

Metformin: myths, misunderstandings and lessons from history

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Clinical trials of new drugs may overstate efficacy and not identify adverse effects. It is therefore unusual for the passage of time to reveal that a drug is less toxic, has greater efficacy and a wider range of uses than first claimed. For decades metformin was misunderstood, vilified and banned in many countries, but it is now one of the most prescribed drugs in the world. In 2010 there were more than 100 million prescriptions worldwide for metformin, alone and in combination tablets.

Metformin was developed from a herb, *Galega officinalis**, which was used for centuries to treat many ailments including polyuria. It is a rich source of the toxic substance guanidine. A less toxic alkaloid, galegine, was identified in France just before World War I. Its pharmacology and toxicology were studied in Paris and its structure was identified in Edinburgh. In 1922 metformin (dimethyl biguanide) was synthesised in Dublin and shown to lower blood glucose with fewer gastrointestinal adverse effects than its predecessors. However, in the same year insulin was used for the first time, distracting interest from other glucose-lowering drugs.

In Paris in 1957 metformin, by then called glucophage ('glucose eater'), was studied in trials and shown to lower blood glucose in patients with type 2 diabetes, but not in people without diabetes. Unlike sulfonylureas, metformin did not stimulate insulin release, but increased its peripheral uptake and also reduced the release of glucose from the liver. Metformin had gastrointestinal adverse effects which

could be minimised by a 'start low, go slow' approach to dosing.

Also in 1957 an American group published similar results for phenformin (phenylethyl biguanide). Phenformin was energetically marketed worldwide by Ciba-Geigy, but by 1959 an association with lactic acidosis was reported. Unfortunately, this report generated little interest. In contrast, metformin was manufactured by a small French company and, among developed countries, was only the preferred biguanide in France and Scotland.

In the 1970s the number of reports of phenformin-related lactic acidosis and deaths increased. In 1977 it was removed from the market in the USA and also withdrawn from many other countries. The Australian Drug Evaluation Committee recommended severe restrictions on both phenformin and metformin in spite of the different pharmacokinetics of the two drugs. Phenformin is metabolised by the liver and accumulates in patients with a genetic deficiency of the enzyme cytochrome P450 2D6. Metformin is renally excreted and all serious reports of its association with lactic acidosis and deaths are in overdoses or in people with advanced renal failure.¹

Endocrinologists in France and Scotland, who had considerable experience of using metformin safely, continued to prescribe it extensively. In 1968² and 1977³ Scottish studies comparing metformin with chlorpropamide found that glucose control was the same with both drugs, but patients on metformin had less hypoglycaemia and lost weight, while those on the sulfonylurea gained weight. In spite of similar findings published in leading journals, it took the rest of the world a very long time to reach the same conclusions because of unwarranted fears of lactic acidosis. In 1995 the benefits of metformin were rediscovered in the USA⁴ and restrictions were eased in Australia.

Of the many subsequent studies perhaps the most influential has been the UK Prospective Diabetes Study.⁵ This was a randomised, multicentre, parallel group trial of 3867 patients over 10 years. Independently of blood glucose control, metformin

From the Editor



While prescribers are alert for drug-drug interactions, patients may be more interested to know if they can drink alcohol with their medicine. Graham Vernon reviews some drug interactions that consumers are concerned about, and Helen and John Conaglen discuss some of the drugs which can cause sexual dysfunction.

Many people consume nutritional supplements, but these are not always necessary. Serena Parker, Patrick Hanrahan and Claire Barrett consider the harms and benefits of folate.

Concern about the harmful effects of metformin restricted its use for many years. Gillian Shenfield reflects on how this misunderstanding delayed metformin becoming a first-line drug for type 2 diabetes.

* known by many other names including goat's rue, Spanish sanfoin, false indigo, Italian fitch, French lilac and professor-weed

reduced the risks of myocardial infarction and all-cause mortality. As a result metformin became the first-choice treatment for obese patients with type 2 diabetes. Later subgroup analyses showed that it had similar vascular protective effects in all patients, but it took another decade for these findings to be translated into official recommendations. In 2012 diabetes experts in the USA and Europe⁶ declared that metformin is the drug of first choice for all patients with type 2 diabetes. The Australian National Health and Medical Research Council is considering a similar recommendation.

The story is not yet over. Nephrologists believe metformin is underused in kidney disease. Metformin is now also used to treat polycystic ovary syndrome, gestational diabetes and is showing early promise as a treatment for cancer. Recent meta-analyses controversially suggested that metformin may not prevent macrovascular disease⁷, however the risk of cardiovascular events with metformin may be less than with sulphonylureas⁸.

There are many lessons from this saga:

- it takes a very long time to collect good population efficacy and safety data
- medications can produce more benefits and harms than first claimed
- drugs marketed by large pharmaceutical companies dominate the market⁹ and using new drugs with limited, short-term data from restricted trial populations is a risky activity
- wider understanding of pharmacodynamics and pharmacokinetics could prevent the belief that all drugs in a chemical group have the same actions and adverse effects
- the long delay of translating evidence into practice is occurring with other medicines such as aspirin for preventing cardiovascular disease. ◀

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Letters to the Editor

Complementary medicines

Editor, - I work regularly in a large public hospital anaesthetic preadmission clinic. I am no longer surprised at how many patients take expensive complementary medicines with little or no validation of their efficacy - for example fish oil to improve vision, ginkgo for Alzheimer's disease, coenzyme Q for cardiac failure. Some patients are on over 10 different products! Can someone please explain the lack of government regulation?

My concerns regarding complementary medicines (and I include here all the usual suspects such as herbals, minerals and vitamins) are:

- some are expensive and could exhaust patients' limited budgets
- some, in fact, may do no good at all or at least there is minimal evidence they do good
- some patients maintain adverse lifestyle choices because they felt, or wanted to believe,



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