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# New oral agents for type 2 diabetes

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During the past half-century, oral antidiabetic drugs have played a major role in the treatment of type 2 diabetes. First came the biguanides, ie phenformin, metformin and buformin, and the first generation of sulphonylureas, ie tolbutamide, chlorpropamide and tolazamide.[1] It is a testament to their efficacy and safety, if used appropriately, that both classes are used extensively even today. Modern sulphonylureas offer easier dosing regimens, improved safety profiles and a minimal risk of idiosyncratic reactions; as a consequence, these have largely replaced the progenitors. Metformin (dimethylbiguanide) is now the only biguanide currently in use in the UK, phenformin (phenylethybiguanide) having been withdrawn in the 1970s due to an unacceptable risk of lactic acidosis.[2] The United Kingdom Prospective Diabetes Study (UKPDS), which reported its findings in 1998, bolstered the role of metformin. The drug was unique in significantly reducing myocardial infarction and diabetes-related deaths in overweight and obese patients randomised to the drug as monotherapy.[3] Various modified release preparations of metformin and some sulphonylureas as well as fixed-dose combinations of these and other agents have become available in recent years.

So what is new in the armoury of oral drug treatment for type 2 diabetes? Three new classes of oral antidiabetic drugs shown below have been introduced in the last decade or so.[4]

- *α–glucosidase inhibitors.* These agents retard the absorption of carbohydrates by inhibiting brush border enzymes of the small intestine, their greatest affinity being for glycoamylase. Acarbose, a pseudo-tetrasaccharide, was introduced in the UK in the early 1990s and remains the only example of this class available in this country; miglitol and voglibose are available elsewhere. Acarbose failed to take off in the UK largely because of unpleasant – and rather antisocial – gastrointestinal side effects allied to glucose-lowering effects that are generally accepted as being inferior to other oral antidiabetic agents.[5] On the positive side, acarbose has a good safety profile, reflecting low (<2%) systemic absorption of the drug. A recent multinational clinical trial of acarbose created a stir in the diabetes community: not only did acarbose retard the progression from impaired glucose tolerance to type 2 diabetes in high-risk subjects, the incidence of myocardial infarction and new cases of hypertension were also apparently reduced when compared with placebo.[6] However, the study has attracted criticism for failings in design and analysis[7] and a renaissance for acarbose seems unlikely.
- *Rapid-acting insulin secretagogues.* These agents, sometimes called meglitinide analogues, provide an alternative to sulphonylureas. By causing prompt and relatively short-lasting release of insulin from islet beta-cells, repaglinide and nateglinide preferentially reduce the rise in postprandial glucose concentrations.[8] The drugs offer a low risk of severe hypoglycaemia and flexibility for patients whose mealtimes are unpredictable. However, they are expensive compared with generic sulphonylureas and their use necessitates multiple daily dosing. Neither has been enthusiastically embraced in the UK.
- *Thiazolidinediones.* Also known as glitazones, these drugs arrived as the mammoth enterprise that was the UKPDS was coming to a close. These drugs have made the greatest impact on clinical practice of the three classes, but they have generated a fair amount of controversy along the way. Thiazolidinediones are synthetic agonists for the nuclear receptor peroxisome proliferator-activated receptor (PPAR)-gamma, the role of which in human metabolic

disease is now well established.[9] Excitement about a new class of drugs that target a fundamental biochemical defect in type 2 diabetes, ie impaired insulin action, was rapidly tempered by the withdrawal of troglitazone from the UK market after only a few weeks. The reason? Idiosyncratic hepatotoxicity, sometimes fatal or requiring liver transplantation. Fears that this devastating side effect might extend to other agents in this class (rosiglitazone and pioglitazone) have now been firmly refuted,[10] only for another major safety concern to rear its head. There has been much debate about the potential for drug-induced fluid retention precipitating heart failure in patients with a compromised myocardium.[11] The risks of fluid retention appear greatest when thiazolidinediones are combined with insulin, this combination being contraindicated in Europe until very recently. The issue of fluid retention came to a head recently with another controversial clinical trial that examined the effects of pioglitazone on secondary prevention of cardiovascular disease in patients with type 2 diabetes.[12] The study led to a rapid polarisation of views about the net benefits of the drug.[13] The trial demonstrated a cardioprotective effect of pioglitazone along with other clinically important benefits for high-risk patients; the higher incidence of heart failure with pioglitazone did not result in an excess of deaths.

What of the future? Daily clinical experience tells us that more efficacious drugs are required. The scene is set for further interesting developments such as a new class of oral agents – the dipeptidyl peptidase-4 (DDP-4) inhibitors – that increase plasma levels of the insulinotropic gut hormone glucagon-like peptide 1 without inducing further weight gain.[14] Lack of effective strategies for tackling obesity is a major shortcoming in the prevention and treatment of type 2 diabetes. The first in yet another new class of agents – the selective cannabinoid receptor antagonist, rimonabant – was licensed in June 2006. Rimonabant offers the prospect of attenuating one of the major drivers to insulin resistance, type 2 diabetes and cardiovascular risk, ie central obesity.[14] Improvements in waist circumference, lipid profiles and glycaemic control have been reported,[14,15] in concert with a potential reduction in nicotine dependency. High drop-out rates, however, make some of the data from some clinical trials difficult to interpret. Additional evidence from clinical practice should help clarify the therapeutic role of rimonabant. Care is needed in patients wth a history of depression.[15]

With type 2 diabetes affecting increasing numbers of ever younger subjects who face a lifetime of exposure to risk factors for vascular disease[16] the safety of new antidiabetic drugs must remain a paramount consideration. The recent discontinuation of several dual PPAR-alpha/gamma agonists (glitazars) during late stages of development will resonate with diabetologists senior enough to recall the history of phenformin, and more recently, troglitazone. Modulating PPARs or other types of nuclear receptor[14] could also carry long-term risks to humans that are difficult to predict.

## Competing interests

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