

Thiazolidinediones and type 2 diabetes: new drugs for an old disease

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ABSTRACT

- Thiazolidinediones are a new class of drugs for the treatment of type 2 diabetes, and act by improving insulin sensitivity in adipose tissue, liver and skeletal muscle.
- Rosiglitazone and pioglitazone are registered for use in monotherapy, and in combination with sulfonylureas and metformin. Pioglitazone is also licensed for use in combination with insulin.
- There is level II evidence that in patients with inadequate glycaemic control
 - both drugs reduce the level of HbA_{1c} and fasting plasma glucose (FPG) when used as monotherapy and in combination with sulfonylurea or metformin or insulin; and
 - both drugs increase levels of HDL and LDL and lower free fatty acid levels, but only pioglitazone significantly lowers triglyceride levels.
- Both drugs lower fasting insulin and C-peptide levels.
- In monotherapy, they may be slightly less potent at reducing the level of HbA_{1c} than sulfonylureas or metformin.
- The maximal effect of these agents may not be seen for 6–14 weeks after commencement.
- Both drugs are well tolerated but liver function must be checked at baseline every second month for the first year, and periodically thereafter.
- The drugs are currently contraindicated in patients with moderate to severe liver dysfunction and alanine aminotransferase levels more than 2.5 times normal, New York Heart Association III-IV cardiac status, pregnancy, lactation and in children.
- The main side effects include weight gain, oedema, and mild dilutional anaemia.

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THE RECENT AUSDIAB DATA show that 7.2% of Australians over 25 years of age have type 2 diabetes mellitus and a further 16.1% have impaired glucose tolerance. In fact, 20% of Australians over 65 years have type 2 diabetes and it is well known that morbidity and mortality are significantly increased in affected patients.^{1,2} However, there is evidence from the United Kingdom Prospective Diabetes Study (UKPDS) that good glycaemic control can improve morbidity by improving microvascular complications of type 2 diabetes, such as retinopathy, nephropathy and neuropathy³ (E2). (See Box 1 for an explanation of level-of-evidence codes.) There is a well-recognised and strong association of type 2 diabetes with obesity and the insulin resistance syndrome. "Syndrome X"⁵ refers to a collection of pathophysiological sequelae resulting from insulin resistance and includes type 2 diabetes, as well as hypertension, dyslipidaemia, hyperuricaemia and elevated plasminogen-activator-inhibitor-1 levels.⁶

Pathophysiologically, type 2 diabetes is characterised by defects in insulin action (ie, insulin resistance) and secretion (ie, β -cell dysfunction), and increased hepatic glucose output.² It is also well established that type 2 diabetes is a progressive condition, and that β -cell failure ensues in many patients. The UKPDS showed that, although monotherapy with sulfonylureas, metformin or insulin can achieve good glycaemic control initially, sustained control with these agents fails in 50% of patients after three years. Most patients will require multiple therapies to obtain adequate long term glycaemic control (E2).⁷

Currently available therapies

Currently available therapies for type 2 diabetes include various oral agents such as sulfonylureas, metformin, α -glucosidase inhibitors (such as acarbose) and insulin. These agents can be used as monotherapy or in combination therapy. They have been used extensively, are efficacious and have a low incidence of serious adverse events. Recently, a new class of oral agents, the thiazolidinediones (TZDs), which act to improve the insulin sensitivity of peripheral tissues, has become available for use in clinical practice. Troglitazone was the first agent in this class and was effective, but was withdrawn because of severe and unpredictable hepatic failure. Newer TZDs such as rosiglitazone and pioglitazone are now available and have been approved by the Therapeutic Goods Administration (TGA) for use as monotherapy in patients with type 2 diabetes inadequately controlled by lifestyle measures, and also for use in combination with sulfonylureas or metformin in patients with inadequate glycaemic control.^{8,9} Pioglitazone is also licensed for use in combination with insulin.⁹ To date, hepatotoxicity does not appear to be a significant problem with these newer

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1: Level-of-evidence codes

Evidence for the statements made in this article is graded according to the NHMRC system⁴ for assessing the level of evidence.

- E1** Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.
- E2** Level II: Evidence obtained from at least one properly designed randomised controlled trial.
- E3₁** Level III-1: Evidence obtained from well-designed, pseudo-randomised controlled trials (alternate allocation or some other method).
- E3₂** Level III-2: Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series without a parallel control group.
- E3₃** Level III-3: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- E4** Level IV: Evidence obtained from case-series, either post-test, or pre-test and post-test.

agents. Neither drug is listed on the Pharmaceutical Benefits Scheme yet. A profile of these two drugs is shown in Box 2.

Thiazolidinediones and peroxisome proliferator-activated receptor γ

TZDs reduce hyperglycaemia by improving insulin sensitivity in a manner distinct from that of metformin. These drugs increase peripheral glucose utilisation in skeletal muscle and adipose tissue, reduce hepatic glucose output, increase fatty acid uptake and reduce lipolysis in adipose cells. This ultimately leads to a reduction in fasting and post-prandial plasma glucose, insulin and circulating free fatty acid (FFA) levels.¹⁰ TZDs are believed to exert most of their effects through binding to and activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR γ). PPAR γ is a member of the steroid hormone nuclear receptor superfamily, and is found in adipose tissue, cardiac and skeletal muscle, liver and placenta. On activation of this nuclear receptor by a ligand such as a TZD, PPAR γ -ligand complex binds to a specific region of DNA and thereby regulates the transcription of many genes involved in glucose and fatty acid metabolism.¹⁰ An endogenous ligand for this receptor has not been identified. Activation of PPAR γ also leads to stimulation of adipogenesis,¹¹ and this occurs more so in the subcutaneous rather than the omental fat depot.¹²

There are other isoforms of PPAR, and one of these, PPAR- α , is predominantly expressed in liver and is activated by hypolipidaemic agents such as fibrates. It mediates the triglyceride-lowering and high density lipoprotein (HDL)-raising effects of fibrates. Recent research has identified agents which are capable of activating PPAR γ and PPAR α simultaneously, and which could potentially have even greater beneficial effects than current TZDs. The development of TZDs has also led to the identification of non-TZD compounds which are capable of acting as full or partial agonists or as antagonists of PPAR γ , depending on the tissue type and the specific target gene, in a manner analogous to the selective oestrogen receptor modulators

2: Drug profile of rosiglitazone and pioglitazone

Action: TZDs activate peroxisome proliferator-activated receptor γ (PPAR γ) and thereby regulate a number of genes involved in glucose and lipid metabolism. They act to improve insulin sensitivity.

Onset: Both rosiglitazone and pioglitazone are rapidly absorbed and have high bioavailability. The timing of dose in relation to food does not significantly affect absorption or serum levels. Changes in fasting plasma glucose may start to be seen within two weeks, but maximal effects on glycaemic control may not be evident until 6–14 weeks after commencement of therapy.

Dosing: Both rosiglitazone and pioglitazone are available as oral formulation. Rosiglitazone comes in 2 mg, 4 mg and 8 mg tablets and pioglitazone in 15 mg, 30 mg, and 45 mg tablets. No dosage adjustment is required for renal impairment.

- **Recommended dose for rosiglitazone (Avandia; GlaxoSmithKline)** — Commence at 4 mg per day, and, if necessary, increase to 8 mg per day after 6–8 weeks as a single or divided dose given with or without food. There is no additional benefit from doses higher than 8 mg per day. The largest dose given in combination with sulfonylurea in clinical studies was 2 mg twice daily.
- **Recommended dose for pioglitazone (Actos; Eli Lilly)** — Commence at 15 mg per day, and, if necessary, increase to 30 mg per day up to a maximum of 45 mg per day after 4–6 weeks. Give as a single dose with or without food. The largest daily dose used in clinical studies of pioglitazone in combination with insulin or sulfonylurea was 30 mg.

Metabolism: Both drugs are extensively metabolised by hepatic cytochrome P450. Rosiglitazone metabolites are essentially inactive and mainly excreted in the urine. Some of the pioglitazone metabolites are active and are excreted in faeces and urine. Neither drug inhibits cytochrome P450. Although no significant drug interactions have so far been identified, prescribers should be vigilant for possible interactions, especially with drugs metabolised by or affecting the cytochrome P450 system.

Adverse effects: Both drugs are well tolerated. There have been some case reports of hepatic dysfunction in patients taking the two drugs but causation was not definite. The incidence of elevations in enzyme levels on liver function tests was the same in treatment and placebo groups. The most common adverse effects include weight gain, oedema and dilutional anaemia. Because of fluid retention, these drugs may exacerbate heart failure and should not be prescribed to patients with New York Heart Association III-IV cardiac status. The drugs are also contraindicated in pregnancy and lactation and have not been tested in children. In women with polycystic ovarian syndrome with insulin resistance, treatment with these drugs may restore ovulation and appropriate advice regarding contraception should be given. When used in combination with other antidiabetic drugs, rosiglitazone and pioglitazone have been associated with mild hypoglycaemia requiring dose reduction of sulfonylurea, metformin or insulin.

(SERMs). It is therefore possible that future agents will be more selective and specific in their effects and potentially safer and more efficacious.¹³

Clinical trials

Although the evidence for therapy with these two agents is Level II, some of the data have either been published in abstract form only, or are only available from pharmaceutical company sources or websites or other organisations like the United States Food and Drug Administration (FDA). There are few studies which directly compare these agents

as monotherapy or combination therapy with current standard treatment regimens. There are also no long term data on safety or effects on morbidity or mortality related to diabetes and cardiovascular disease. There are no studies directly comparing rosiglitazone and pioglitazone. The clinical trial data are summarised below.

◆ **Both drugs lower HbA_{1c} and fasting plasma glucose (FPG) levels when used as monotherapy^{8,9,14-22} (E2)**

■ For rosiglitazone, there was a dose-dependent reduction in HbA_{1c}. The greatest effect was seen with a divided dose of 4 mg twice daily. In the various studies, this resulted in a reduction in HbA_{1c} level of between -0.6 and -0.8 percentage points compared with baseline, and -1.5 to -1.8 compared with placebo. The FPG level was reduced by 2.3-3.6 mmol/L compared with baseline and 3.4-4.6 mmol/L compared with placebo.

■ For pioglitazone, there was also a dose-dependent reduction in HbA_{1c} level of -0.9 percentage points compared with baseline, and -1.6 compared with placebo, for patients taking 45 mg per day. The FPG level was reduced by 3.1 mmol/L compared with baseline, and 3.6 mmol/L compared with placebo.

■ For both drugs, patients who were already receiving treatment with other agents at recruitment into the studies responded less well when swapped to monotherapy with the TZD than drug-naïve patients.

◆ **Rosiglitazone and pioglitazone lower HbA_{1c} and FPG levels when used in combination with a sulfonylurea or metformin^{8,9,23-26} (E2)**

■ Rosiglitazone (2 mg twice daily) added to various sulfonylureas over 26 weeks resulted in a reduction in HbA_{1c} level of -0.8 percentage points compared with baseline, and -1.0 compared with placebo plus sulfonylurea. The FPG level was reduced by 2.09 mmol/L.

■ When added to metformin (2.5 g), rosiglitazone (8 mg per day) reduced the HbA_{1c} level by -0.78 percentage points and the FPG level by 2.7 mmol/L compared with baseline, and reduced the HbA_{1c} level by -1.2 percentage points and the FPG level by 2.9 mmol/L compared with placebo plus metformin.

Pioglitazone (30 mg) added to sulfonylurea reduced the HbA_{1c} level by -1.3 percentage points compared with baseline and the FPG level was reduced by 2.9 mmol/L.

■ When pioglitazone was added to metformin, the HbA_{1c} level was reduced by about -0.7 percentage points, and the FPG level fell by 2.4 mmol/L compared with baseline. Compared to placebo plus metformin, pioglitazone (30 mg) plus metformin reduced the HbA_{1c} level by -0.83 percentage points and the FPG level by 2.1 mmol/L.

◆ **Rosiglitazone and pioglitazone lower HbA_{1c} and FPG levels when used in combination with insulin^{8,9,27,28} (E2)**

■ Rosiglitazone (4 mg or 8 mg per day) added to insulin reduced HbA_{1c} levels by -0.6 and -1.2 percentage points

(respectively) compared with baseline and -0.7 and -1.3 compared with placebo plus insulin. Congestive heart failure was reported in two patients in each rosiglitazone group (comprising 106 and 103 patients) and one in the placebo group (103 patients). Rosiglitazone is not registered for use in combination with insulin.²⁷

■ Pioglitazone (15 mg or 30 mg) per day added to insulin reduced HbA_{1c} levels by -0.99 and -1.26 percentage points (respectively) compared with baseline and -0.73 and -1.00 compared with placebo plus insulin. Sixteen per cent of patients in the 30 mg pioglitazone plus insulin group had a reduction in their insulin dose of more than 25%.²⁸

■ In these two studies, the incidence of oedema was significantly increased in the groups treated with TZD plus insulin.^{27,28}

◆ **Both drugs lower fasting insulin and C-peptide levels when used as monotherapy or in combination therapy^{8,9,14-26} (E2)**

■ The significant reduction in insulin and C-peptide levels is consistent with the mechanism of action of these drugs as insulin sensitisers.

◆ **Both drugs increase HDL and LDL and decrease FFA levels; pioglitazone lowers triglyceride levels^{8,9,14-32} (E2)**

■ Rosiglitazone significantly increased low-density lipoprotein (LDL) levels (mean increase, 15%-20%²⁹) compared with baseline and controls, whereas, although pioglitazone increased LDL levels compared with baseline, there was no difference compared with controls.

■ Rosiglitazone also tends to increase total cholesterol level and studies have reported variable effects on ratios of total cholesterol to high-density lipoprotein (HDL) and of LDL to HDL. In patients taking rosiglitazone, the ratios are either unchanged or increased. In studies over six months, the ratios tended to be unchanged because LDL reached a plateau and HDL continued to increase. There is a trend for these ratios to decrease in patients treated with pioglitazone.

■ A recent, small, non-randomised and unblinded study suggested that pioglitazone increased levels of HDL to a greater, and LDL to a lesser, extent than rosiglitazone³⁰ (E4). No randomised comparative study has been undertaken.

■ It is known that modest increases in LDL levels correlate with increased cardiovascular risk. However, as has been reported for troglitazone,⁶ the increase in LDL level associated with rosiglitazone and pioglitazone is mainly in the larger, more buoyant and less atherogenic particles of LDL.^{31,32}

■ Pioglitazone significantly reduced triglyceride levels.

■ The long term effects of these alterations in lipid profile are unknown.

Comparison with current antidiabetic drugs

In a published abstract and in the product information, rosiglitazone (2 mg twice daily and 4 mg twice daily) was directly compared with glibenclamide (or glyburide) at

3: Important messages for patients

Thiazolidinediones (TZDs):

- Are a new type of drug for the treatment of type 2 diabetes.
- Improve diabetic control by increasing the body's sensitivity to insulin.
- Can cause mildly low blood sugar levels if they are used in combination with other medications for diabetes.
- Can cause some weight gain and mild fluid retention.
- Should not be taken if you are pregnant or breastfeeding or if you have significant heart or liver problems.

Your doctor may need to advise you about methods of contraception, as you should not become pregnant while taking these medications.

You will need to have regular liver function tests.

“optimally titrated dose”. Patients in all three groups showed a statistically significant improvement in glycaemic control. The HbA_{1c} level fell 0.27% and 0.53%, respectively, for the two rosiglitazone groups and 0.72% for the glibenclamide group at one year.^{8,33} Rosiglitazone was said to be “statistically equivalent” to glibenclamide at lowering HbA_{1c} at one year, although the mean dose of glibenclamide is not stated (but, according to the FDA website, is 7.5 mg/day),²⁹ and the graph in the product information shows that there was a deterioration in glycaemic control in the first six months in the two rosiglitazone groups. There was no statistical analysis provided for any time points other than one year. Rosiglitazone at 4 mg twice daily resulted in a significantly greater reduction in FPG level at one year than glibenclamide (−2.3 mmol/L v −2.0 mmol/L, respectively; $P < 0.033$).³³ A study comparing rosiglitazone with metformin has not been published, but some information can be accessed through the FDA website.²⁹ Patients were placed on metformin therapy at recruitment and the dose was increased to 2.5 g per day. They were then randomly allocated to continue to take metformin, to stop taking metformin and start taking rosiglitazone (4 mg twice daily) or to add rosiglitazone (4 mg twice daily) to their metformin therapy. The combination of the two agents was better than either used as monotherapy, but there was also a subset of patients in the group converted from metformin to rosiglitazone monotherapy who showed an abrupt deterioration of glycaemic control over the 24 weeks.^{29,34} However, no statistical analysis is provided. There are no similar studies published for pioglitazone. DeFronzo has reviewed studies of monotherapy with conventional agents and compared the efficacy of sulfonylureas, metformin, acarbose and troglitazone. From a similar starting HbA_{1c} level, sulfonylureas and metformin reduced the HbA_{1c} level by 1.5%–2.0% and the acarbose level by 0.7%–1.0%. Troglitazone reduced the HbA_{1c} level by 1%–1.2%.² The monotherapy studies described above indicate that the reduction in HbA_{1c} level with rosiglitazone and pioglitazone is probably less than that with sulfonylureas or metformin.

Concerns about hepatotoxicity

Troglitazone was the first agent in this class to be marketed in the United States and was withdrawn by the FDA in

March 2000 because of severe and unpredictable hepatotoxicity and 61 related deaths.³⁵ The incidence of troglitazone-induced acute liver failure is estimated to be 1 in 8000 to 1 in 20 000 patients treated.³⁶ The side chain of troglitazone, an α -tocopherol (vitamin E) moiety, or its quinone metabolites, may be the reason for its hepatotoxicity, and therefore this may not represent a class effect.¹⁷ To date, there have been three case reports of hepatotoxicity potentially caused by rosiglitazone and one potentially caused by pioglitazone. The agent was not proved to be the cause in any of these cases, all of which resolved with supportive care and withdrawal of the agent.^{37–40} In clinical trials, asymptomatic, reversible elevations of hepatic enzymes during treatment with both drugs have been noted, but rates were similar to those with placebo and resolved without withdrawal of the drug.⁴¹ The product information for both drugs states that these agents are contraindicated in patients with alanine aminotransferase (ALT) levels more than 2.5 times the normal level at baseline. Caution should be exercised when using these drugs in patients with hepatic enzyme level elevations of 1–2.5 times normal at initiation. It is also recommended that liver function tests (LFTs) be performed at baseline and every second month for the first year of therapy, and then periodically thereafter. If symptoms of liver dysfunction occur, LFTs should be checked. If the ALT remains elevated to more than three times the normal level, with or without symptoms, the drug should be discontinued.^{8,9}

Adverse reactions and side-effects

In all clinical trials for both rosiglitazone and pioglitazone, the incidence of adverse events, with the exception of weight gain and peripheral oedema, was similar to placebo.

As monotherapy, neither drug caused hypoglycaemia, but in combination therapy mild hypoglycaemia has been reported and, in some cases, the dose of sulfonylurea, insulin or metformin was reduced.^{8,9,23–28} (E2). Dose-dependent weight gain of 0.5–3.7 kg has been noted in the clinical trials and seems to be a class effect. The least weight gain was seen when used in combination with metformin.^{8,9,14–17,20–28} Weight gain is likely to be multifactorial in nature and could be the result of increased adipogenesis, increased appetite and oedema.^{11–15} Despite the weight gain, there are clearly improvements in insulin sensitivity and glycaemic control. Some studies report that the weight gain is associated with a reduction in waist:hip ratio, supporting the theory that there is a “shift” in fat distribution from visceral to subcutaneous fat depots, which confers less cardiovascular risk.¹⁵

In all studies, oedema occurred more frequently in the TZD treatment groups, although it was generally mild and did not lead to withdrawal from treatment. The incidence of oedema is about 3%–5%, although, when rosiglitazone or pioglitazone was combined with insulin therapy, the incidence rose to 13%–16%, compared with 5%–7% in the group receiving insulin plus placebo.^{8,9,14–17,20–28} There is also an increase in plasma volume of 6%–7%, and patients with New York Heart Association Class III and IV cardiac

status were excluded from the studies (both drugs are contraindicated in these patients). This increase in plasma volume is also likely to be responsible for the mild reduction in haemoglobin level seen with all TZDs.⁶

Precautions

There are no data on the use of these drugs in pregnancy or lactation. In animal studies both drugs cross the placenta, and fetal loss, retarded fetal development and suppression of postnatal growth have been seen in rats.^{8,9} There were no significant effects on levels of the oral contraceptive pill in healthy women taking rosiglitazone, and the drug's manufacturer reports that no impairment of efficacy would be expected.^{8,42} There is no similar study for pioglitazone, but the product information recommends that alternative modes of contraception be used.⁹ Women with polycystic ovarian syndrome and insulin resistance should be advised that treatment with TZDs may result in resumption of ovulation and advice regarding suitable contraception should be given.^{8,9}

Both drugs are contraindicated in moderate to severe liver dysfunction. Dose reduction is not required in elderly patients or those with renal impairment.^{8,9} Although animal studies have shown tumour-inducing effects for familial adenomatous polyposis and sporadic colon cancer in mice, there are no clinical data yet.⁴³ However, mutagenicity and carcinogenicity studies have not raised any other significant concerns.^{8,9} These agents should be avoided in patients with significant cardiac dysfunction. There are no data in humans under 18 years of age.

Conclusions and recommendations

The thiazolidinediones are a unique class of drugs for the management of type 2 diabetes and they act to improve insulin resistance. Current evidence suggests that they are effective in the treatment of type 2 diabetes, but there is no evidence to suggest that they are better than currently available drugs and no data on long term safety or effects on morbidity and mortality related to diabetes and cardiovascular disease. Since the mechanism of action of TZDs is different from other currently available antidiabetic agents, it seems logical that they would be useful in combination therapy. So far, there are no studies assessing the effect of the TZDs when added to the combination of sulfonylurea and metformin, or to insulin combined with sulfonylurea or metformin. There is little difference between the two agents, although pioglitazone may have a more favourable effect on lipid profile than rosiglitazone. There are some data that show that these drugs may preserve beta-cell function, and it has been suggested that they should therefore be used early in the disease process, but there are no studies to support this hypothesis. Until there are more data available, these agents should probably be reserved for use in combination therapy in patients who are unable to be managed with current standard treatment combinations (ie, metformin, sulfonylurea, acarbose and insulin),^{44,45} and who fulfil the

current prescribing guidelines. The development of thiazolidinediones has opened the door to some exciting research and to the development of other new agents for the treatment of type 2 diabetes mellitus. Important messages for patients are shown in Box 3.

Competing interests

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book review

A weight of evidence

Clinical evidence. A compendium of the best available evidence for effective health care. 5th edition. London: BMJ Publishing, 2001 (xxiii + 1432 pp + CDROM, \$217 (personal), \$473.70 (institutional)). ISBN 0 7279 1612 2.

BEING ASKED TO REVIEW *Clinical evidence* is a bit like being asked to review the Bible — the previous edition is on the desk of about 600,000 people around the world; I expect thunderbolts from the high priests of evidence-based medicine if I criticise it; and, at 2.6 kilos, it weighs about as much as the average tablet of stone.

It certainly meets its stated aim of summarising the current state of knowledge and uncertainty about the prevention and treatment of clinical conditions, but I would use it more frequently if it were more portable. That is the major problem with this book — it is not yet available in a pocket-sized version (either for Palm or paper). Such a concise version with “smart” summaries will be piloted in the next edition, and specialist versions are planned to cater for the exotic tastes of single-organ doctors. In the meantime, carrying it around helps to protect my aging bones against osteoporosis (one of the topics not yet covered).

The availability of evidence at the bedside is an important factor in determining whether it is used to support daily decision-making about patient care. Clinical evidence, while useful to consult in a contemplative fashion when reviewing cases, has not yet become as essential to me as the stethoscope. The on-line and (new to this edition) CD-ROM versions do increase the number of points in the hospital system where it can be

accessed, but most Australian public hospitals do not yet have enough point-of-care terminals for these formats to have a huge impact. Few general practitioners would have time to refer to it during the average short consultation either.

The CD-ROM is fast and reasonably intuitive to use. The ubiquitous Microsoft Internet Explorer platform means that embedded links to abstracts of original articles are available via PubMed if you are using a computer with an Internet link. The glossary is also helpful.

These variations in packaging may increase sales, but I feel obliged to point out that the hope expressed in the introduction, that *Clinical evidence* will improve patient care, has yet to be demonstrated in a randomised controlled trial. Perhaps Australia's contribution to evidence-based medicine could be to demonstrate that a resource ranked by doctors in their top three favourite sources of information improves the care we deliver.

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