Prescribing challenges in diabetes

Colin Kenny
GP in Dromore, County Down, Northern Ireland

Safe and effective prescribing in diabetes care has always been a challenge for primary care teams, but an additional layer of complexity has been added to these prescribing decisions in the past few months. A potential scare about established drugs in widespread use is always a cause for concern. In this edition of the journal, we present a Primary Care Diabetes Society (PCDS) Committee statement about the safety of incretin-based therapy.

We know that adherence to diabetes drug regimens can be suboptimal, but how often do we ask the people we see with diabetes about what they are taking in addition to their prescribed medication? In this edition, we review the potential for harm from additional, often herbal, agents that our patients may be taking. We also return to the new sodium–glucose cotransporter 2 (SGLT2) inhibitor class of drugs and explore frequently asked questions, covering the first available product as well as examining the pipeline of other emerging agents in this class.

Incretin-based therapy – thoughts on the potential safety concerns

On 10 June, Channel 4 aired a *Dispatches* documentary in the UK about the safety record of glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors in the treatment of type 2 diabetes. The programme suggested that there might be an increased risk of pancreatitis and pancreatic cancer with these drugs. The documentary research was carried out by an investigative journalist from the BMJ Group, who followed up the documentary with the publication of a detailed report calling into question the pancreatic safety of these drugs (Cohen, 2013). The Channel 4 documentary, in my experience at least, caused concern among people with diabetes, and the PCDS Committee published a statement on its website to help primary care teams deal with concerned individuals. In this edition of the journal (starting on page 180), you can read the Committee's statement, which has been updated to take account of subsequently published comment and reports from the European Medicines Agency and US Food and Drug Administration.

What does the evidence tell us? The Channel 4 programme and BMJ investigation named one GLP-1 receptor agonist and one DPP-4 inhibitor as being associated with an increased risk of pancreatitis, and people following the coverage could have been left with the impression that this was a new finding. In fact, the potential link between these therapies and pancreatitis has been known for several years and is reflected in current Summaries of Product Characteristics (available from: http://medicines.org.uk/emc/). The PCDS Committee's statement reinforces the need for thoughtful engagement with the person with diabetes and accurate questioning about risk factors for pancreatitis, or previous history of the disease, and suggests empowering the patient through shared decision-making by acknowledging the risks of such therapy.

Patients expect risks to be clearly demarcated, whereas we know it is often not completely clear-cut. This investigation drew heavily on a study involving a small number of pancreatic tissue samples from organ donors with and without diabetes, demonstrating pre-cancerous cellular changes, called pancreatic-duct metaplasia, in people with type 2 diabetes treated with incretin-based therapies (Butler et al, 2013). The evidence seems to be confounded by a recent study showing a reduction in beta-cell mass in rodents treated with GLP-1 receptor agonists (Ellenbroek et al, 2013) rather than an expansion of endocrine pancreatic tissue, as demonstrated by Butler et al.

PCDS members will be aware of a number of drug scares during recent times, in different therapy areas, some of which have led to agents being withdrawn. The person with diabetes is at the forefront of the PCDS's mission statement and therefore the PCDS Committee will monitor all emerging evidence carefully, and update this statement if new evidence emerges. Based on the information available to date, however, the Committee recommends that primary care teams do not need to alter their approach to incretin-

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based therapies, other than engaging carefully with people with diabetes about the risk of pancreatitis, as should already be occurring.

Medication taken in addition to prescribed therapy

In this edition of the journal, we publish an important article (starting on page 193) that has been prepared by the *Stockley's* team on the topic of drugs and supplements that patients may be taking in addition to prescriber-recommended therapy. The article outlines a growing market for herbal medication as demonstrated by global sales of the products. Interestingly, the reporting on incretin-based therapy is largely based on published trials from the pharmaceutical companies themselves. There are very few such trials of herbal products – in part, perhaps, because the public considers them to be safe on face value alone. The authors of the article urge healthcare professionals to be cautious when advising patients on the use of herbal products, if they are already taking conventional medicines. This is particularly important where such drugs have a narrow therapeutic window, or where it is necessary to keep concentrations of the drug, or its pharmacological effect, within a specific range. Understanding the pharmacology of the herbal products involved may alert us to potential adverse effects. Drug interactions with herbal products are particularly likely in older people or those with long-standing diabetes because of reduced liver and renal function.

In a linked comment piece (on page 170), Gilani urges active questioning of people with diabetes about additional therapies that they are taking, particularly if interactions are a concern, and emphasises that these products can be popular in some ethnic minority groups in the UK.

The SGLT2 inhibitor drug class

In June, NICE (2013) published its technology appraisal for dapagliflozin, the first SGLT2 inhibitor to gain a licence in the UK. This agent is recommended by NICE for use in dual therapy regimens in combination with metformin, if it is used as described for DPP-4 inhibitors (NICE, 2009), in adults with type 2 diabetes. Dapagliflozin is also recommended for use in combination with insulin in treating type 2 diabetes. Monotherapy with the drug is not recommended, and triple therapy with metformin and a sulphonylurea is also not recommended except as part of a clinical trial.

In this edition of the journal, Munro et al return to answer prescribers' frequently asked questions on this new class (starting on page 172). The authors appraise the derivation of the class, outline ongoing research programmes and discuss late-stage pipeline agents. Reassuringly, they suggest that studies show there to be a lower incidence of genital infections than might be expected from the mechanism of action of the drugs. The potential for weight loss is discussed, as are the various licences obtained to date on an international level.

Emerging algorithms

Primary care teams accustomed to NICE (2009) and SIGN (2010) guidelines for prescribing in type 2 diabetes will be familiar with the somewhat complex algorithms for the initiation and escalation of antidiabetes therapy. In the person with diabetes, generally speaking, metformin is the first-line therapy, with a sulphonylurea second in both these algorithms. Additional therapy beyond this has a number of caveats depending on licences. Additional newer agents add a further layer of complexity to this. Interestingly, the European Association for the Study of Diabetes and American Diabetes Association's joint guidance is less prescriptive, and can be individualised according to the patient (Inzucchi et al, 2012). It will be interesting to see how these algorithms develop with time. However, fundamental principles of safety and efficacy remain paramount, in what have now become complex and detailed prescribing decisions.

These are challenging times in which to be delivering diabetes care, with newly launched drugs, additional possible side effects of established drugs, multiple potential co-morbidities and the increasing complexity of guidelines. However, all of these factors also encourage us to think carefully and individualise care, ensuring that we choose the right drug for the right person. This is something that must ultimately improve the quality of the care we provide. ■

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