

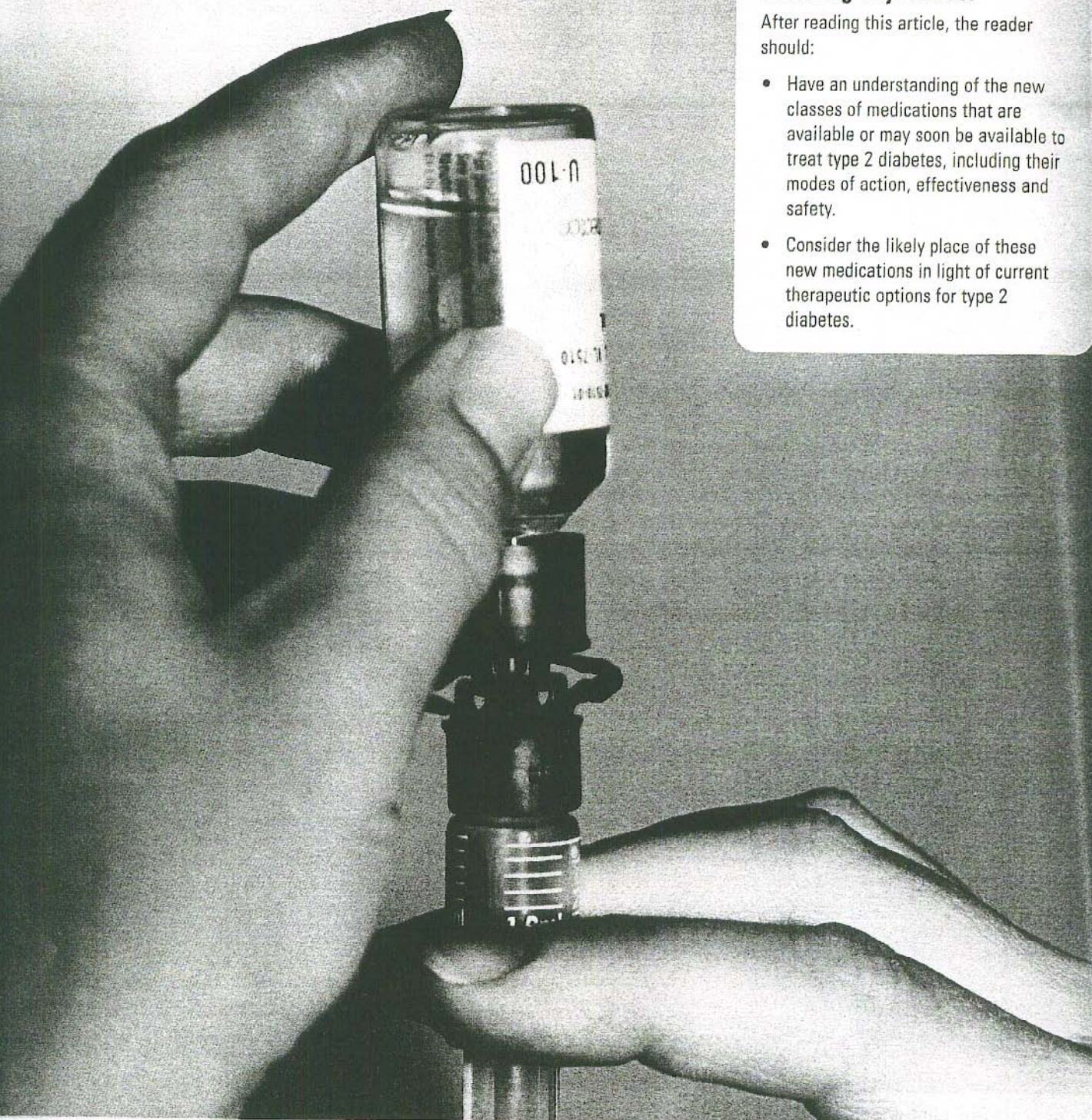
New medications to treat type 2 diabetes

By Dr Luke Bereznicki and Professor Gregory Peterson

Learning objectives:

After reading this article, the reader should:

- Have an understanding of the new classes of medications that are available or may soon be available to treat type 2 diabetes, including their modes of action, effectiveness and safety.
- Consider the likely place of these new medications in light of current therapeutic options for type 2 diabetes.



Introduction

The number of Australians with type 2 diabetes has tripled since 1981 and continues to increase. It is projected that 1.6 million Australians will have type 2 diabetes by 2030.¹ Effective treatment of hyperglycaemia is a priority, given that strict glycaemic control reduces the microvascular complications of type 2 diabetes.^{2,3} Epidemiological data from the UK suggests that improving glycaemic control will also reduce the risk of macrovascular complications (e.g. cardiovascular disease),⁴ although this is controversial and it is recognised that improving glycaemic control is only one of a number of possible strategies to reduce the macrovascular risk associated with diabetes. Health professionals involved in the management of diabetes should focus on blood pressure management, cholesterol lowering and the use of low-dose aspirin as means of reducing cardiovascular risk, as well as control of blood glucose.⁵ The treatment of hyperglycaemia in type 2 diabetes is complicated, and combination hypoglycaemic therapy is often required to achieve and maintain target blood glucose levels. Unfortunately, recent Australian data suggests that target glycated haemoglobin (HbA_{1c}) levels are achieved in only 30-50% of type 2 diabetics who are managed in the primary care setting.⁶⁻⁸ The focus of this article is to review the evidence for the latest medications to emerge in the battle to manage hyperglycaemia in type 2 diabetes.

A range of options

The pathogenesis of diabetes has been traditionally characterised by absolute or relative loss of pancreatic β cell function and insulin deficiency or tissue resistance.⁹ More recently, it has become clear that additional pancreatic and gut hormones play an important role in glucose homeostasis. These hormones now provide additional therapeutic targets for medications to treat hyperglycaemia associated with diabetes. Table 1 lists the main characteristics of medication classes that are or may soon be available to treat type 2 diabetes. The Food and Drug Administration (FDA) approved the incretin mimetic exenatide in the US in 2005. Last year exenatide gained approval in Australia as adjunctive therapy for patients who have not achieved adequate glycaemic control with metformin, a sulfonylurea, or both. Pramlintide, an injectable synthetic hormone that resembles human amylin, was also approved by the FDA in 2005. In 2006, the FDA approved the first oral incretin enhancer, sitagliptin, for use as monotherapy or in combination with metformin or a thiazolidinedione for type 2 diabetes. Sitagliptin (*Januvia*) was registered by the Therapeutic Goods Administration as a combination therapy with metformin, a sulfonylurea or a thiazolidinedione in December 2007. The first inhaled insulin to market, *Exubera*, was withdrawn from the US market in October 2007 due to poor sales. However, other inhaled insulin products are in the

advanced stage of clinical trials and are likely to be approved in the US in the near future.

Incretin therapy

The incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose in the gastrointestinal tract.¹⁰ This theory is based on the observation that an oral dose of glucose causes more insulin secretion than the same amount given intravenously. Improved understanding of this effect has led to the development of new antidiabetic agents. The incretin effect results primarily from the actions of two peptides, glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide 1 (GLP-1).¹⁰ Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP4), resulting in a short half-life.¹⁰ The action of this pathway appear to be diminished in type 2 diabetes, making the pathway a target for novel pharmacologic agents.¹¹ GLP-1, in addition to potentiating glucose stimulated insulin secretion, also inhibits glucagon secretion, retards gastric emptying and reduces appetite. In animal studies, GLP-1 stimulates proliferation of β cells and inhibits their apoptosis,¹² an encouraging finding that is yet to be confirmed in human studies.

Incretin mimetics: GLP-1 analogues

Exenatide was the first incretin mimetic resistant to DPP4 degradation approved by the FDA.¹⁰ Unlike GLP-1, exenatide is not rapidly inactivated, allowing it to be administered twice-daily. Exenatide is administered by subcutaneous injection before the morning and evening meals. However, a once-weekly administered long-acting formulation of exenatide has recently been tested.¹³ Liraglutide, another GLP-1 analogue, may be administered once daily. It is likely that the FDA will consider approving this product in 2008.

A systematic review and meta-analysis of GLP-1 analogues (exenatide and liraglutide) was conducted recently.¹⁰ It included eight published trials ($n = 3,139$ adult participants in which a GLP-1 analogue was used for type 2 diabetes. GLP-1 analogues were added to existing inadequate therapy (lifestyle or oral hypoglycaemics) and compared with a double-blind, injectable placebo, metformin, or open-label subcutaneous insulin (glargine or biphasic aspart).¹⁰ Another small study ($n = 45$) was included in which a long-acting formulation of exenatide was compared to placebo in patients taking metformin. The duration of GLP-1 analogue use in these studies ranged from 15 to 52 weeks. GLP-1 analogue therapy resulted in a statistically significant reduction in HbA_{1c} from baseline compared to placebo (weighted mean difference -0.97%, 95% confidence interval [CI] -1.13% to -0.81%). In open-label studies comparing exenatide with subcutaneous insulin there was no difference in HbA_{1c}. Patients receiving exenatide were more likely to achieve target HbA_{1c} levels

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Table 1. Characteristics of currently available blood glucose lowering medications (modified from Heine et al. 2000)

Medication(s)	Delivery	Reduction in HbA _{1c} (%)	Main mode of action	Benefits	Side effects and limitations
Metformin	Oral	1.5	Lowers production of hepatic glucose	No weight gain; cheap	Gastrointestinal complaints; lactic acidosis (very rare)
Sulfonylureas (glibenclamide, glimepiride, gliclazide, glipizide)	Oral	1.5	Stimulates insulin secretion	Cheap	Hypoglycaemia; weight gain
Thiazolidinediones (pioglitazone, rosiglitazone)	Oral	0.5-1.5	Improve insulin sensitivity	Increases HDL levels	Fluid retention, which may lead to heart failure; weight gain; increased risk of CVD; expensive
β-glucosidase inhibitors (acarbose)	Oral	0.5-0.8	Retard intestinal absorption of glucose	No weight gain	Gastrointestinal side effects; multiple daily dosing required; expensive; low potency
Meglitinides (repaglinide)	Oral	1-1.5	Stimulate insulin secretion	Short-acting; less risk of hypoglycaemia	Need to be taken at meal time; expensive
Dipeptidyl peptidase-4 (DPP-4) inhibitors*	Oral	0.6-0.9	Stimulate insulin secretion	Low risk of hypoglycaemia	Limited experience; expensive
Glucagon-like peptide-1 analogues (exenatide)	Subcutaneous injection	0.8-1.1	Stimulates insulin secretion; suppresses glucagon; retards gastric emptying and reduces energy intake	Weight loss	Need to be injected; gastrointestinal side effects; limited experience; expensive
Pramlintide	Subcutaneous injection	0.5-1.0	Retards gastric emptying and reduces energy intake	Weight loss	Needs to be injected before meals; gastrointestinal side-effects; expensive; experience limited
Subcutaneous insulin	Subcutaneous injection	> 2	Stimulates peripheral glucose uptake and inhibits glucose output	Reduces severe hyperglycaemia; cheap; extensive experience	Weight gain; hypoglycaemia; needs to be injected; monitoring requirements
Inhaled insulin*	Inhaled	0.5-1.0	Stimulates peripheral glucose uptake and inhibits glucose output	No injections required	Multiple daily dosing; monitoring requirements; long term pulmonary effects unknown; expensive and experience limited

*Not currently approved for use in Australia.

compared to those taking placebo (45% versus 10%, respectively), but there was no difference between exenatide and insulin in comparative studies. Exenatide was superior to insulin at reducing postprandial glycaemia, while there was no difference in fasting plasma glucose. One key advantage of the GLP-1 analogues compared to their comparators is weight loss (weighted mean difference -2.37 kg; 95% CI -3.95 to -0.78 kg). Weight loss was more pronounced when exenatide was compared to insulin (weighted mean difference -4.76 kg; 95% CI -6.03 to -3.49 kg) than with other agents. Weight loss was progressive, dose dependent and did not appear to plateau at week 30.

Severe hypoglycaemia (requiring intervention) was rare with GLP-1 analogues and has only been reported in patients also

receiving sulfonylureas. The risk of hypoglycaemia was similar between exenatide and insulin (approximately 2% in each group). Nausea and vomiting were the most commonly reported adverse events with exenatide compared to a comparator, with nausea and vomiting occurring in up to 57% and 17% of patients treated with exenatide, respectively. Nausea was most common early in the course of therapy and declined thereafter. In the comparative study with insulin glargine, 19% of patients using exenatide dropped out of the trial, compared to 10% of patients using the insulin.¹⁴ Gastrointestinal adverse reactions were common and contributed to these withdrawals. Diarrhoea was also more common in patients receiving GLP-1 analogue therapy. Exenatide therapy commonly (in up to 67% of patients) results in the formation of antibodies to the molecule, as it is not identical to human GLP-1. However,

this has not been associated with any effect on outcomes or adverse events.¹⁰ It is recommended that exenatide is initiated at a dosage of 5mcg twice-daily to improve tolerability and increased to a maximum dosage of 1mcg twice-daily.¹⁵

Incretin enhancers: DPP4 inhibitors (the 'gliptins')

Given that GLP-1 analogues require injection, considerable effort has been made to develop oral agents that target the incretin pathway. Inhibition of DPP4 extends the half-life of native incretins, prolonging their action.¹⁰ A systematic review and meta-analysis of DPP4 inhibitors (sitagliptin and vildagliptin) was conducted recently.¹⁰ DPP4 treatment was compared to placebo as monotherapy or as add-on therapy to oral hypoglycaemic agents or insulin in 13 randomised trials ($n = 4,780$). The duration of these trials ranged from 12 to 52 weeks. The incretin enhancers lowered HbA_{1c} compared with placebo with similar effectiveness as monotherapy or as add-on therapy (weighted mean difference -0.74% ; 95% CI -0.85% to -0.62%). Sitagliptin and vildagliptin have not been directly compared, but seem to be similarly effective in lowering HbA_{1c} compared to placebo. In four trials ($n = 3,053$) comparing a DPP4 inhibitor to other hypoglycaemic agents (glipizide, metformin or a thiazolidinedione), the DPP4 inhibitors were slightly less effective at lowering HbA_{1c} (weighted mean difference -0.21% ; 95% CI 0.02% to 0.39%). Patients treated with DPP4 inhibitors were more likely to achieve target HbA_{1c} levels compared to placebo (43% versus 17%, respectively). Compared to placebo, DPP4 inhibitors were associated with a small increase in weight (weighted mean difference 0.5 kg; 95% CI 0.3 to 0.7 kg). This was mainly because metformin was associated with an average 2.2 kg weight loss compared to vildagliptin. However, sitagliptin and vildagliptin were associated with weight loss compared to glipizide and thiazolidinediones, respectively. Severe hypoglycaemia was rare with DPP4 inhibitors, and there was no difference in the incidence of mild to moderate hypoglycaemia between DPP4 inhibitors and comparators. DPP4 inhibitors were well tolerated, with no increased risk of gastrointestinal adverse effects (nausea, vomiting, abdominal pain and diarrhoea). Adverse effects noted significantly more frequently with DPP4 inhibitors compared to comparators included nasopharyngitis, urinary tract infection and headache.¹⁰

Amylin analogue: pramlintide

Amylin is produced by the β cells of the pancreas and is secreted together with insulin in response to meals. Its role is to complement the action of insulin by regulating the rate of glucose entry into the circulation following a meal.¹⁶ It achieves this by slowing gastric emptying, suppressing inappropriate postprandial glucagon secretion and regulating food intake.¹⁶ Amylin concentrations are deficient in patients with type 1 diabetes who are also deficient in insulin.¹⁶ Native amylin exhibits poor solubility and a tendency to aggregate,

and is not suitable for clinical use. Pramlintide is a synthetic, soluble analogue of amylin with similar mechanisms of action that regulate the appearance of glucose in the circulation following meals.¹⁷ In the US, pramlintide is indicated as an adjunct to mealtime insulin in patients with type 1 and 2 diabetes. In clinical studies, pramlintide improved postprandial glucose control when added to insulin therapy in people with type 1 or 2 diabetes and was also associated with weight loss.¹⁸ In people with type 2 diabetes who require insulin therapy, pramlintide therapy has been shown to reduce HbA_{1c} and body weight.¹⁸ In one 52 week study, patients treated with pramlintide (75 or 150mcg tds) had a reduction of HbA_{1c} of 1% compared to 0.5% ($P < 0.01$) for the placebo group.¹⁹ Additionally, patients in each of the pramlintide dosage groups had significant decreases in mean body weight compared to placebo. Other studies have reported similar results in type 2 diabetics treated with a range of doses of pramlintide (60mcg tds, 90mcg tds or 120 mcg bd).^{20,21} Nausea was more than twice as likely in patients treated with pramlintide than with placebo in these studies, although it did not increase drop-out rates. In people with type 1 diabetes, pramlintide reduced insulin requirements by 7-8%, without increasing the risk of hypoglycaemia compared to placebo.²² In the majority of studies, pramlintide was administered by injection, 15 minutes prior to meals and separated from the insulin injection. However, some smaller studies have demonstrated that combining insulin and pramlintide in the same injection does not attenuate the therapeutic effects of pramlintide.²³

Inhaled insulin

The major drawback to traditional insulin therapy is its need for injection. This has led to attempts to develop a suitable alternative that can be administered by a more desirable route for diabetic patients. Pharmacokinetic studies have demonstrated that inhaled insulin is similar to the rapid-onset insulin analogues (lispro and aspart) but possesses a slightly longer duration of action.²⁴ It is therefore regarded as a rapid-acting insulin and is suitable for control of postprandial hyperglycaemia. Inhaled insulin has been compared with subcutaneous insulin regimens in patients with type 1 and type 2 diabetes, and with oral hypoglycaemics in those with type 2 diabetes.²⁵ The combination of inhaled insulin, taken before each meal, and ultralente at night resulted in similar glycaemic control as a combination of lente and regular insulin two to three times daily among patients with type 1 and type 2 diabetes. Patients receiving the inhaled insulin regimen had slightly lower rates of hypoglycaemia.^{26,27} In people with type 2 diabetes, the addition of inhaled insulin to existing oral therapy was shown to be more effective over 3-6 months than adding a second oral hypoglycaemic medication.²⁸ Inhaled insulin, however, is consistently associated with a higher risk of hypoglycaemia than is associated with oral agents.²⁵ In clinical trials, patients were generally more satisfied with inhaled insulin than with subcutaneous insulin.^{26,27,29}

Unfortunately, at present, inhaled insulin therapy is limited by a number of drawbacks. These include expense, the potential for a reversible decline in lung function associated with its use, a theoretical risk of formation or promotion of cancer with chronic use and the possibility that practical issues such as smoking and the presence of upper respiratory tract infections may affect the degree of insulin absorption and the risk of hypo- or hyperglycaemia.²⁴ It is also short-acting and would not replace the need for a basal insulin. Inhaled insulin is more suitable for patients with HbA_{1c} levels that remain elevated after fasting glucose levels have been controlled with a basal insulin.

The technology required for the administration of inhaled insulin is also more demanding than for other inhaled medications, where such a high degree of precision in dosing is not required. In the case of *Exubera*, this resulted in difficulties in dosing. The dosage of *Exubera* was measured in milligrams, not units, and initial dosing was based on body weight rather than the carbohydrate content of meals. Most of the devices required to inhale insulin are relatively large and awkward, requiring time and skill to master, although they will hopefully improve with further development.²⁴

Place of newer agents in the treatment of type 2 diabetes

A recent systematic review provides some evidence on the relative safety and effectiveness of older oral medications (metformin and sulfonylureas) in comparison with newer oral agents (thiazolidinediones, α -glucosidase inhibitors and meglitinides).³⁰ The review found that compared with the newer, more expensive agents, older medications have similar or superior effects on glycaemic control, lipids and other intermediate endpoints. This finding supports the status of the newer agents as add-on therapy to metformin, a sulfonylurea or both in type 2 diabetes.³¹

The roles of exenatide and sitagliptin in the treatment of type 2 diabetes are unclear. At present, if optimum therapy with oral hypoglycaemics does not control the disease, subcutaneous insulin is the next step.³¹ Exenatide may have similar effects on HbA_{1c} to insulin glargine,¹⁴ or twice-daily insulin aspart,³² but it causes more adverse effects. The ideal patient for whom exenatide could be considered is obese, with elevated glucose concentrations in spite of therapy with oral hypoglycaemics.¹⁸ The effects of pramlintide on blood glucose and body weight are more modest compared with those of exenatide. Pramlintide may have a greater role in type 2 diabetic patients who have longstanding disease and are more insulin-deficient, as exenatide requires β cell function to achieve its therapeutic actions, whereas pramlintide does not.¹⁸ It is likely that the practical drawbacks associated with inhaled insulin will be overcome in time, but they are significant at present. This is perhaps most evident in the decision to remove the first inhaled insulin from the market

in the US recently due to poor sales. Newly developed inhaled insulin products may prove more successful. The new classes of hypoglycaemic agents will need continued evaluation in terms of long-term efficacy and safety to fully determine their role among the well-established therapies for type 2 diabetes.

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