In recent years, the number of drugs being added to the diabetes armamentarium has been impressive. Journals and conferences are dominated by cutting edge research on the sodium–glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagonlike peptide-1 (GLP-1) receptor agonists.

Yet quietly, in the background, metformin, the workhorse of the Type 2 diabetes field, plods on unperturbed by the new kids on the block. It is safe in the knowledge that, thanks to its popularity as the first-line drug of choice, it is metformin – and not any of the other diabetes drugs – that is recognised on the World Health Organization’s List of Essential Medicines.1

Metformin is a slightly modified version of a compound that is found in the plant Galega officinalis, better known as French lilac or goat’s rue. In his 1640 treatise, Theatrum Botanicum, John Parkinson, an English herbalist, recommended goat’s rue as the go-to plant for, among other things, bites and stings of any venomous creature, measles, smallpox and worms in

Last year, metformin celebrated its 60th anniversary and is still the first-line treatment for Type 2 diabetes. And recent research suggests new applications of this traditional medication in cancer, cardiovascular risk, ageing and pregnancy. Dr Eleanor Kennedy explains how metformin is enjoying a new lease of life.
In recent years, metformin has undergone something of a transformation. It has been repositioned for use in a number of different ways, from Type 1 diabetes to dementia, flouting the old adage that you can’t teach an old dog new tricks.

A number of studies now suggest that metformin could be used not just as a treatment for cancer, but as a way to prevent it in those at increased risk.

**Metformin and cancer**

A number of epidemiological and laboratory research studies now suggest that metformin could be used not just as a treatment for cancer, but as a way to prevent it in people at increased risk. And one of the very first studies to demonstrate this was a Diabetes UK-funded studentship awarded to Professor Dario Alessi at the University of Dundee in 2005. “Just days before the student was due to start, new work was published that I had a feeling was going to be very important, and, although concerned that this work was more about cancer than diabetes, we started to investigate a molecule called LKB-1, an upstream regulator of AMP-activated protein kinase or AMP kinase. The AMP kinase enzyme is activated by exercise but it is also stimulated by metformin. So, the theory was that, because exercise is known to be beneficial in the prevention of certain cancers, perhaps metformin could reduce the risk of cancer in patients with Type 2 diabetes because of its effects on the same enzyme.”

At the time, health informatics was still very much in its infancy but, along with Professor Andrew Morris, the group investigated patient databases in Scotland and demonstrated that metformin may be associated with up to a 30 per cent reduced risk of cancer in patients with Type 2 diabetes because of its effects on the same enzyme.

Although a small study, it catalysed a lot of further research and there is now a growing body of evidence to suggest that metformin can delay certain soft tissue tumours.

With more than 120 million prescriptions of metformin written annually for treatment of Type 2 diabetes, Professor Lewis Cantley, the director of the Cancer Centre at Weill Cornell Medicine known for his seminal work on understanding the metabolism of cancer, once noted wryly “Metformin may have already saved more people from cancer deaths than any drug in history”.

**Metformin and Type 1 diabetes**

And it’s not just the cancer field where metformin is causing a frisson of excitement. It is well known that insulin treatment in people with Type 1 diabetes has shortcomings and, despite careful management, many patients struggle to achieve glycaemic and metabolic targets. Metformin is sometimes used in patients with Type 1 diabetes off-label to help limit the insulin requirement, but there have been only a handful of randomised clinical trials of metformin therapy in Type 1 diabetes.

These suggested that metformin can reduce insulin dose requirement but, because the studies that had been conducted were predominantly short, it was not possible to assess any longer-term benefits.

It was with an eye on the cardiovascular effects of Type 1 diabetes that the JDRF-sponsored REducing Lesions (REMOVAL) trial was created. This double-blind, placebo-controlled trial was carried across more than 20 hospital diabetes clinics in five countries. Metformin was chosen as the intervention because of existing evidence of its ability to reduce HbA1c and to decrease cardiovascular disease in Type 2 diabetes. The progression of the primary outcome – mean carotid artery intima-media thickness (cIMT) – was not significantly reduced with metformin and there were only minor effects on HbA1c and insulin requirement. However, the reduction in weight, LDL cholesterol and the tertiary outcome of maximal cIMT indicated that metformin may have a wider role in cardiovascular risk management.

Professor John Petrie from the University of Glasgow and the principal investigator on the REMOVAL study says: “The American Diabetes Association’s new Standards of Medical Care in Diabetes now list these effects of metformin in Type 1 diabetes, while noting that metformin is not FDA approved for use in these patients. This is being interpreted by some diabetologists as qualified support for using metformin in Type 1 diabetes, but more research is needed to clarify the longer term effects of metformin in the condition.”

**Metformin and ageing**

As the science behind the ageing process continues to be unravelled, there is a dawning realisation that ageing can be targeted. Research is demonstrating that certain drugs like aspirin and acarbose can, for example, extend lifespan in male mice. Humble metformin is now also being touted as one to watch.

Biguanides like metformin can increase the lifespan of the nematode, C. elegans, by approximately 26 per cent compared with controls in a dose-dependent manner. However, the drug has the opposite effect in Drosophila. Although at lower concentrations, it has no effect, at higher doses, it actually resulted in a dose-dependent decrease in lifespan. And in rodent models, there is significant variation with increases, decreases and no change having already been reported in the literature. In humans, however, the jury is still out and research needs to be done to determine if, and at what dose, metformin could perhaps reverse the signs of premature ageing in humans.

Professor Nir Barzilai, Director of the Institute for Aging Research at the Albert Einstein College of Medicine in New York, is spearheading the possibility of using metformin in this way. He explains: “The Targeting Aging with Metformin study is a double-blind placebo-controlled trial of metformin that will run for six years in a diverse population of approximately 3,000 men and women without diabetes aged between 65 and 80 years old. There are several end points that we will be investigating which can be categorised as clinical, functional and biological.”

These aims will capture whether...
metformin can prevent the incidence of a new age-related chronic disease like cardiovascular disease, cancer or dementia and test whether metformin alters a panel of biomarkers selected to assess biological hallmarks of ageing. Although the study has yet to start, there is palpable excitement that a drug that has been approved by the Food and Drug Authority in the USA for more than 50 years could actually help to modify the ageing process in humans.

Other possibilities

It appears that there is no end to metformin’s talents as it is not just in the cancer, Type 1 diabetes and ageing fields that it is auditioning for a role.

The drug is already widely used during pregnancy in women with polycystic ovary syndrome (PCOS). The most common endocrine disorder in women of reproductive age, women with PCOS are more likely to suffer pregnancy-related problems compared with healthy women. Metformin during such pregnancies can reduce certain pregnancy-related problems compared with PCOS are more likely to suffer certain complications like gestational diabetes (GDM) and gestational hypertension in these women, but more research is needed.

And, although its use is still controversial, guidelines in several countries, including Australia and Portugal, recommend metformin in cases of GDM. “Several large studies have indicated that outcomes from metformin use in GDM are no worse than insulin and user satisfaction surveys indicate that women also prefer taking metformin to insulin injections,” explains Dr Elisabeth Qvigstad from Oslo University Hospital in Norway. Although the use of metformin in animal studies has suggested gonadal function issues like smaller testes and fewer Sertoli cells in male offspring, to date, no human studies have demonstrated similar problems. “As a word of caution, however, it’s important to note that we don’t yet have any long-term follow-up studies to confirm this,” continues Dr Qvigstad. “So far, only data from prepubertal boys are available. Hence, long-term follow-up of metformin-treated offspring is necessary to ascertain gonadal effects or whether there are, for example, cardiovascular problems that are picked up later in life.”

Recently, metformin has also been implicated as a potential treatment for arteriogenic erectile dysfunction. This is caused by endothelium-dependent vasodilatory impairment, sympathetic nerve activity elevation and atherosclerotic luminal narrowing.

And all of these have been linked to insulin resistance, perhaps making an insulin-sensitising drug like metformin the perfect solution.

Conclusion

It would appear that, despite no one being 100 per cent certain about how metformin works, it being long off patent and costing just a few pounds per tablet, this wonder drug has much still to give – and not just to the diabetes world. It is not without its detractors though. Everyone is aware of its side effect profile – the most frequently reported being gastrointestinal issues. But, as big pharma moves relentlessly forward, it would be easy to sweep metformin to one side as a drug that has had its day. However, there are few, if any, drugs that have commanded an entire edition of a journal being dedicated to it.

There are new lifelines with research into its effects on cancer. Type 1 diabetes and ageing represent perhaps just the tip of the iceberg. And there is possibility of reinventing metformin as part of a ‘polypill’ with, for example, aspirin and a statin or rolled up with its new counterparts in the diabetes market like SGLT-2 inhibitors. Either way, there’s a very good chance that metformin is here to stay.

REFERENCES:

1. www.who.int/topics/essential_medicines
11. Anisman VN (2013). Metformin: do we finally have an anti-aging drug? Cell Cycle12 (22); 3483–3489
15. 60 years of metformin use: a glance at the past and a look to the future. Diabetologia 2017 60 (9)