New therapies available for the treatment of type 2 diabetes

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Summary
In type 2 diabetes multiple lesions have been identified; new drugs are being developed that target these lesions. This review considers the most recent pharmaceutical options to reduce hyperglycaemia. Two new classes of agents were introduced in the USA in 2005, both of which are administered by injection. The first agent, pramlintide, is a soluble analogue of the islet peptide amylin which is used as an adjunct to insulin therapy. Exenatide is an analogue of the incretin hormone GLP-1 and has similar actions to native GLP-1. Both agents reduce hyperglycaemia without causing weight gain and can aid weight loss. A cannabinoid receptor antagonist (rimonabant) which aids weight loss and improves glycaemic control in type 2 diabetes has recently received marketing approval as an antiobesity agent in Europe. The gliptins and glitazars are at advanced stages of development and fixed-dose combination '2.4.1' tablets containing established agents are being introduced.

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Key Words
Type 2 diabetes; pramlintide; exenatide; glitazars; gliptins; GLP-1; amylin

Introduction

The 20th century witnessed a revolution in the diagnosis, monitoring and treatment of diabetes. Until the advent of insulin therapy in 1923 extreme dietary and lifestyle interventions were the only conventional options to prolong life. Although insulin was originally hailed as a cure for diabetes the search for an oral treatment continued. Traditional medicines were considered of particular benefit for what is now termed type 2 diabetes and several reports from the 1920s and 1930s describe the glucose-lowering effects of plant remedies – some of which were administered to reduce insulin dosage.[1] The wider availability of insulin drove the differentiation between type 1 and type 2 diabetes and raised the possibility of oral treatments for the latter.

It was not until the late 1950s that sulphonylureas and biguanides (phenformin, buformin and metformin) appeared for the treatment of type 2 diabetes. Over the last half-century sulphonylureas have been developed with varying durations of action and reduced side-effect profiles, and of the biguanides only metformin remains in general use – indeed it is now the most widely prescribed antidiabetic agent worldwide (aided by its introduction to the USA in 1994). In 1990s Europe the oral agent armamentarium saw the addition of alpha-glucosidase inhibitors and for a brief period (1998–1999 in the UK) the thiazolidinedione (TZD) troglitazone. This agent was withdrawn mainly due to idiosyncratic liver failure. The early 21st century saw the introduction of TZDs (pioglitazone and rosiglitazone) with safer side-effect profiles, and the meglitinides (repaglinide and nateglinide). The main actions of these established classes of oral antidiabetic agent are summarised in Table 1.[2]

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Combinations

Type 2 diabetes is a progressive disease characterised by insulin resistance and beta-cell failure. Insulin resistance is usually well established and beta-cell failure is evident by the time of diagnosis, but insulin replacement therapy is not necessary until there is evidence of beta-cell exhaustion. Agents currently available target aspects of these lesions (Table 1), for example metformin reduces insulin resistance and sulphonylureas stimulate insulin secretion. The UK Protective Diabetes Study (UKPDS) demonstrated the inability of one therapy alone to maintain adequate glycaemia in the majority of patients.[3] For example, after 3 years of treatment, using a sulphonylurea, metformin or insulin, about half the patients studied had inadequate glycaemic control (HbA_{1c} >7%) and by 9 years of treatment with any one of these agents about three-quarters of all patients had HbA_{1c} >7%. Thus these patients are candidates for combination therapy to improve glycaemic control.

A new approach to combination therapy is the introduction of

Class of agent	Main action
Sulphonylurea	↑ insulin secretion
Meglitinide (prandial insulin releaser)	↑ insulin secretion
Biguanide (only metformin)	↓ insulin resistance
Thiazolidinedione (TZD = glitazone)	↑ insulin sensitivity
Alpha-glucosidase inhibitor	↓ rate carbohydrate digestion

Table 1. Main actions of oral antidiabetic agents

'2.4.1' tablets containing fixed-doses of established antidiabetic agents with complementary modes of action[4] (see Table 2). Glucovance® (glibenclamide and metformin), the first '2.4.1' antidiabetic tablet, was introduced in the USA in 2000.

It is well recognised that increasing the pill burden reduces compliance, but '2.4.1' tablets help circumvent this problem. Studies using Glucovance have shown that this approach is more effective at improving glycaemic control than administration of metformin and glibenclamide as single tablets (Figure 1).[5] This improvement is accounted for by altered pharmacokinetics due to the formulation of the Glucovance tablet.[6] However when using '2.4.1' combination tablets it is necessary to observe the precautions associated with each of the agents, be mindful of interactions and take account of the individual actions of the agents.[7] For example, the onset of action of thiazolidinedione therapy is slow and it may take at least six weeks for maximal glucose-lowering efficacy to be achieved in patients who respond to treatment with these agents, and combinations with sulphonylureas increase the risk of hypoglycaemia.

Tablet®	Components	Strengths (mg)
Avandamet[b] http://www.avandia.com/about_avandamet/avandamet.html	metformin + rosiglitazone	(500:1; 500:4)[c] 500:2; 1000:2; 1000-4
Actoplus met[c]/Competact[g] http://www.actos.com/sub_sec8_about_plus.asp	metformin + pioglitazone	500:15; 850:15/850:15
Metaglip[c] http://www.bms.com/products/data/ (complete search bar)	metformin + glipizide	250:2.5; 500-2.5; 500-5
Glucovance[d] http://www.bms.com/products/data/ (complete search bar)	metformin + glibenclamide[e]	250:1.25; 500:2.5; 500-5
Avandaryl[c]/Avaglim[f] http://www.avandia.com/about_avandaryl/avandaryl.html	rosiglitazone + glimepiride	4:1; 4:2./ 4:4, 8:4

[a]availability of tablets and component strengths differ between countries, but all tablet types are available in the USA.
[b]licensed for use throughout Europe
[c]not used in Europe
[d]available in some countries in Europe
[e]glibenclamide = glyburide
[f]April 2006 received a positive opinion on initial marketing authorisation from the Committee for Medicinal Products for Human Use (CHMP) as Avaglim®
[g]June 2006 received a positive opinion on initial marketing authorisation from the CHMP as Competact®

Table 2. '2.4.1' oral antidiabetic tablets[a]

Amylin analogue

The first new class of antidiabetic agent to receive regulatory approval in the 21st century was the soluble amylin analogue pramlintide (Symlin®).[8] It is also the first non-insulin antidiabetic agent to be administered by injection. Pramlintide received marketing approval in the USA in March 2005 as an adjunct therapy in people with type 1 and type 2 diabetes who use mealtime insulin injections (± concurrent sulphonylurea and/or metformin therapy in type 2 diabetes), but fail to achieve adequate glycaemic control despite optimal insulin therapy.[9]

In non-diabetic individuals amylin (insulin amyloid polypeptide/IAPP) is co-secreted with insulin and as insulin secretion declines so does amylin secretion. Thus in advanced stages of type 2 diabetes circulating amylin concentrations are low. Pramlintide acts like endogenous amylin (Figure 2). It suppresses the secretion of glucagon (when not normalised by insulin alone) which decreases hepatic glucose output to reduce postprandial hyperglycaemia. However, the administration of pramlintide alone will not cause hypoglycaemia. Gastric emptying and the rate of digestion are also decreased; these actions result in a slower and smoother appearance of glucose in the circulation, without altering overall nutrient absorption. All these effects are mediated by the activation of amylin receptors within the area postrema of the brain. Pramlintide is also thought to act in the central

regulation of energy balance as it enhances satiety, reducing ad libitum meal calorie consumption by about 20%, which in association with its gastrointestinal actions can reduce obesity.[10] Compared to patients with type 2 diabetes treated with insulin alone, those who also received pramlintide (30 μg four times daily) experienced weight loss (decrease ≥1 kg) and improved glycaemic control (reduction in HbA_{1c} 0.5–1%).

Pramlintide is a peptide hormone analogue and should therefore be stored in a refrigerator at 2–8°C (36–46°F). Pramlintide is prescribed in micrograms, but patients are more familiar with dosing in units; the recommended starting dose of 60 μg in type 2 diabetes converts to 10 units. Ideally a 0.3 ml U–100 unit insulin syringe should be used for the injection of pramlintide. Pramlintide should be administered subcutaneously into the thigh or abdominal area just prior to a meal. The arm should be avoided due to increased variability in pramlintide action when using this injection site. A meal comprises at least 250 calories or ≥30 g carbohydrate and pramlintide should not be administered if a meal cannot be consumed or if glucose concentrations are already low. Pramlintide must be administered as a separate injection to insulin as differences in pH can alter the pharmacokinetic properties of both peptides. Injection sites should be rotated and the pramlintide and insulin should be injected at separate sites at least 5 cm (2 inches) apart.

The effects of pramlintide last for about 3 hours and it is during this time that the patient is most susceptible to insulin-induced hypoglycaemia. To reduce this risk it is recommended that the mealtime insulin dose is reduced by 50% when initiating pramlintide therapy. The commonest pramlintide-associated side-effects are gastrointestinal – mainly nausea – but these generally resolve if the pramlintide dose is gradually titrated up to the maintenance dose of 120 μg (20 units). However, if nausea persists it will be necessary to return to the 60 μg dose. On establishing the regular pramlintide dose further dose adjustment of insulin (and possibly oral agents) may be necessary. It is important that blood glucose is closely monitored (before and after meals, and before bedtime) until a regimen providing optimal glycaemic control has been established.

Particular caution is advised during pregnancy and lactation since there are reports of effects on the foetuses of some animal species. It should also be noted that there is a risk of hypoglycaemia if the patient is taking an oral antidiabetic agent such as a sulphonylurea. The reduction in gastric emptying rate normally precludes use of pramlintide with agents that alter gastrointestinal motility or depend upon achieving threshold levels.

In type 2 diabetes pramlintide offers the advantages of improving glycaemic control without increasing the insulin dose and without causing weight gain. The association of pramlintide with weight loss makes it especially attractive to patients, despite the need for more injections. To date pramlintide is only available in the USA.

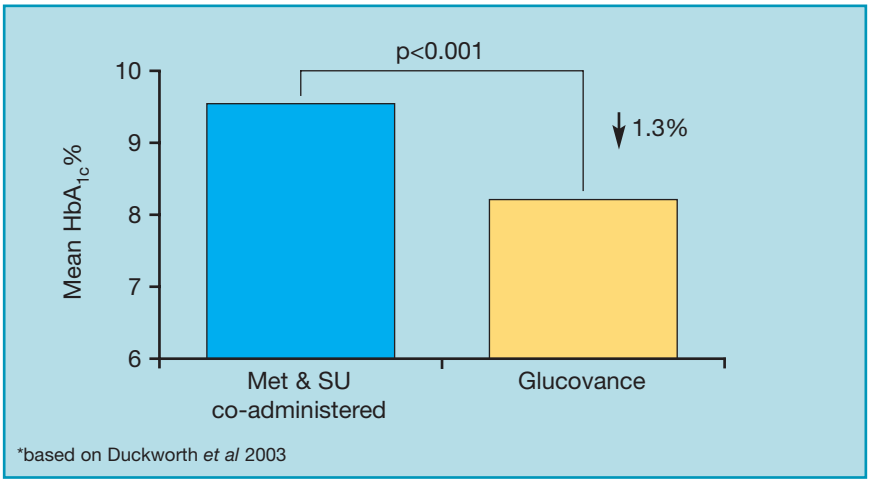

Figure 1. Glycaemic benefit of switching from co-administration to '2.4.1' combination therapy (metformin and glibenclamide)*[5]

Incretin mimetics

Incretin hormones form the basis of the enteroinsular axis. In response to nutrient absorption these intestinal hormones exert a range of effects, the most notable of which is the stimulation of postprandial insulin release. Insulin-releasing agents are usually associated with hypoglycaemic episodes, but the glucose-dependent nature of incretin hormone action makes hypoglycaemia unlikely. Meal-stimulated levels of circulating glucagon-like peptide-1 (GLP-1) are reduced in type 2 diabetes but injection of GLP-1 improves the glucoregulatory response to food. However, the plasma half-life of GLP-1 is very short (<2 minutes) as it is rapidly degraded by the dipeptidyl peptidase-IV (DPP-4) enzyme. Nevertheless, incretin-based therapies offer several advantages beyond short-term glycaemic control in the treatment of type 2 diabetes (see Table 3). Thus longer acting GLP-1 analogues are receiving attention.[11] The main pathways via which GLP-1 acts are outlined in Figure 3.

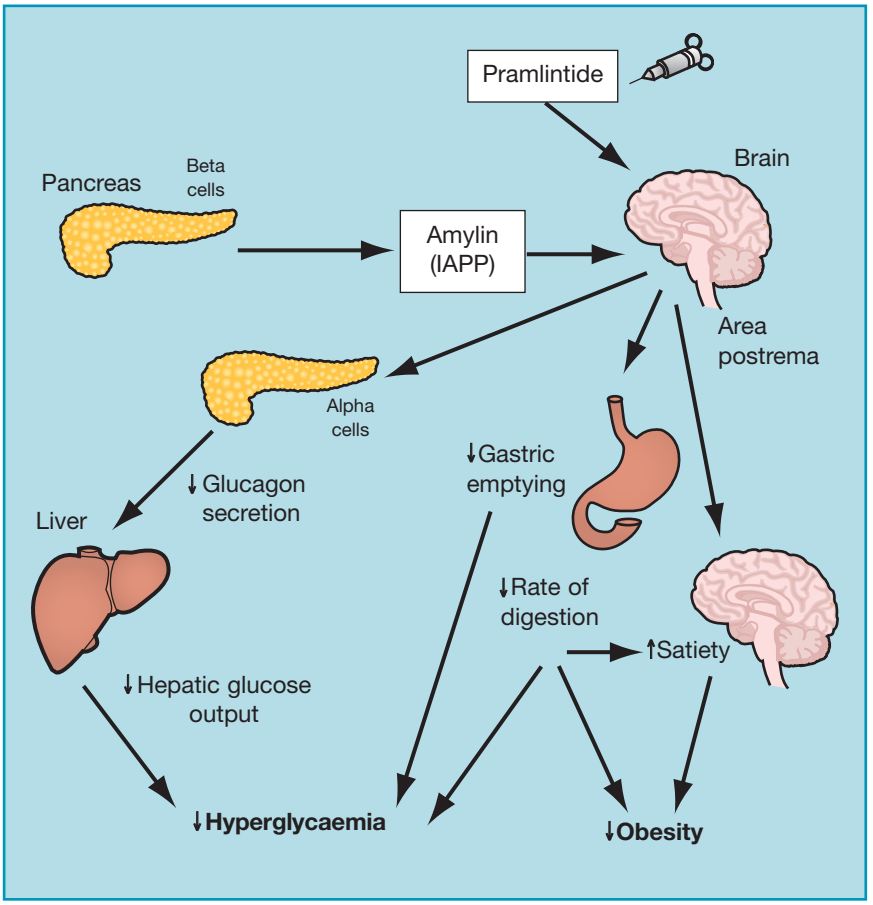

Figure 2. Sites of action of amylin/pramlintide to reduce hyperglycaemia and weight gain (Adapted with permission from CJ Bailey)

GLP-1 analogues

The second new type of antidiabetic agent to receive regulatory approval in 2005 was an incretin mimetic. The GLP-1 analogue exenatide, which is marketed in the USA as Byetta®, was approved as an adjunct therapy for type 2 diabetic patients who are inadequately controlled taking metformin, a sulphonylurea, or a combination of both.[12] Patients already receiving a sulphonylurea are advised to take a dose reduction when initiating exenatide.

Exenatide

Exenatide is a 39-amino-acid synthetic version of exendin-4 (originally isolated from Gila monster saliva) which exhibits similar glucoregulatory effects to GLP-1 (Figure 3). However, exenatide has a much longer plasma half life (2.4 hours) than GLP-1 because it is resistant to degradation by the enzyme DPP-4.[13] Since exenatide is a peptide hormone analogue it has to be administered by injection and should be stored in a refrigerator at 2–8°C (36–46°F).

Exenatide is available in reusable, prefilled, fixed-dose injection pens which are compatible with a range of needles. The pens, which contain a 30-day supply of either 5 µg or 10 µg premeasured doses, have associated procedures and mechanisms that should prevent accidental overdosing. Exenatide should be injected subcutaneously into the abdomen, thigh or upper arm up to a maximum of 60 minutes before consuming a meal. It is recommended that exenatide is administered twice daily – once before breakfast and again before the evening meal, but it should not be taken after a meal, if a meal cannot be consumed or glucose levels are already low.

It is usual to commence exenatide on a dose of 5 µg twice a day for the first 30 days of treatment and this may be increased thereafter to a maximum dose of 10 µg twice daily if necessary. It is advisable to reduce the sulphonylurea dosage on commencing exenatide to avoid possible hypoglycaemia. The addition of exenatide (10 µg twice daily) to oral therapy reduces HbA_{1c} by up to 1% and decreases body weight by 2–3 kg. Data from ongoing open-label studies have shown mean reductions of 1.1% HbA_{1c} and 4.5 kg body weight.[14]

Since exenatide slows gastric emptying it can cause feelings of nausea, especially during the first few weeks of therapy. Some patients also report diarrhoea, and these symptoms may limit titration. As with any agent that slows gastric emptying this can affect the efficacy of any oral medication that is dependent on a threshold concentration, e.g. oral contraceptives and antibiotics. These agents should be taken an hour before the exenatide injection. In preclinical studies exenatide reduced both foetal and neonatal growth; it is therefore advised to withhold this therapy during pregnancy and lactation.

Exenatide offers the advantages of improving glycaemic control, aiding weight loss and deferring the need for insulin therapy which has a higher risk of hypoglycaemia. It is only available in the USA where, despite the need for injection, it is proving popular with patients. Indeed, 87% of the 1125 patients who completed 30-week placebo-controlled trials opted to participate in open-label extension studies.[14]

There are several GLP-1 analogues in development, the most advanced of which are exenatide LAR, liraglutide and CJC-1131.[11] Exenatide has entered the European regulatory process.

New classes of agents

There are several new classes of agent in development. Those which are most advanced are the DPP-4 inhibitors, known as gliptins, and the dual peroxisome proliferator-activated receptor alpha/gamma agonists (PPARα/γ) known as glitazars.

DPP-4 inhibitors

DPP-4 is a peptidase enzyme that is found on the cell surface and in the circulation. It deletes the N-terminal residues of endogenous GLP-1 which results in this intestinal hormone having a very short half life (<2 minutes). Thus agents which can inhibit the action of DPP-4 will prolong the activity of endogenous incretin hormones and thereby improve glycaemic control.[15] Vildagliptin (Galvus®), sitagliptin (Januvia®) and saxagliptin are the most advanced in development and the first two agents have been submitted for regulatory approval in the USA. Studies have shown that the gliptins as monotherapy or in combination with metformin improve glycaemic control while being weight-neutral. For example, vildagliptin (50 mg once daily) added to metformin therapy for 52 weeks reduced HbA_{1c} (about 1.0%) compared to patients on metformin, and both groups lost an average of 0.2 kg.[16,17] Sitagliptin is also suitable for once-daily dosing. Although gliptins are generally considered to create most of their glucose-lowering effects by extending the half life of incretin hormones, it is possible that they influence glycaemic control through other modes of action, since there are many other peptides in the circulation that will be upregulated as a consequence of DPP-4 inhibition.

Only interact with specific receptors on target cells
Glucose-dependent stimulation of insulin release
Short duration of insulin-releasing effect
Enhance beta cell survival
Increase beta cell mass and insulin biosynthesis
Extra-pancreatic glucose lowering actions

Table 3. Advantages of using incretin hormone-based therapies in type 2 diabetes

Dual-PPARα/γ agonists

Dual-PPARα/γ agonists (glitazars) stimulate PPARα in a similar manner to fibrates and stimulate PPARγ in a similar manner to TZDs. Thus these agents exert the combined actions of fibrate – such as triglyceride-lowering and TZD – such as glucose-lowering effects.[16] Several glitazars are being investigated but some clinical trials have been suspended due to concerns regarding tumours in preclinical toxicity studies. The glitazars most advanced in development are

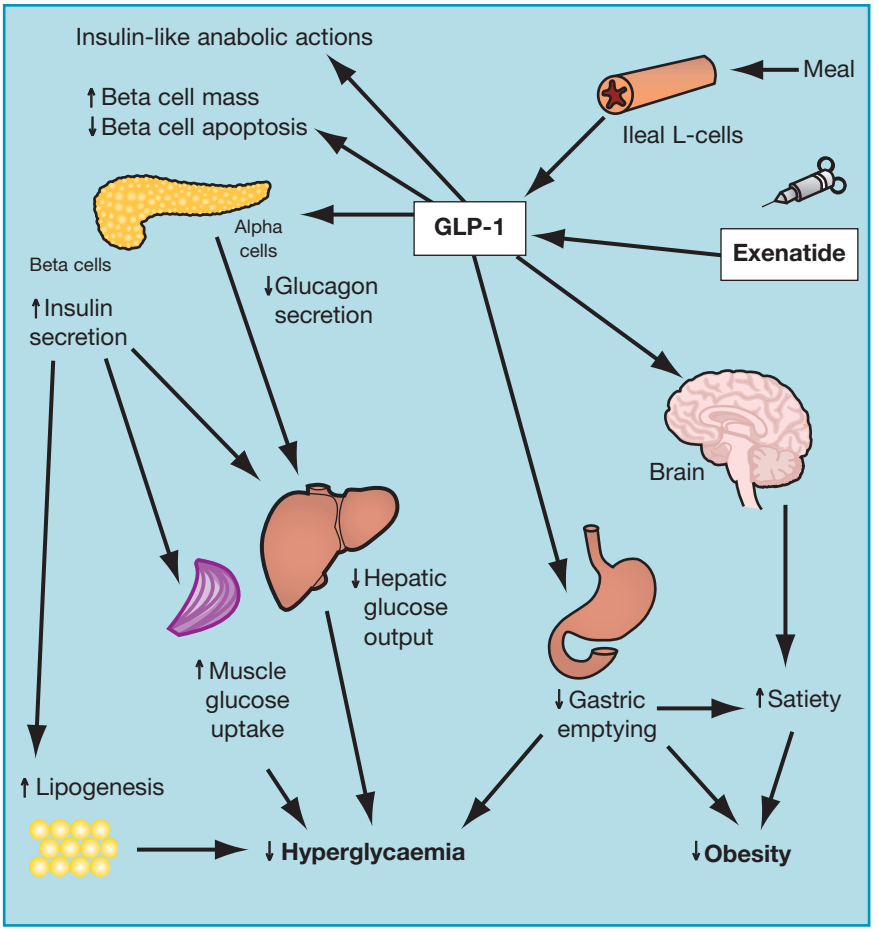

Figure 3. Sites of action of GLP-1/exenatide to reduce hyperglycaemia and weight gain (Reproduced with permission from CJ Bailey)

muraglitazar (Pargluva®) and tesaglitazar (Galida®). However, tesaglitazar has been discontinued on recent completion of phase III studies (May 2006) due to concerns regarding raised creatinine levels. Following a recent meeting, the US Food and Drug Administration's (FDA) Endocrinologic and Metabolic Drugs Advisory Committee voted to recommend approval of muraglitazar for use as monotherapy and in combination with metformin – but not with a sulphonylurea – in the oral treatment of type 2 diabetes. However, additional long-term cardiovascular safety studies were requested. The cost and uncertainty of a 5 year safety study coupled with the withdrawal of a co-development partner lead to the decision (May 2006) to discontinue development of muraglitazar.[18] The future of the glitazar class is therefore undecided.

Anti-obesity agents

Obesity is a major driver and complication of type 2 diabetes and reduction of adiposity is a recognised means of improving glycaemic control in these patients. Rimonabant(Acomplia®/Zimulti®), a new type of antiobesity agent, has recently (April 2006) received regulatory approval in Europe. It causes satiety by inhibiting cannabinoid receptors in the brain that normally drive appetite. This new agent (20 mg once daily) typically causes a weight loss of about 4 kg in patients with diabetes and reduces waist circumference, suggesting a preferential reduction in visceral fat, which is most strongly associated with cardiovascular risk.[19] During trials in patients with diabetes rimonabant reduced HbA_{1c} by about 0.6%, which is probably more than might be expected from the extent of weight loss alone.

Conclusion

In type 2 diabetes multiple lesions have been identified and are being targeted in pre-clinical studies, but it is a long haul from bench to bedside and many potential treatments are discarded en route – usually due to toxicity and efficacy issues. Of the agents which have passed phase III clinical trials, pramlintide and exenatide are only available in the USA. However the latter has entered the European regulatory system, as has the DPP-4 inhibitor vildagliptin, and the recently approved rimonabant offers a new approach to the treatment of obese patients with type 2 diabetes. The advent of fixed-dose '2.4.1' tablets combining established oral antidiabetic agents provides opportunities to simplify treatment regimens and enhance glycaemic control.

Conflict of interest statement

Dr Day has not received any funding to write this manuscript and has not received research support from pharmaceutical companies involved with the drugs mentioned in the manuscript.

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