



Systematic review

For type 2 diabetes poorly controlled by metformin monotherapy, the addition of any non-insulin antidiabetic drug reduces HbA1c to a similar extent, but with differing effects on weight and hypoglycaemic risk

Srikanth Bellary

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Heartlands Biomedical Research Centre

Correspondence to:

Srikanth Bellary
Heart of England NHS Foundation Trust, Bordesley Green East, Birmingham B95SS, UK; srikanth.bellary@heartofengland.nhs.uk

Commentary on: **Phung OJ**, Scholle JM, Talwar M, *et al.* Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* 2010;**303**:1410–18.

Context

Current guidelines recommend metformin as initial therapy in patients with type 2 diabetes.¹ With time, as β cell function declines, most patients require additional therapy.² While there is now an expanding list of drugs available to be used as second-line agents, studies that directly compare the efficacy of these agents are lacking.¹ The choice of a second-line agent is, therefore, less clear. In this meta-analysis, Phung and colleagues address this important issue and evaluate the efficacy of currently available non-insulin diabetes therapies.

Methods

The investigators used a combination of traditional and mixed-treatment comparison meta-analysis approach to evaluate the glycaemic and non-glycaemic effects of the different classes of drugs. Studies were identified using a systematic literature search of MEDLINE and Cochrane databases from 1950 to January 2010. Only parallel-design randomised controlled trials (RCT) that evaluated the combination of non-insulin hypoglycaemic agents in patients poorly controlled on stable doses (at least 1500 mg/day) of metformin and were in treatment for 12–52 weeks duration were included. Outcome measures included changes in HbA1c, achievement of target HbA1c <7%, hypoglycaemic episodes and changes in weight. Weighted mean differences (WMD) for changes in HbA1c and body weight from baseline and RR with 95% CIs were calculated using mixed-treatment comparison analysis. All data were independently abstracted by two investigators. Heterogeneity and methodological quality of studies were assessed using validated techniques.

Findings

A total of 27 RCTs met the inclusion criterion ($n=11\ 198$ participants; age range 53–62 years; mean trial duration 32 weeks). All classes of drugs had comparable glucose-lowering effects (HbA1c reductions 0.64–0.97%) and demonstrated similar efficacy in achieving HbA1c targets of <7% (RR 2.25–3.20 compared to placebo). Significant differences in non-glycaemic effects were

observed between the different classes. Favourable effects on weight were observed with glucagon-like peptide-1 (GLP-1) analogues (WMD -1.74 kg; 95% CI -3.11 to -0.48 kg), dipeptidyl peptidase-4 (DPP4) inhibitors (-0.14 kg; 95% CI -0.94 to 0.63 kg) and α -glucosidase inhibitors (AGI) (-1.80 kg; 95% CI -3.79 to 0.21 kg). In contrast, weight gain was more noticeable with sulfonylureas (2.06 kg; 95% CI 1.15 to 2.96 kg), glinides (1.77 kg; 95% CI 0.46 to 3.28 kg) and thiazolidinediones (2.08 kg; 95% CI 0.98 to 3.17 kg). There was a significantly greater risk of hypoglycaemia associated with sulfonylureas (RR 4.57; 95% CI 2.11 to 11.45) and glinides (RR 7.50; 95% CI 2.12 to 41.52) treatment.

Commentary

The treatment algorithm suggested by the joint ADA/EASD guidelines has drawn much criticism for not giving much consideration to some of the newer therapies used in diabetes management.³ Several new therapies have been available for treatment of type 2 diabetes in recent years, and experience with some of these agents has increased steadily during this time.^{4,5} Although these agents have been shown to be effective in clinical trials, studies that compare them with some of the established therapies are lacking. The meta-analysis by Phung and colleagues comparing all existing non-insulin diabetes therapies is timely and attempts to highlight the glycaemic and non-glycaemic differences between them. The results of this meta-analysis show that the glucose-lowering effects of all the different classes are comparable when used in combination with metformin. What do these results indicate? First, they offer the healthcare professionals and patients greater choice in making treatment decisions to achieve tight glycaemic control. Such a choice is extremely important, given that the risks and needs of each patient are very different. Second, it allows the health professionals to recommend a different combination if a particular drug is not well tolerated, without necessarily compromising on glycaemic control.

Most guidelines recommend a target HbA1c of less than 7%.⁶ Achieving these targets without increasing the risk of hypoglycaemia or causing weight gain has been a major challenge until recently. Obesity is a major risk factor for cardiovascular disease, and even modest weight loss

is associated with significant benefits for most patients.⁷ Similarly, frequent hypoglycaemic episodes are unpleasant and a major cause of morbidity in the older people.⁸ In this context, the non-glycaemic effects of some of the newer therapies may offer specific advantages.⁴ The risk of hypoglycaemia was noticeably lower with thiazolidinediones, AGI, DPP4 inhibitors and GLP-1 analogues compared to sulfonylureas and the glinides; whereas the DPP4 inhibitors and the AGI had neutral effect on weight, weight loss associated with GLP-1 analogues was highly significant. These attributes would clearly favour the use of these agents early on in diabetes treatment pathways and particularly those obese and the older people. It must, however, be emphasised that these expectations must be balanced against the knowledge that the long-term safety of these agents is still unknown. Past experience indicates that any enthusiasm for the new therapies must also be accompanied by a degree of caution.⁹

The study has the obvious weaknesses of a meta-analysis and is also limited by the fact that other factors such as contraindications, effects on other risk factors and cost of therapy are not evaluated. These factors are important when making treatment decisions and could be addressed in future studies. Despite these limitations, the findings of this study have practical implications for diabetes management. They provide clinicians with more number of therapeutic options than that presently suggested by the guidelines and the much-needed evidence concerning diabetes treatments.

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