Oral antidiabetic agents: Is it time to combine therapies?

Caroline Day

Article points

1. The progressive nature of type 2 diabetes requires periodic revision of treatment.
2. Within 9 years of diagnosis, the UK Prospective Diabetes Study found that about 75% of participants required combination therapy to achieve adequate glycaemic control.
3. It is important to consider contraindications and drug interactions of all agents being prescribed.
4. Combination therapy requires oral antidiabetic agents with different modes of action which can produce complementary and additive benefits.
5. Concordance is enhanced by simplification of treatment regimens, which may be achieved, in part, by reducing the pill burden.

Key words

- Glycaemic control
- Combination therapy
- Polypill

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Type 2 diabetes is a condition of worsening glycaemic control with associated metabolic disturbances, all of which need targeting in order to reduce the consequent associated morbidity and early mortality. Complex multi-drug regimens, while being logical to recommend, are often difficult to incorporate into daily life (Day, 2006). Reducing the pill burden makes it easier to adhere to treatment strategies (Day, 2006). In this review Caroline Day focuses on approaches to improve glycaemic control by innovative packaging of currently available oral antidiabetic agents.

The evidence base to justify intensive management of type 2 diabetes is now irrefutable (Bailey et al, 2005) and the need for multiple medications is becoming the accepted norm. A requirement for combinations of agents to treat hypertension (Williams et al, 2004) and some lipid disorders (Fodor et al, 2000) is well appreciated, and the use of combinations of agents to treat hyperglycaemia is becoming increasingly necessary to achieve recommended targets for glycaemic control (Turner et al, 1999). Nevertheless, it could be argued that all people with diabetes initially do receive combination therapy – diet and exercise – upon which multiple medications may be added.

This article considers the rationale, practicalities and evidence base for using combinations of oral antidiabetic agents to optimise glycaemic control in people with type 2 diabetes.

Why the need for combination therapy?

The UK Prospective Diabetes Study (UKPDS; UKPDS Group, 1998) provides a clear example of the progressive nature of type 2 diabetes, with respect to glycaemic control, whether treated by conventional (diet and exercise) or intensive (target-led pharmacological) therapy (*Figure 1*). Other studies (such as Gaede et al, 2003) have affirmed that improved metabolic control and attention to vascular risk factors can defer the onset and reduce the severity of vascular complications, thereby providing a mandate for intensive management. Indeed, the epidemiological analysis of the UKPDS demonstrated that significant reductions in morbidity and mortality were associated with a 1% reduction in HbA_{1c} over 12 years ($P<0.0001$; Stratton et al, 2000; *Figure 2*).

Another important piece of evidence from the UKPDS was the inability of one pharmacological therapy alone to maintain adequate glycaemia in the majority of people with diabetes (Turner et al, 1999). For example, after 3 years of monotherapy using any of the agents tested (a sulphonylurea, metformin or insulin) about half of all people with diabetes studied had less than adequate glycaemic control as indicated by an HbA_{1c} of >7%. By 9 years of monotherapy with any of these agents about three-quarters of all participants showed an HbA_{1c} >7%; such individuals are, therefore, candidates for a combination of pharmacological therapies to improve glycaemic control.

Burden of polypharmacy

It has generally been accepted that polypharmacy reduces concordance to treatment. The Diabetes Audit and Research in Tayside Scotland (DARTS) study, among others, has shown that

the situation is worse than assumed (Donnan et al, 2002). Only 13% of study participants who were prescribed a free combination of a sulphonylurea and metformin showed adequate concordance, while about one-third of those on sulphonylurea or metformin monotherapy were taking adequate medication (*Figure 3*). Perhaps the poor concordance to oral antidiabetic therapy should not be so surprising since people with type 2 diabetes usually have co-morbid conditions that require an increasing number of medications upon which complex regimens are imposed. Indeed, people receiving a once-daily sulphonylurea regimen had improved concordance compared with those on more than two doses per day (Donnan et al, 2002; Emslie-Smith et al, 2003). Coping with the burden of polypharmacy highlights the importance of building a positive therapeutic alliance with the person with diabetes (Emslie-Smith et al, 2003).

Simple once-daily dosing may not always be possible when striving for optimal glycaemic control, but the pill burden can be lightened by providing '2-4-1' combination tablets.

'2-4-1' tablets

Two pharmacological agents with different modes of action in one tablet seems like a sales promotion, but it might be a pill bargain that helps people with diabetes achieve glycaemic targets. For example, it can be useful to combine metformin and a thiazolidinedione because they improve insulin action by different mechanisms that have additive glucose-lowering effects and complementary and reinforcing effects on cardiovascular risk factors (Bajaj and DeFronzo, 2004). Several '2-4-1' combinations are available that improve glycaemic control (Bailey, 2005a; Day, 2006; *Table 1*), but, at the time of writing this article, only a single-tablet combination of metformin and rosiglitazone (Avandamet; GlaxoSmithKline, Uxbridge) was licensed for use in the UK (Bailey and Day, 2004). (It is noteworthy that most people with diabetes will already be receiving a statin and probably low-dose aspirin, not to mention antihypertensives and other therapies.) Generally, combinations of oral antidiabetic agents do not significantly interfere with prescribing practice (Bajaj and DeFronzo, 2004), but it is important that the contraindications of all component agents are carefully observed.

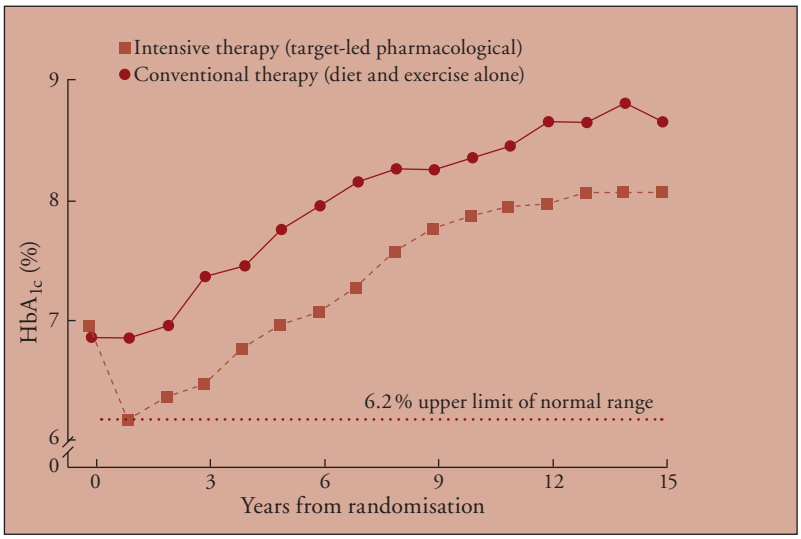

Figure 1. The continual decline in glycaemic control of people with type 2 diabetes regardless of treatment strategy, as demonstrated by the UK Prospective Diabetes Study Group (1998; from where this figure is adapted).

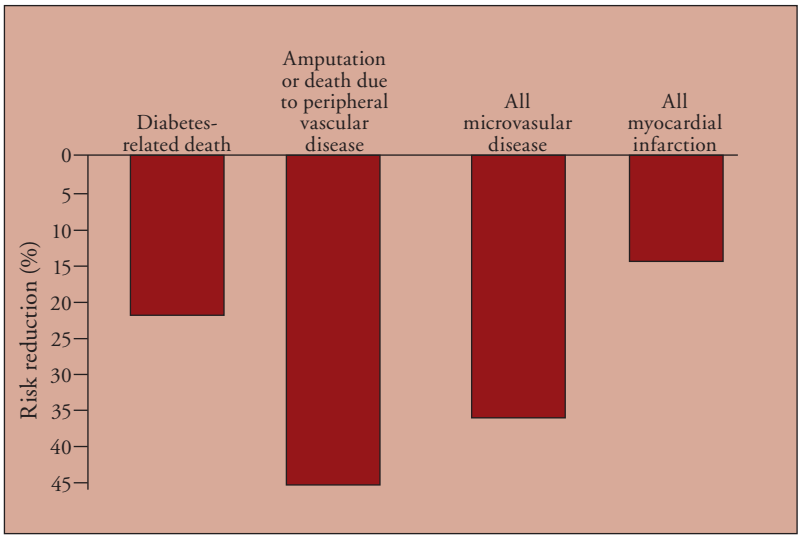

Figure 2. Some clinical benefits of a 1% reduction in HbA_{1c} as demonstrated by the UK Prospective Diabetes Study (data from Stratton et al, 2000).

Can combination therapy improve control?

The main classes of oral antidiabetic agents and their actions are summarised in *Table 2*. Many studies have affirmed the use of two oral antidiabetic agents, with differing modes of action, which can produce complementary and additive benefits to improve metabolic control and

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1. It is not appropriate to use triple therapy when there is substantial and rising hyperglycaemia with two agents (possibly accompanied by unintentional weight loss and polyuria and complications), which signals some beta-cell failure and the need for insulin therapy.
2. The introduction of insulin therapy for people with type 2 diabetes is mostly contemplated when adequate control has not been achieved with the use of two or more oral antidiabetic agents.

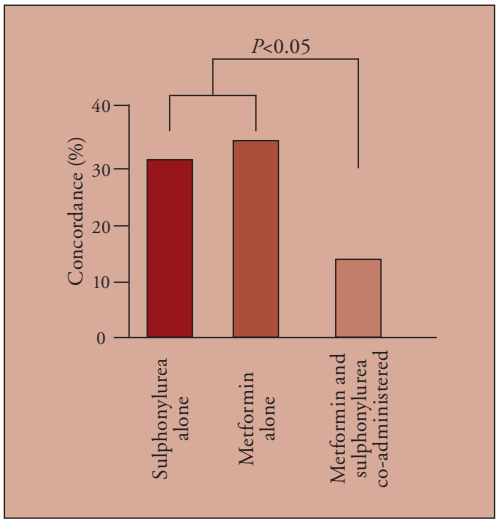

Figure 3. Concordance of people with type 2 diabetes to pharmacological monotherapy or combination therapy (adapted from Emslie-Smith et al, 2003).

cardiovascular risk factors (Campbell, 2000; Bajaj and DeFronzo, 2004). Most such studies have been conducted with groups of people with type 2 diabetes who have inadequate but stable glycaemic control on a high dose of one oral agent. The addition of a second agent has typically reduced the study participants' HbA_{1c} by 0.6–1.5%, thus enabling an increased number of individuals to achieve acceptable glycaemic control (*Table 3*). Options for different oral combination therapy are shown in *Table 4*.

Starting oral antidiabetic drug therapy with a combination

If presenting hyperglycaemia is high (for example, HbA_{1c} >10%) it is unlikely that one oral agent will achieve an HbA_{1c} value within the recommended target range (Turner et al, 1999). Provided that the individual does not have late onset type 1 diabetes (requiring insulin therapy), the early use of combination therapy may produce a substantial fall in HbA_{1c} (Bailey et al, 2005). Indeed, lower-dose combination therapies may be more effective than maximal-dose monotherapy (Blonde et al, 2002).

An open-label study using an initial single-tablet combination of metformin and glibenclamide (Glucovance; Bristol-Myers Squibb, New York, US) noted an approximate 3.5% fall in HbA_{1c} over 26 weeks (from 10.6% to 7.09%; Garber et al, 2002). A random chart review of initial treatments in 300 people with type 2 diabetes revealed that those commencing treatment with once-daily combined metformin and rosiglitazone (n=86; Avandamet, GlaxoSmithKline, Uxbridge) showed the greatest proportion of individuals (91.9%) achieving an HbA_{1c} value of less than 7% (Bell and Ovalle, 2004).

Table 1. '2-4-1' oral antidiabetic tablets. Availability and component strengths differ between countries, but all tablet types are available in the US (data based on Bailey, 2005a; Day, 2006).

Brand name	Components	Available concentrations (mg)
Avandamet[a]	metformin and rosiglitazone	500–2[b]; 1000–2[b]; 1000–4[b]; (500–1; 500–4)
Actoplus Met[c]	metformin and pioglitazone	500–15; 500–2.5; 850–15
Metaglip	metformin and glipizide	250–2.5; 500–2.5; 500–5
Glucovance	metformin and glibenclamide	250–1.25; 500–2.5; 500–5
Avandaryl[d]	rosiglitazone and glimepiride	4–1; 4–2

a, b Available in the UK
c, d Received European marketing authorisation in Summer 2006 (Competact and Avaglim, respectively)

Triple oral therapy

If a combination of two differently acting oral antidiabetic agents does not achieve adequate control, triple therapy may be helpful (Dailey et al, 2004; Orbay et al, 2004; Scheen, 2005). The most commonly used triple therapy is metformin with a sulphonylurea and a thiazolidinedione (rosiglitazone has been approved for triple therapy in the UK). It is important that three oral antidiabetic agents are not used in place of insulin therapy when insulin is necessary (Bajaj and DeFronzo, 2004). It is not appropriate to use triple therapy when there is substantial and rising hyperglycaemia with two agents (possibly accompanied by unintentional weight loss and polyuria and complications), which signals some β-cell failure and the need for insulin therapy.

Insulin plus oral antidiabetic agents

The introduction of insulin therapy for people with type 2 diabetes is mostly contemplated when adequate control has not been achieved with the use of two or more oral antidiabetic agents (Bajaj and DeFronzo, 2004). It is often useful to continue the use of metformin with insulin as it reduces the amount of insulin required, helps to

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1. There may be some value in using a sulphonylurea with insulin provided there is adequate β-cell function remaining.
2. Continuing sulphonylurea usage when insulin is introduced may improve the opportunity for reducing postprandial hyperglycaemia.
3. When continuing an oral antidiabetic agent and starting insulin, the dosage of oral agent can usually be lowered.

Table 2. Principal actions of the main classes of oral antidiabetic agents.

Class of agent	Main action
Sulphonylurea	Increases insulin secretion
Meglitinide	Increases insulin secretion
Biguanide	Decreases insulin resistance
Thiazolidinedione	Increases insulin sensitivity
α-glucosidase inhibitor	Decreases the rate of carbohydrate digestion

reduce glycaemic excursions, reduces weight gain and may reduce the risk of hypoglycaemia (Douek et al, 2005). An insulin-sparing effect of 15–32% has been reported with concomitant metformin and insulin use in people with type 2 diabetes (Buse, 2000).

There may be some value in using a sulphonylurea with insulin provided there is adequate β-cell function remaining (Krentz and Bailey, 2005). Continuing sulphonylurea usage when insulin is introduced may improve the opportunity for reducing postprandial hyperglycaemia (Krentz and Bailey, 2005): the sulphonylurea will increase endogenous insulin secretion during meal digestion, which will increase the amount of insulin delivered to the liver, which will, in turn, facilitate faster and greater suppression of hepatic glucose production, thereby reducing daily glycaemic variations. A meta-analysis of 16 randomised placebo-controlled studies concluded that this approach to combination therapy improved glycaemic control (decreasing HbA_{1c} by 1.1% compared with a 0.24% reduction on insulin monotherapy), enabled a modest reduction of insulin dosage and did not significantly increase body weight (Johnson et al, 1996).

When continuing an oral antidiabetic agent and starting insulin, the dosage of oral agent can usually be lowered (Krentz and Bailey, 2005). It is noteworthy that insulin with a thiazolidinedione is not approved in the UK, although this combination is used in North America (Raskin et al, 2001).

Table 3. Effect of the addition of a second oral antidiabetic agent to metformin or a sulphonylurea as measured by a reduction of HbA_{1c} (data collated by the author from randomised controlled trials lasting between 16 and 52 weeks).

First agent	Second agent	HbA_{1c} reduction after addition of second agent (%)
Metformin	Sulphonylurea	1–2
	Rosiglitazone	0.8–1.5
	Pioglitazone	0.6–1.4
	Repaglinide	1.4
	Nateglinide	0.7
	Acarbose	0.8
Sulphonylurea	Rosiglitazone	0.9
	Pioglitazone	1.2
	Acarbose	0.8

Table 4. Possible combinations of oral antidiabetic agents.

First agent (monotherapy)	Combination therapy (agent to add to monotherapy)
Metformin (biguanide)	Sulphonylurea, meglitinide, α-glucosidase inhibitor, thiazolidinedione
Sulphonylurea or repaglinide	Metformin, thiazolidinedione, α-glucosidase inhibitor
Thiazolidinedione*	Sulphonylurea, meglitinide, metformin, α-glucosidase inhibitor
Acarbose (an α-glucosidase) inhibitor)**	Sulphonylurea, meglitinide, metformin, thiazolidinedione

**A thiazolidinedione can be used as monotherapy if metformin monotherapy is inappropriate.*
*** Combinations which include an insulin secretagogue increase the risk of hypoglycaemia.*

Advantages and limitations of different oral antidiabetic combinations

The relative advantages and disadvantages of the combination therapies discussed above have been reviewed recently (Campbell, 2000; Bajaj and DeFronzo, 2004). When combination therapy is introduced early in the pathogenesis it is often possible to achieve the required glycaemic target with sub-maximal doses of two oral hypoglycaemic agents rather than a maximal dose of one agent (Garber et al, 2002). This can reduce the incidence and severity of drug-associated side effects and give the physician some flexibility in selecting drug combinations that will address the clinical and lifestyle requirements of the person with diabetes (Bailey, 2005b). Theoretically, early achievement of glycaemic control should, by addressing more than one of the main underlying lesions of type 2 diabetes, assist in sustained maintenance of control within the target range (Bailey et al, 2005). It is important for the prescriber to appreciate the contraindications for each agent

and also the interaction between the oral antidiabetic agents, particularly in reference to hypoglycaemia.

It should be noted that additional glucose-lowering effects cannot be achieved by adding together two different sulphonylureas since these agents act through the same cellular mechanism (Bailey and Krentz, 2005). Combination of a sulphonylurea with a meglitinide is excluded for the same reason, although there would be a theoretical justification based on the faster onset and shorter duration of action of the meglitinides (Bailey and Krentz, 2005), which could enable individuals to address the meal-related (rather than the basal) component of daily hyperglycaemia. Most commonly, however, it is the combination of an agent that promotes insulin secretion with an agent that counters insulin resistance that is preferred.

Observing exclusions and precautions

It is necessary to observe the precautions to each of the agents used in combination therapy and to be vigilant for any drug–drug interactions, especially with respect to hypoglycaemia, if a sulphonylurea or meglitinide is involved (*Table 5* summarises some precautions associated with oral antidiabetic agents).

The onset of action of thiazolidinediones is slow and it may take at least 6 weeks for this class of agent to exert the maximal glucose-lowering effect in people who are responsive to these agents (Bailey and Feher, 2004). Unwanted weight gain is associated with the sulphonlyureas, the thiazolidinediones and to a lesser extent the meglitinides (Bailey and Fehrer, 2004). Metformin and acarbose do not promote weight gain and some studies have noted weight loss in overweight or obese people treated with metformin (Bailey and Feher, 2004).

Polypills, compliance and future fixed-dose combinations

People with type 2 diabetes are at increased vascular risk and generally require treatment for several different conditions. As with intensive glycaemic management more than one agent is often required to achieve lipid and blood pressure targets. The development of '2-4-1' tablets is not confined to the management of hyperglycaemia. The following two examples have recently been approved in the US (Bailey, 2005a): niacin extended-release and lovastatin combination (Advicor; Kos Pharmaceuticals, Miami, US) is a once-daily option for the treatment of dyslipidaemia; and lipid-lowering and antihypertensive therapy is provided by single-tablet atorvastatin and amlodipine (Caduet; Pfizer, New York, US). The Steno-2 trial showed that intensive multifactorial intervention against a range of cardiovascular risk factors reduced both the morbidity and mortality associated with type 2 diabetes (Gaede et al, 2003) and this approach has been supported by meta-analyses and mathematical modelling (Wald and Law, 2003; Patel et al, 2004).

The progression from free combination to '2-4-1' to polypill is a logical move to ease the pill burden for people who require treatment for a range of conditions that increase cardiovascular risk. Indeed, people with type 2 diabetes with inadequate glycaemic control (HbA_{1c} >8%) on a free combination of metformin and glibenclamide experienced a significant mean decrease in HbA_{1c} of 1.3% (P<0.001) when transferred to the '2-4-1' combined preparation of these agents, Glucovance (Duckworth et al, 2003; see *Figure 4*). Presumably a polypill to additionally treat multiple cardiovascular risk factors would similarly engender a range of improved outcomes (Patel et al, 2004; Bailey, 2005a). Although a '2-4-1' or polypill reduces physician-prescribed dosing flexibility,

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1. Earlier intensification of therapy using a range of oral antidiabetic agents reduces the morbidity and premature mortality associated with type 2 diabetes.
2. Concordance is enhanced by simplification of treatment regimens which may be achieved in part by reducing the pill burden.
3. A polypill which addresses the multiplicity of cardiovascular risks associated with type 2 diabetes is awaited.

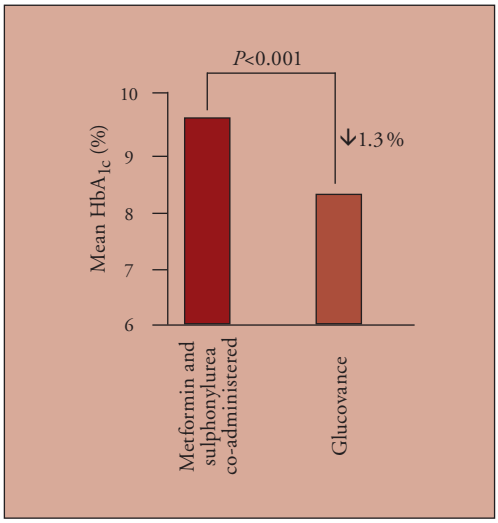

Figure 4. Benefits of switching people with type 2 diabetes from co-administered pharmacological therapy to a '2-4-1' drug (adapted from Duckworth et al, 2003).

this loss in precision may be, in the author's opinion, more than compensated for by improved concordance to medication regimens.

Conclusions

Earlier intensification of therapy using a range of oral antidiabetic agents reduces the morbidity and premature mortality associated with type 2 diabetes (Bailey et al, 2005). Concordance is enhanced by simplification of treatment regimens which may be achieved in part by reducing the pill burden. A polypill which addresses the multiplicity of cardiovascular risks associated with type 2 diabetes is awaited. However, we do have multi-tasking monotherapy in the form of metformin, and the thiazolidinediones also appear to improve some cardiovascular risk factors, thus offering a bonus when added to monotherapy with an agent that has a different mode of action (see *Table 4*).

The dual peroxisome proliferator activated receptor-α/-γ agonist is a new class of agent that addresses hyperglycaemia and aspects of dyslipidaemia (Conlon, 2006) and may one day offer combination-action monotherapy. ■

Conflict of interest

The author has declared she has no conflicts of interest.

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Table 5. Main precautions associated with oral antidiabetic agents.

	Sulphonylureas and meglitinides	Metformin	Thiazolidinediones	Acarbose
Main exclusions	?Liver, renal[a]	Renal, liver, hypoxia[b]	CHF, liver,[c] oedema, anaemia	GI[d]
Tolerability		GI[e]		GI[e]
Safety	Hypoglycaemia[f]	LA[g]	Oedema, anaemia	
Monitor		Creatinine, vitamin B_{12} or haemoglobin[h]	LFT[c]	?LFT[d]

a *If liver or renal disease is present a sulphonylurea with appropriate pharmacokinetics should be used and monitored. Caution should be taken with regard to drug–drug interactions.*

b *Excluded by renal impairment, serious liver disease and any condition that predisposes to hypoxia.*

c *Liver function should be checked (for example, by measuring serum alinine transaminase) prior to treatment and at regular intervals thereafter.*

d *Should be avoided in intestinal disease.*

e *Should be taken with meals and titrated slowly to avoid GI problems.*

f *Glucose levels should be monitored with all antidiabetic drugs, especially during titration to avoid hypoglycaemia.*

g *Risk of LA is very low.*

h *Creatinine and vitamin B_{12} or haemoglobin levels should be checked annually.*

CHF, congestive heart failure; GI, gastrointestinal; LA, lactic acidosis; LFT, liver function test

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'When combination therapy is introduced early, with respect to diagnosis of type 2 diabetes, it is often possible to achieve the required glycaemic target with sub-maximal doses of two oral hypoglycaemic agents rather than a maximal dose of one agent. This can reduce the incidence and severity of drug-associated side effects and give the physician some flexibility in selecting drug combinations that will address the clinical and lifestyle requirements of the person with diabetes.'