

# Second steps in managing type 2 diabetes

## SUMMARY

In type 2 diabetes, diet, exercise and attaining a healthy weight should be encouraged at every opportunity.

Metformin is the usual first-line drug management.

Sulfonylureas are appropriate as second-line drugs for many patients. Other oral drugs are preferable if weight gain or hypoglycaemia are significant problems.

If a combination of metformin and a sulfonylurea is not suitable, either a dipeptidyl peptidase-4 inhibitor or sodium-glucose co-transporter 2 inhibitor can be prescribed. The patient characteristics and the beneficial and adverse effects of the drug should be considered when selecting second-line therapy.

Due to their adverse-effect profiles, thiazolidinediones and acarbose should be reserved for patients with contraindications to all other oral drugs, and those who will not tolerate injectable drugs.

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## Keywords

incretin mimetics, metformin, oral hypoglycaemic drugs, sodium-glucose co-transporter 2 inhibitors, sulfonylureas, type 2 diabetes

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## Introduction

Type 2 diabetes is a common medical condition, with the prevalence increasing to 1 million people in Australia in 2014-15.<sup>1</sup> The goals of therapy should be individualised, based on patient characteristics, including age and comorbidities. Diet, exercise and a healthy weight are important components of the management.

The range of drugs for type 2 diabetes (see Table) has increased in recent years, delaying the need for insulin therapy, but adding complexity to treatment algorithms. Metformin is first line for drug therapy.<sup>2</sup> Sulfonylureas have a major role as second-line drugs, however there are a number of alternative options that should be considered when weight gain and hypoglycaemia are to be avoided. The choice of second-line drug should be individualised, based on the degree and timing of hyperglycaemia, comorbid conditions and the drug's beneficial and adverse-effect profile.

The Pharmaceutical Benefits Scheme (PBS) has placed some limitations on the prescribing of second- and third-line drugs for type 2 diabetes. These restrictions need to be considered when prescribing, especially as they change from time to time.

## Treatment targets

The treatment targets relating to overall glycaemic control, glycated haemoglobin (HbA1c) and glucose monitoring for patients with type 2 diabetes are an important consideration when selecting a second-line drug. These should be individualised, with age, comorbidities, diabetes-related complications, and

the person's preferences among a number of factors to be considered. The risk of hypoglycaemia should always be balanced against the benefits of tight glycaemic control.

The Australian Diabetes Society has created a [website](#) that includes an algorithm for the management of type 2 diabetes and provides case studies to assist with setting targets. Once a target has been set, treatment should be escalated if the concentration of HbA1c is above the target, or has not improved by at least 0.5% after three months.

## Monitoring

The recommended frequency of self-monitoring of glucose depends on the drugs prescribed. For people taking insulin, more frequent monitoring is required, compared to drugs that do not pose a significant risk of hypoglycaemia. However, when starting a second-line drug, it is important to be able to both assess the efficacy of the treatment, as well as ensure that there is no significant hypoglycaemia. Glucose should be monitored at least daily and at varied times across the day to provide a picture of the overall glycaemic profile, in particular the effect of meals and activity on glycaemic control. Once someone is stable on a new drug, with the exception of insulin, monitoring frequency can be reduced.

## Management

It is essential to counsel people on the importance of diet, exercise and a healthy weight for improving control of type 2 diabetes. These should be discussed regularly to optimise glycaemic control and minimise the dose or number of drugs required to

Table Second-line drugs for type 2 diabetes

Class	Approximate HbA1c reduction*	Benefits in addition to glucose-lowering	Adverse effects	Precautions
Sulfonylureas	0.5–1.3%	Nil	Hypoglycaemia, weight gain	Kidney impairment (dose reduction may be required), severe liver disease, elderly
Dipeptidyl peptidase-4 inhibitors	0.7–1%	Minimal hypoglycaemic risk	Pancreatitis	Pancreatic disease, kidney impairment (dose reduction may be required)
Glucagon-like peptide-1 analogues	0.8–0.9%	Weight loss	Nausea and vomiting	Kidney impairment (contraindicated if CrCl <30 mL/min), pancreatic disease, gallbladder disease, pre-existing gastrointestinal symptoms, family or personal history of thyroid cancer (based on animal models)
Sodium-glucose co-transporter 2 inhibitors	0.5–0.7%	Lowering of blood pressure, cardioprotection, weight loss	Genitourinary infections, euglycaemic ketoacidosis	Fasting or peri-operative state, acute intercurrent illness, taking loop diuretics, kidney impairment (contraindicated if CrCl <45 mL/min)
Insulin	Superior to other diabetes drugs	Nil	Hypoglycaemia, weight gain	Inability to safely administer insulin or monitor glucose
Acarbose	0.8%	Nil	Gastrointestinal symptoms	Gastrointestinal disease, kidney impairment (contraindicated if CrCl <25 mL/min), note glucose (not sucrose) must be administered to treat hypoglycaemia
Thiazolidinediones	0.7–0.8%	Nil	Worsening of heart failure, increased fracture risk, macular oedema, cardiac ischaemia, bladder cancer	Osteoporosis, macular oedema, heart failure, liver disease

CrCl creatinine clearance

\* The approximate glycated haemoglobin (HbA1c) reduction is based on studies using the class of drug as adjuvant therapy to metformin.

maintain control. Non-drug management is of equal importance in people of healthy weight, as it is in those who are overweight or obese.

### Metformin

Metformin is typically prescribed as the first-line drug for type 2 diabetes.<sup>2</sup> It improves insulin sensitivity and is effective in improving glycaemic control. There is no weight gain and a limited risk of hypoglycaemia.

There are some situations in which metformin is contraindicated, such as end-stage kidney disease (creatinine clearance <15 mL/min), or not tolerated, for example, because of gastrointestinal adverse effects. If metformin was not used as the initial drug to manage type 2 diabetes, and no contraindications or previous intolerance exist, then it could be considered as a second-line drug. A dose reduction is required for metformin if the patient's creatinine clearance is less than 90 mL/min. Conditions that alter kidney function may increase the risk of lactic acidosis.

### Sulfonylureas

Sulfonylureas such as gliclazide and glibenclamide have traditionally been used as second-line oral drugs, as add-on therapy to metformin. They are effective drugs that should be considered when metformin therapy does not achieve the target for glycaemic control. The reduction in HbA1c is 0.5–1.3% when used in addition to metformin.<sup>3</sup> Sulfonylureas are particularly recommended as second-line drugs if it is anticipated that the patient is likely to need a glucagon-like peptide-1 (GLP-1) analogue as a third-line drug in the relatively near future, for example in an overweight or obese person whose HbA1c is significantly above target.

Sulfonylureas act as insulin secretagogues, so there is a risk of hypoglycaemia and weight gain. Hypoglycaemia is a significant risk in patients with kidney impairment and the elderly, particularly because of the long duration of action.

### ***Incretin mimetics***

Incretins are neuroendocrine hormones produced by the gastrointestinal tract in response to food. They are involved in stimulating insulin secretion and suppressing glucagon secretion. Incretins also suppress appetite and inhibit gastric emptying. The major incretin hormones are glucagon-like peptide and glucose-dependent insulinotropic polypeptide (GIP). These hormones are metabolised by dipeptidyl peptidase-4 (DPP-4).

There are currently two types of incretin mimetic drugs that are effective in the management of type 2 diabetes. These are the oral DPP-4 inhibitors and the injectable GLP-1 analogues. The choice between a DPP-4 inhibitor and a GLP-1 analogue may be influenced by a number of factors including patient preference regarding route of administration, desired weight loss (more likely with GLP-1 analogue), and the magnitude of improvement needed for glycaemic control (tends to be greater with GLP-1 analogue when weight loss and appetite effects are also factored in).

### ***Dipeptidyl peptidase-4 inhibitors***

DPP-4 inhibitors, also known as gliptins, are effective in reducing postprandial glucose, without a risk of hypoglycaemia. DPP-4 inhibitors are weight neutral, and are generally well tolerated. As adjuvant therapy to metformin, they result in a modest reduction in HbA1c, in the order of 0.7–1%.<sup>4-7</sup> They have been associated with pancreatitis, so should not be prescribed to people with a previous history of pancreatic disease. Regular monitoring of pancreatic function is not required, however the drug should be stopped if people develop symptoms consistent with pancreatitis and this is confirmed on blood tests.

### ***Glucagon-like peptide-1 analogues***

GLP-1 analogues are given by subcutaneous injection. These drugs predominantly target postprandial glucose, without a risk of hypoglycaemia. They have the beneficial effects of increasing satiety, thereby reducing dietary intake and causing weight loss. The expected HbA1c reduction from GLP-1 analogues is 0.8–0.9%.<sup>8,9</sup> An expected adverse effect is nausea and vomiting, in particular triggered by certain food types and large portion sizes. Like DPP-4 inhibitors, GLP-1 analogues have an increased risk of pancreatitis and pancreatic malignancy, but no routine monitoring of pancreatic function is required.

Several GLP-1 analogues are approved by the Therapeutic Goods Administration, however only exenatide and dulaglutide are currently listed on the PBS. Exenatide is available in a standard-release formulation administered as a twice-daily injection and an extended-release formulation injected weekly.

Dulaglutide is administered as a weekly injection. Current PBS authority criteria restrict GLP-1 analogues to use as third-line drugs, prescribed in combination with both metformin and a sulfonylurea, or with either metformin or a sulfonylurea if there is a contraindication to a combination of both oral drugs.

### ***Sodium-glucose co-transporter 2 inhibitors***

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, or gliflozins, are the latest class of oral hypoglycaemic drugs. They work by blocking the renal sodium-glucose co-transporter, resulting in an increase in urinary glucose excretion. In combination with metformin they reduce HbA1c by 0.5–0.7%. SGLT2 inhibitors, such as dapagliflozin and empagliflozin, have the beneficial effect of mild weight and blood pressure reduction, due to the diuretic action. Another significant benefit is the cardioprotective effect reported in the EMPA-REG trial,<sup>10</sup> which makes the drugs a good choice for people with or at high risk of cardiovascular disease.

SGLT2 inhibitors can cause a number of adverse effects, which may make them intolerable. The glycosuria results in an increased risk of genital candidiasis and urinary tract infections, which can be severe and recurrent. SGLT2 inhibitors can cause kidney impairment, which is often transient. It is usually due to hypovolaemia as a consequence of the diuretic effect of the SGLT2 inhibitor, and those with pre-existing kidney impairment are at particular risk. There is also a small but clinically significant risk of euglycaemic ketoacidosis,<sup>11</sup> particularly in the perioperative period, when it is recommended that SGLT2 inhibitors are withheld for three days pre- and postoperatively.

### ***Insulin***

The role of insulin as a second-line drug is predominantly in people with hyperglycaemia who do not respond adequately to oral hypoglycaemic drugs or incretin mimetics, or in those who have significant symptomatic hyperglycaemia requiring immediate glucose-lowering. Insulin comes in a number of forms, with the frequency of subcutaneous injections ranging from once daily to five times a day. A variety of regimens can be prescribed. These include:

- basal insulin alone
- a basal-plus regimen (basal insulin with a rapid-acting insulin analogue with one meal)
- a basal-bolus regimen (rapid-acting insulin analogue administered with each meal)
- pre-mixed insulins injected one to three times daily.

When insulin is prescribed in type 2 diabetes, it is usually taken in addition to, not instead of, the other hypoglycaemic drugs, minimising the insulin doses required. In particular, metformin should

always be continued. Sulfonylureas are an exception, however, and should be stopped once rapid-acting or pre-mixed insulin is commenced, as they will not provide any additional improvement in glycaemic control. They can, however, provide ongoing benefit in those taking only long-acting insulin. The other exception relates to PBS prescribing – the extended-release formulation of exenatide, and dulaglutide are not currently PBS-approved in combination with insulin. If appropriate, these can be switched to the immediate-release formulation of exenatide, which is approved for use in combination with insulin.

The HbA1c reduction varies depending on dosage and regimen, but it is superior to all other drugs for diabetes.<sup>11</sup> Adverse effects include hypoglycaemia and weight gain. Access to refrigeration is needed to store insulin before use.

### Acarbose

Acarbose is an oral hypoglycaemic drug, which has a limited role in the management of type 2 diabetes. It acts by delaying the intestinal absorption of carbohydrates, which causes the undesirable adverse effects of flatulence and other gastrointestinal symptoms. As an adjuvant to metformin, acarbose lowers HbA1c by 0.7%,<sup>11</sup> however this was based on only a few studies with small numbers of patients. Acarbose is generally considered to be less effective at improving glycaemic control than other oral hypoglycaemic drugs, which should be prescribed in preference.

### Thiazolidinediones

Thiazolidinediones, also known as glitazones, act as insulin sensitisers, and reduce HbA1c by 0.7–0.8% when used with metformin.<sup>11</sup> These drugs are no longer commonly used because of their adverse

effects. Rosiglitazone was associated with an increase in the risk of cardiac ischaemia, and pioglitazone with an increase in the risk of bladder cancer. Both these thiazolidinediones are associated with worsening heart failure, increasing the risk of fracture in people with osteoporosis, and worsening diabetic macular oedema.

### Conclusion

There are a number of drugs that are suitable for use as second-line therapy in the management of type 2 diabetes. However, there is no single drug that is consistently superior as adjuvant therapy to metformin and, as a result, treatment algorithms are complex. The choice of second-line therapy should be based on the individual, considering the treatment goals, comorbidities, degree and timing of hyperglycaemia, and the beneficial and adverse effects of each class of drug.

Many people will progress to require more than two drugs to adequately manage their type 2 diabetes. There are a number of possible combinations, the most common being metformin, a sulfonylurea and one of a DPP-4 inhibitor, SGLT2 inhibitor or GLP-1 analogue. The combination of metformin, a DPP-4 inhibitor and an SGLT2 inhibitor has recently gained PBS approval, and is also an effective management option. Specialist advice should be sought if appropriate glycaemic control is unable to be achieved with these combinations, if hypoglycaemia is preventing overall adequate glycaemic control, or if there are significant diabetes-related complications. ◀

*Conflict of interest: none declared*

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