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Title **Newer Agents for Blood Glucose Control in Type 2 Diabetes: Systematic Review and Economic Evaluation**

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Aim

To review the newer agents available for blood glucose control in type 2 diabetes: the glucagon-like peptide-1 (GLP-1) analogue, exenatide; dipeptidyl peptidase-4 (DPP-4) inhibitors, sitagliptin and vildagliptin; the long-acting insulin analogues, glargine and detemir; and to review concerns about the safety of the thiazolidinediones.

Conclusions and results

Clinical effectiveness. Exenatide and the gliptins are clinically effective in improving glycemic control. Exenatide improved glycemic control by around 1%, with the added benefit of weight loss. The gliptins were effective in improving glycemic control, reducing HbA1c level by about 0.8%, and were weight neutral. Glargine and detemir were equivalent to Neutral Protamine Hagedorn (NPH) insulin (and to each other) in terms of glycemic control, but had modest advantages in terms of hypoglycemia (especially nocturnal). Detemir, used once daily, appeared to cause slightly less weight gain than glargine, but the clinical significance was doubtful, and a slightly higher dosage was required. The glitazones can cause heart failure and fractures, but rosiglitazone appears to slightly increase the risk of cardiovascular events whereas pioglitazone reduces it. Eight trials examined the benefits of adding pioglitazone to an insulin regimen; in our meta-analysis, the mean reduction in HbA1c level was 0.54% (95% confidence interval [CI] −0.70 to −0.38). Hypoglycemia was marginally more frequent in the pioglitazone arms (relative risk [RR] 1.27, 95% CI 0.99 to 1.63). In most studies, those on pioglitazone gained more weight than those who were not.

Costs and cost effectiveness. Since glargine and detemir appeared to have only slight clinical advantages over NPH, but have much higher costs, they did not appear to be cost effective as first-line insulins for type 2 diabetes. Hence, the recent NICE guidelines recommended that NPH should be the preferred first-line insulin in treating type 2 diabetes. Neither did exenatide appear to be cost effective compared to NPH, but when used as third drug after failure of dual oral combination therapy, exenatide appeared cost effective compared to immediate glargine. The gliptins are similar to the glitazones in glycemic control and costs, and appeared to have fewer long-term side effects. Comparisons of sitagliptin and rosiglitazone, and of vidagliptin and pioglitazone, slowed clinical equivalence in terms of quality-adjusted life-years (QALYs), but the gliptins were marginally less costly. In terms of annual drug acquisition costs (in 2008), the gliptins were the cheaper of the new drugs, with annual costs of between 386 and 460 pounds sterling (GBP). Exenatide was more expensive, with an annual cost of around GBP 830. The cost of NPH insulin was much lower than the cost of glargine and detemir. Exenatide and the gliptins are useful additions to diabetes treatments.

Methods

See Executive Summary link www.hta.ac.uk/project/1743.asp.

Further research/reviews required

More economic analysis is required to establish when it becomes cost effective to switch from NPH to a long-acting analogue. Long-term follow-up studies of exenatide and the gliptins are needed to confirm safety and to provide data on how long they are efficacious in a progressive disease. The combination of insulin and GLP-1 analogue therapy appears logical, and trials are required. More research is needed on how to motivate people with type 2 diabetes to lose weight.

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