureas

Sulphonylureas directly stimulate insulin secretion. They have demonstrated outcome data for microvascular complications.<sup>1</sup> They may be associated with weight gain. Hypoglycaemia is the major side effect. Patients allergic to sulphur-containing drugs may not be allergic to sulphonylureas. Long-acting drugs (gliimepiride, glibenclimide and slow-release gliclazide) are more

commonly associated with hypoglycaemia. Patients with renal impairment are more likely to have hypoglycaemic events and should be prescribed a short-acting sulphonylurea (gliclazide, glipizide). Long-acting drugs are usually given once a day and should be prescribed before the period of highest blood glucose. For patients who have predominantly fasting hyperglycaemia, the long-acting sulphonylureas can be given with the evening meal.

### Insulin

Once insulin secretion declines sufficiently the patient will have symptoms of insulin deficiency and no oral agent will suffice. A new onset of lethargy accompanied by worsening home-monitoring results and rising HbA1c in a previously stable patient with reasonable dietary habits often indicates the need for insulin. A recent change in dietary habits, reduction in physical activity or onset of new intercurrent illness should also be

**Table 1. Suggested uses for various blood glucose-lowering medicines in type 2 diabetes after metformin and sulphonylureas**

	Insulin	DPP-IV inhibitor	SGLT-2 inhibitor	TZDs	GLP-1 agonist	Acarbose
Suggested uses	<ul style="list-style-type: none"> <li>• Clear symptoms of insulin deficiency</li> <li>• Failure of oral agents</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin intolerance</li> <li>• Alternate to sulphonylurea if metformin-sulphonylurea combination inadequate</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin intolerance</li> <li>• Alternate to sulphonylurea if metformin-sulphonylurea combination inadequate</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin intolerance</li> <li>• Inadequate control with metformin-sulphonylurea combination</li> </ul>	<ul style="list-style-type: none"> <li>• Significant dietary problems</li> <li>• Inadequate control with metformin-sulphonylurea combination</li> </ul>	<ul style="list-style-type: none"> <li>• Inadequate control with metformin and a sulphonylurea</li> </ul>
<b>PBS restrictions</b>						
Triple therapy with metformin and a sulphonylurea	Yes	No	No	Pioglitazone	Exenatide	Yes
Approximate monthly cost (\$)*	86.50	59.20	58.66	49.56	131.65	45.87
<b>Non-PBS supported indications†</b>						
Monotherapy	Yes	Linagliptin Sitagliptin Vildagliptin	Canagliflozin Dapagliflozin Empagliflozin	Pioglitazone	No	No
Triple therapy with metformin and sulphonylurea		Linagliptin Saxagliptin Sitagliptin Vildagliptin	Canagliflozin Dapagliflozin Empagliflozin	Pioglitazone	Once weekly exenatide liraglutide‡	
Use with insulin	N/A	Alogliptin Linagliptin Saxagliptin	Canagliflozin Dapagliflozin‡ Empagliflozin	Pioglitazone	Exenatide	No

DPP, dipeptidyl peptidase; GLP, glucagon-like peptide; PBS, Pharmaceutical Benefits Scheme; SGLT, sodium-glucose co-transporter; TZD, thiazolidinediones  
 \*Based on dispensed price for maximum quantity and using maximum dose of cheapest medicine in each class: metformin costs \$10.87/month and gliimepiride \$11.02/month; insulin price is based on 20 units glargine insulin per day; †once weekly exenatide and liraglutide have non-PBS-supported indications that have not been included in this table; ‡as of April 1 2015, dapagliflozin is PBS-listed for use with insulin

considered. Weight loss often accompanies this situation and is mistaken for the benefits of good dietary habits rather than poor diabetes control. For other patients inadequate blood glucose control despite a reasonable trial of oral agents indicates the need for insulin.

### Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 (DPP-4) hydrolyses the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Inhibition of these enzymes results in increased GLP-1 and GIP activity. Their effects, therefore, are similar to those of the GLP-1 agonists. Side effects are similar, although skin rash has been reported with most drugs and patients should be warned of this. Of the five available drugs, only linagliptin does not require dosage adjustment in patients with renal impairment. All but vildagliptin can be taken once daily at the maximum dose.

DPP-4 inhibitors can be considered in patients who cannot tolerate metformin or as an alternative to a sulphonylurea in those not achieving adequate blood glucose control but who do not appear to require insulin. There are no long-term outcome data supporting their use.

### Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT-2) is located in the proximal renal tubule and is responsible for reabsorption of filtered glucose in the kidney. Disrupting this enzyme leads to reduced reabsorption of glucose and, therefore, osmotic diuresis. Loss of glucose in the urine can promote weight loss of 1–2 kg over 26 weeks on average, although some patients seem to do substantially better.<sup>8,9</sup> Urinary tract infection and genitourinary tract candidiasis are commonly reported side effects, and diuretic therapy may have to be adjusted early in the course of treatment. These drugs lose efficacy as renal function declines. Of the two available agents, dapagliflozin is not recommended at eGFR below 60 mL/min, and canagliflozin is used at reduced doses (100 mg daily versus 300 mg daily) at an eGFR down to 45 mL/min and contraindicated at an eGFR below 45 mL/min.

SGLT2 inhibitors can be considered in patients who cannot tolerate metformin or as an alternative to a sulphonylurea in those not achieving adequate blood glucose control but who do not appear to require insulin. They may be especially effective when dietary adherence is a particular issue. If substantial improvement in HbA1c is not achieved after 3–4 months, treatment should be suspended. There are no long-term outcome data supporting their use.

### Thiazolidinediones

The thiazolidinediones (TZDs) rosiglitazone and pioglitazone are ligands of the peroxisome proliferator activated receptor gamma (PPAR-γ). By increasing insulin-dependent glucose uptake in muscle and suppressing insulin-mediated hepatic glucose

output, they can promote reasonable improvements in blood glucose control in some patients. The use of TZDs, particularly rosiglitazone, has been considerably hindered by the debate over their cardiovascular safety,<sup>10</sup> although this seems to have been resolved in favour of the drugs,<sup>11</sup> despite their substantial side-effect profile. Weight gain, fluid retention, bladder cancer (pioglitazone), reduced bone density and non-axial fractures in women are all recognised side effects.<sup>12</sup> Fluid retention promotes peripheral oedema in many patients, and worsens the control of heart failure or make asymptomatic patients symptomatic. Pioglitazone, in particular, remains an affordable option as the PBS subsidises its use in combination with metformin and a sulphonylurea or with insulin.

The benefits of TZDs on blood glucose control take some weeks to develop. An HbA1c measurement within 3 months of initiation is not likely to reflect the true impact of the drug and a longer time period is required. Pioglitazone has been associated with a reduced risk of macrovascular events in one trial of high-risk patients.<sup>13</sup>

**Table 2. Suggested algorithm for commencing glucose-lowering medicines**

<b>Step 1</b>	Good dietary habits and physical activity
<b>Step 2</b>	Add metformin (use a sulphonylurea if metformin not tolerated or contraindicated)
<b>Step 3</b>	Add a sulphonylurea
<b>Step 4</b>	<ul style="list-style-type: none"> <li>i. If symptoms of insulin deficiency start insulin</li> <li>OR</li> <li>ii. If only on a sulphonylurea add:                             <ul style="list-style-type: none"> <li>a DPP-4inhibitor</li> <li>or</li> <li>an SGLT-2 inhibitor</li> <li>or</li> <li>a thiazolidinedione</li> </ul> </li> <li>OR</li> <li>iii. If obesity and/or poor dietary habits add a GLP-1 agonist</li> <li>OR</li> <li>iv. pioglitazone or acarbose can be added to metformin/sulphonylurea combination.</li> <li>OR</li> <li>vi. a DPP-4 inhibitor or SGLT-2 inhibitor can be tried in place of sulphonylurea (with metformin)</li> </ul>
<b>Step 5</b>	<ul style="list-style-type: none"> <li>i. Continue metformin if able</li> <li>ii. If symptoms of insulin deficiency start insulin</li> <li>iii. use an alternate oral agent eg SGLT-2 inhibitor for DPP-4 inhibitor</li> <li>OR</li> <li>iv. Use triple therapy with metformin + sulphonylurea and either pioglitazone, acarbose or a GLP-1 agonist</li> </ul>
<b>Step 6</b>	Start insulin

## Glucagon-like peptide 1 receptor agonists

Activation of the glucagon-like peptide 1 (GLP-1) receptor results in an increase in glucose-dependent insulin secretion, impaired glucagon secretion and delayed gastric emptying. As the increased insulin secretion is glucose-dependent, hypoglycaemia is not a side effect of these drugs. Nausea and, sometimes, vomiting are common, especially early after initiation and tend to abate within 2 weeks of starting treatment. Exenatide should start at 5 µg twice daily and increase to 10 µg daily after 1 month. Exenatide seems particularly useful in patients who struggle with dietary adherence. Modest weight loss can be achieved (2–3 kg over 24 months, compared with placebo).<sup>14</sup> Blood glucose levels usually respond promptly to initiation of treatment. Treatment should be stopped at 3–4 months if no substantial improvement in HbA1c is seen. There are no long-term outcome data supporting the use of GLP-1 agonists.

Acute pancreatitis has been reported with both exenatide and liraglutide.<sup>15</sup> A history of pancreatitis is considered a contraindication to their use; however, GLP-1 agonists are an attractive option for patients who are obese or have hyperglycaemia and a history of triglyceride-induced pancreatitis. Further clarification for the risk of pancreatitis with GLP-1 agonists is needed.

## Acarbose

Acarbose inhibits alpha-glucosidases, which are enzymes in the gastrointestinal tract that metabolise carbohydrates, reducing their availability for absorption and attenuating postprandial blood glucose excursions. The main side effects of acarbose are flatulence and diarrhoea, resulting from excess carbohydrates reaching the distal small bowel, particularly in those patients not strictly adhering to an appropriate diet. Acarbose is excreted predominantly through the gastrointestinal tract, but it is contraindicated in patients with renal impairment. Side effects and the need to take two tablets three times a day at maximum dose make these drugs unpopular with patients. There are no clear long-term outcome data supporting their use.

## Conclusions

There is an increasing number of options available for blood glucose-lowering in patients with type 2 diabetes. For patients with symptoms of insulin deficiency, insulin is appropriate and trials of other agents only avoid the inevitable.

Significant outcome data support the use of metformin and sulphonylurea as the first- and second-line therapies, respectively, although the risk of hypoglycaemia needs to be considered when a sulphonylurea is used.

Poor dietary adherence is always an impediment to improving blood glucose control. However, the GLP-1 agonists and SGLT2 inhibitors may have an advantage in this group of patients. DPP-4 inhibitors and SGLT-2 inhibitors are an option when

metformin cannot be tolerated, or as an alternative to a sulphonylurea when blood glucose control is inadequate.

Effectiveness of any drug should be assessed before deciding to continue therapy. Most new drugs should produce an improvement in home blood glucose monitoring within days. Improvements in HbA1c will be seen more slowly but should be evident by 6 months. The TZDs require a longer period of time to be effective. If an adequate response is not seen within an appropriate time frame the drug should be stopped and an alternative considered.

## Key points

- Metformin is the drug of first choice for glucose lowering in patients with type 2 diabetes.
- A sulphonylurea is an appropriate second option.
- GLP-1 agonists and SGLT-2 inhibitors provide some benefits for weight loss.
- DPP-4 inhibitors are reasonable substitutes when metformin and/or a sulphonylurea is contraindicated or apparently ineffective.
- Patients with symptoms of insulin deficiency require insulin.
- The effectiveness of any new treatment should be reviewed at an appropriate time before continuing indefinitely.

## Case 1

Neil, aged 58 years, was diagnosed with type 2 diabetes 4 years ago. His blood pressure and lipids have been well controlled on a combination of perindopril, indapamide and atorvastatin. Neil uses nasal continuous positive airway pressure (CPAP) therapy for obstructive sleep apnoea. Blood glucose control has been a struggle and HbA1c is regularly around 8.5% using metformin 1500 mg bd and gliclazide 4 mg mane. Neil now weighs 94 kg and his body mass index (BMI) is 31.8 kg/m<sup>2</sup>. He struggles with his diet. He commenced treatment with exenatide 5 µg bd and almost immediately noticed a fall in home blood glucose levels. However, he had considerable nausea and intermittent vomiting, but persisted with the exenatide and the nausea abated. On increasing the dose to 10 µg bd, the nausea returned but abated within 1 week. After 4 months, HbA1c improved to 7.3% and he lost 3.6 kg.

## Case 2

Geoffrey, aged 62 years, has had type 2 diabetes of 7 years duration. He had managed to control his blood glucose level with diet and exercise until 3 years ago when his HbA1c level rose to 7.6%. At that time, only his fasting tests were elevated (8–10 mmol/L) and daytime tests were usually 6–8 mmol/L. Gliclazide, added with breakfast, caused intermittent daytime hypoglycaemia but little change in his fasting tests. His weight increased by 2 kg as he was eating to avoid hypos. Gliclazide was moved to the evening meal and the hypos disappeared, weight returned to the previous level and HbA1c improved to 7.0%.

Four years later, HbA1c increased to 7.9% despite good dietary efforts. Geoffrey tried to introduce metformin on two occasions, using the slow-release preparation more recently, but developed severe diarrhoea on both occasions. Graham's general practitioner (GP) considered an SGLT2 inhibitor and a DPP-4 inhibitor as reasonable options. With both, linagliptin 5 mg daily and sitagliptin 100 mg daily, he developed intolerable nausea. He tolerated dapagliflozin at 10 mg daily and HbA1c improved to 7.3%. Graham and his GP are now considering whether to continue with dapagliflozin or move to insulin.

### Case 3

Julia, aged 59 years, has had type 2 diabetes for 9 years. She had managed to maintain reasonable glucose control with a combination of diet, regular swimming and Zumba, metformin and slow-release glicazide. In the past 6 months Julia has become increasingly lethargic and tired. Home blood glucose tests are regularly over 12 mmol/L. She recently started the '5 and 2' diet and thought that might help to control her blood glucose levels as she had lost 2 kg in the past month. HbA1c increased from around 7.3% to 9.2% in the past 6 months. Despite Julia's desire to try one of the new oral hypoglycaemic agents she has read about, her GP convinced her that she needed insulin. She immediately felt better after starting insulin, even though her glucose levels had not yet returned to her usual good levels.

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