Living well with Type 2 diabetes – medicines



How do diabetes medicines work to improve your quality of life? **Najia Siddique** and **John McDermott** explain

The human body is like a finely tuned machine. It tightly controls the levels of a number of substances such as calcium, potassium, sodium and glucose in the blood, so that the body can function at its best. Diabetes mellitus is a medical condition that results in blood glucose levels becoming raised above the normal level.

Insulin, a hormone produced by the specialist beta cells in the pancreas, is the main hormone used by the body to keep glucose levels within the normal range. When glucose levels rise in the blood in healthy individuals, for instance after a meal, the pancreas releases extra insulin to lower the blood glucose level back into the normal range.

Difference between Type 1 and 2

In diabetes, glucose levels rise because of a lack of sufficient insulin. In Type 1 diabetes the insulin-producing cells in the pancreas are destroyed by the body's immune system. This results in a complete absence of insulin – hence people with Type 1 diabetes need insulin injections to survive.

In Type 2 diabetes, the beta cells in the pancreas are able to produce insulin, but the cells in the body are 'resistant' to the effects of this insulin. The pancreas cannot produce enough insulin to overcome this 'block' so the blood glucose levels rise above the normal range. This resistance to insulin's glucose lowering effect most commonly occurs as a result of excess body fat, particularly around the tummy area.

Importance of lifestyle changes

Lifestyle changes are the most important part of caring for Type 2 diabetes. Losing weight can significantly improve the action of the body's own insulin. This can sometimes be enough to control the blood glucose levels without the need for medicines. Even where medicines are needed, a lifestyle with regular exercise and eating a healthy, balanced diet can help it them work better, possibly avoiding the need to take additional medicines later on.

Less than two decades ago there were very few treatments for Type 2 diabetes. These included metformin (known as Glucophage), sulphonylureas (for example Gliclazide or Diamicron) and insulin. This made things straightforward for the doctor treating diabetes, but there was little choice.

Sulphonylureas and insulin, while they can be very effective treatments in the right individual, have downsides.

The huge increase in diabetes cases worldwide means that there is now more research on treatment being done so more drugs are being developed.

New medications have advantages and disadvantages. With discussion between doctor and patient, it is usually possible to find a treatment plan to suit the individual. Where one medicine is tried and doesn't work, or causes side-effects, there are several other options.

Metformin

Metformin (Glucophage) has been used as a diabetes treatment since the 1950s. With its track record we know that it is very safe for long-term use.

The main site of action of metformin is the liver. In diabetes the liver releases too much glucose into the bloodstream, and this is one of the factors that results in elevated blood glucose levels. Metformin reduces the amount of glucose release from the liver. It also increases the amount of glucose entering into muscles, thus lowering the amount present in the blood.

Sulphonylureas

Sulphonylureas, eg. gliclazide (Diamicron) and glimepiride (Amaryl) have become less commonly used as other treatment options have become available. They work quickly by stimulating the pancreas to produce more insulin from the beta-cells – the increased level of insulin in the blood lowers the blood glucose level. Like metformin, they have been available for a long time and therefore have a good track record in side-effects.

Newer 'incretin' based medicines

This group of medicines has been available for more than 10 years and is a useful addition to the range of treatment options. They are based on a natural process that occurs in the body when food is eaten.

When food hits the gut after leaving the stomach, the gut releases a hormonal signal into the bloodstream to allow the body to deal effectively with that food. These hormones are called incretins and the particular one we are most interested in is called GLP-1.

The GLP-1 hormone:

- Tells the pancreas that sugar is on its way, so insulin should be released
- Tells the stomach to slow down digestion – this makes the individual feel full and reduces hunger
- Tells the brain that food has been eaten, and that less food should be eaten.

An important advantage of these GLP-1 analogues is that they can help with weight loss. Also, they are unlikely to cause low blood glucose levels, unless they are being used with sulphonylureas or insulin.

Taken by injection, they are very effective for lowering blood glucose. Once-a-week injections are available, which may suit some people.

Even though this drug is an injectable, there is however, no need to inform the driving licence authority when starting these medications, or to be over-concerned about low glucose levels.

DPP-4 inhibitors

DPP-4 is an enzyme which is responsible for breaking down GLP-1 and making it inactive. DPP-4 inhibitors such as sitagliptin (Januvia), saxagliptin (Onglyza), vildagliptin (Galvus) and linagliptin (Trajenta) block this enzyme, and this means that the body's GLP-1 can last longer, and carry out its beneficial effects.

Although these medications are not as powerful at lowering blood glucose as GLP-1 analogues, they are available in tablet form, which may be preferred. They have very few side-effects. There are no implications for driving when taking these medications.

Another advantage of DPP-4 inhibitors is that they are available in combination preparations with metformin – which means that two medications that work in different ways to lower blood glucose can be given, but in the one tablet.

SGLT-2 inhibitors – newest drugs

SGLT-2 inhibitors are the newest group of medicines for treating diabetes. They come in tablet form, and medications in this group include dapagliflozin (Forxiga), empagliflozin (Jardiance) and canagliflozin (Invokana). They can be used in combination with any other diabetes medication.

When the body is working normally, glucose spills out into the kidneys as a consequence of the kidney filtering waste products from the blood. Glucose is not a waste product however, and the body wants to keep it – hence the kidneys have the ability to reabsorb the glucose back into the body before it is lost in the urine, through special channels called SGLT-2.

However, in diabetes it is beneficial to allow glucose to be passed in the urine rather than kept in the body. SGLT-2 inhibitors block the channels in the kidney that reabsorb glucose. This means that the glucose that is filtered out of the blood by the kidneys enters the urine – so essentially the glucose moves from the blood into the urine, and is ultimately flushed down the toilet. This results in a lowering of blood glucose levels, and an improvement in diabetes control. It also results in the passing of 'sweet' urine, which can result in some side-effects.

A major advantage of these medications is that they can help with weight loss. By losing glucose in the urine, the body is losing calories.

Thiazolidinediones

Thiazolidinediones including rosiglitazone (Avandia) and pioglitazone (Actos) have had a chequered history of side-effects and are used quite infrequently nowadays.

Insulin

Some people may eventually need treatment with insulin – the most powerful agent we have available in terms of its glucose-lowering effect. Insulin may be the best option in a particular individual's circumstance.

Insulin is the most tried and tested treatment for diabetes, having been in use for many years. This means that we know what the side-effects are, and we know that it is safe with long-term use. It is also the most powerful agent for lowering blood glucose – if a particular dose is not lowering glucose enough, the dose is increased to suit the individual.

Insulin works very quickly, and is often given temporarily to hospitalised patients with high glucose as a result of illness or steroid treatment. Insulin can be used in patients with kidney problems, unlike some other medications.

With long-acting insulin preparations available, many patients with Type 2 diabetes can be treated with just one insulin injection a day, in combination with their diabetes tablets.

Research has shown that insulin lowers the risk of diabetes complications by lowering blood glucose levels. However, insulin is the medication with the highest risk of causing a hypo (low blood glucose). This means that people taking insulin need to be educated about how

Oral medication and injections: How they work

The types of medications are categorised according to how they work in the body to lower glucose levels

Oral medications	Drug name	Brand names		How they work	Some side-effects	How to take
Biguanides	Metformin	Glucophage, Metophage, Metformin Bluefish, Metformin Mylan, Metformin Teva, Metformin Aurobind		They increase the effectiveness of the body's insulin and also stop liver producing new glucose	Nausea, abdominal pain, soft bowel motions or diarrhoea, taste disturbance, weight loss	Take as prescribed with food to minimise side-effects
*Sulphonylureas	Gliclazide (slow release)	Diaglyc, Diamicron MR, Diaclide MR, Diacronal MR, Vitile MR		They stimulate the pancreas to make insulin regardless of what the blood glucose level is	May cause low blood glucose levels (hypos). Side-effects may include an upset tummy, headache, and rarely a skin rash. Increased appetite can cause weight gain	Take as prescribed with food
	Gliclazide (short-acting)	Diamicron, Diabrezide, Diaclide				
	Glimepiride	Amaryl				
	Glibenclamide	Daonil				
*Meglitinides (prandial glucose regulators)	Repaglinide	Novonorm		They stimulate extra insulin production when carbohydrate is taken. Its effects do not last very long and therefore is only taken with meals	Most common side-effect is low blood glucose levels (hypos) but it is unlikely due to the short duration of the tablet	Take as prescribed before meals. If you miss a meal, don't take the tablet
Thiazolidinediones (Glitazones)			**In combination with metformin**	They increase the effectiveness of the body's insulin	Fluid retention, weight gain, respiratory infection, abnormal vision and numbness. If you experience fluid retention, shortness of breath and unusual tiredness, report these symptoms to your doctor without delay	Take as prescribed with or without food
	Pioglitazone	Actos	Competact			
SGLT2: Sodium glucose co-transporter 2 inhibitors			**In combination with metformin**	They work in the kidney by removing excess glucose and associated calories in the urine. They have the additional benefit of weight loss	They are associated with a higher incidence of genital infections such as trush and urinary tract infections. They may increase urination	Take as prescribed with or without food
	Dapagliflozin	Forxiga	Xigduo			
	Empagliflozin	Jardiance	Synjardy			
	Canagliflozin	Invokana	Vokanamet			
DPP4 inhibitors			**In combination with metformin**	They have the effect of increasing insulin production when needed and reducing glucose production from the liver when it is not needed	Sore throat, stuffy nose, upper respiratory infection. Report persistent and severe stomach pain to your doctor immediately	Take as prescribed with or without food
	Sitagliptin	Januvia	Janumet			
	Vildagliptin	Galvus	Eucreas			
	Saxagliptin	Onglyza	Komboglyze			
	Linagliptin	Trajenta	Jentadueto			
Alpha-glucosidase inhibitors	Acarbose	Glucobay		They help to slow down the break-down of food in the digestive system and the absorption of glucose into the bloodstream	These can cause stomach upset, flatulence and bloating	Take as prescribed with food to help alleviate side-effects
Injections	**Drug name**	**Brand names**		**How they work**	**Some side-effects**	**How to take**
GLP1 agonists (non-insulin injections)	Exenatide	Byetta		They increase insulin production when food is present and reduce glucose production from the liver to lower blood glucose levels. They also cause a reduction in appetite and delayed stomach emptying which may result in weight loss	Nausea, weight loss, headache, diarrhoea, vomiting, decreased appetite. Persistent and severe stomach pain must be reported to your doctor immediately	These medication are injections but they are not insulin. You should be instructed on how and when to use these medications by a doctor or nurse before it is prescribed
	Exenatide extended release	Bydureon				
	Dulaglutide extended release	Trulicity				
	Liraglutide	Victoza				

*These medications have a risk of hypos; MR = modified release

Adapted from Diabetes Ireland's 2016 Living well with Type 2 Diabetes booklet

to detect, prevent and treat low glucose, and need to test their blood glucose regularly.

Driving guidelines

People taking insulin should be aware of driving guidelines for diabetes and the driving licence authority needs to be informed of their status. Insulin may not be suitable for patients at high risk of hypos, or where low glucose would be particularly dangerous, eg. elderly patients living alone who have difficulty with glucose testing. A side-effect of insulin is weight gain. However, not all patients will gain significant amounts of weight when treated with insulin.

Insulin is only available in injection form. However, with modern insulin pens and needles, some people find injections more convenient than tablets. The injections are virtually painless, and in some patients may be only once a day.

There is no one-size-fits-all, off-the-shelf medication for everyone. You are the expert in your diabetes – the key is to engage with your diabetes team to find a treatment that suits you.

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