New therapeutic agents: Challenges and opportunities

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Primary care diabetes teams need no reminder that they operate in a therapeutic paradox. We have good evidence for the importance of maintaining tight glycaemic control (UKPDS Group, 1998) and now, through the nGMS contract, a financial incentive to do so. Yet helping our patients with type 2 diabetes achieve tight targets can be a challenging process: involving prescribing combinations of hypoglycaemic agents; negotiating side effects with patients; and trying to ensure adherence to increasingly complex regimens. Against this background, the imminent availability of newer hypoglycaemic agents is both welcome in expanding our therapeutic armamentarium, but also adds a further layer of complexity to already challenging prescribing scenarios.

This issue of *Diabetes & Primary Care* includes clear descriptions of the mode of action of the incretin mimetics and DPP-IV inhibitors and advice on where and how to use them (Munro et al, 2007; see page 72). Underpinning their action is the incretin effect. With this effect, when the insulin response to oral and intravenous glucose loads is compared, an enhanced response is seen with oral glucose (Elrick et al, 1964). Although this effect was identified many years ago, it is only recently that its therapeutic potential has been realised, with the development of drugs that can mimic the action of GLP-1 or stop its breakdown.

The incretin mimetics have the apparent disadvantage of being administered subcutaneously, but this may increase the confidence of primary care teams in initiating and prescribing injectable agents. They have the advantage of inducing satiety and therefore weight loss. These characteristics have certainly enhanced their popularity in the US, where there is approximately 1 year's experience of their use. They also commonly cause nausea, but the weight loss and other therapeutic effects are said to be independent of this.

The other new class of agents, the dipeptidyl peptidase-IV (DPP-IV) inhibitors, work by blocking DPP-IV-mediated inactivation of glucagon-like peptide 1 (GLP-1). This, in turn, results in prolongation of endogenous GLP-1 activity, with higher plasma levels being achieved in vivo. The DPP-IV inhibitors, also known as gliptins, can be given orally, and although they do not appear to promote the same weight loss as the GLP-1's, they seem to be better tolerated and may act synergistically with metformin.

The imminent availability of these new therapeutic options raise questions for primary care teams to ponder in the meantime. The recently published ADA/EASD guidelines (Nathan et al, 2006) are now becoming accepted in practice, but were developed before these products became available. Where will these new agents fit into these guidelines? Will the incretin mimetics be used before or instead of long acting analogue insulins? Will the gliptins only be used alongside metformin and the glitazones? Will these drugs be as useful in practice as the phase III trials suggested, or will they prove more difficult to initiate and maintain in practice? Over the past 10 years, other new agents have been used and evaluated by primary care teams. Some have proved practical and effective and have achieved widespread adoption, while others have been rejected. Only time will tell whether these new agents will prove their worth in practice.

Next year will see a revision of the NICE guidance on oral hypoglycaemic agents (NICE, 2002). NICE has a reputation for favouring generic agents, which potentially offer better value for money and on occasion, a more developed evidence base. In the absence of technical appraisals of these new agents, it is unlikely that they will figure in the updated guidance. In turn, there will be debate about whether they will be allowed to appear in practice formularies.

Diabetes teams have much to think about over the next year. The limitations of existing products means that new products will be welcomed, at least initially. Ultimately, people with diabetes will benefit as they are encouraged and become empowered to achieve the tight therapeutic targets recommended in contemporary guidance. ■