Waking up from the DREAM of preventing diabetes with drugs

A drug to prevent diabetes would be attractive. But despite promotion of recent research evidence, **Victor Montori**, **William Isley**, and **Gordon Guyatt** argue that we are not there yet

Diabetes affects about 4% of the world population[1 2] and is associated with important costs, both in financial and human terms.[3] The high prevalence, increasing incidence, and associated costs makes preventing diabetes a public health priority. The diabetes reduction assessment with ramipril and rosiglitazone medication (DREAM) trial recently showed that rosiglitazone reduced the risk of diabetes in people at risk.[4] The results have prompted aggressive marketing of rosiglitazone as a preventive therapy; some clinicians are already responding to this initiative. We argue that the strategy will bring harms and additional costs while the benefits for patients remain questionable.

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Preventing diabetes

Several randomised trials have shown that modest weight loss and physical activity can greatly reduce the risk of diabetes.[5-7] The Diabetes Prevention Program documented a 58% relative risk reduction (confidence interval 48% to 66%) in high risk individuals[5]; other trials have shown similar results.[6 7]

Nevertheless, the possibility of preventing diabetes with drugs has caught the imagination of the drug industry. The medicalisation of pre-disease states and risk factors has become increasingly common, including targets of precursors of hypertension, osteopenia, and obesity. The prospect of marketing existing drugs to otherwise healthy people greatly expands the market for these drugs while increasing costs for society, increasing use of health care, and potentially reducing quality of life by converting healthy people into patients.[8 9]

Effectiveness of drugs

Several trials have assessed the ability of drugs to prevent diabetes (box).[10] Overall, except for metformin, the evidence is inconsistent and comes from trials of limited methodological quality. Two trials included drug discontinuation phases to determine if the drugs had changed the natural course of diabetes or was merely treating diabetes.[5 11] Both discontinuation studies found that the proportion of diabetes diagnoses remained lower in the intervention arm; a third to half of the patients, however, were lost to follow-up and did not provide discontinuation data. Furthermore, the follow-up period after treatment was much shorter than the treatment time. None of the trials showed a reduction in the risk of diabetes complications.

DREAM is a large randomised controlled trial that enrolled patients with impaired fasting glucose concentrations or impaired glucose tolerance and assigned them to high dose rosiglitazone or placebo.[4] The trial effectively concealed allocation, adhered to the intention to treat principle, and achieved negligible loss to follow-up after a median follow-up of three years.

The trial's primary outcome was a composite end point of death and the diagnosis of diabetes. It was stopped early after almost 1000 primary end points had accumulated because of benefit in the treatment arm (table 1). The authors noted that for every 1000 people treated with rosiglitazone 8 mg/day for three years, about 144 people who would otherwise cross the glucose threshold we call diabetes will not do so; four to five patients without congestive heart failure will develop the condition.

Evidence for drug prevention of diabetes

Metformin
- Consistent evidence from 3 randomised trials
- The Diabetes Prevention Program (DPP) found metformin reduced the 3 year risk of diabetes (relative risk 0.69, 95% confidence interval 0.57 to 0.83), but lifestyle change was more effective[5]

Troglitazone (no longer available)
Two trials found troglitazone was effective in preventing diabetes:
- Study in women with a history of gestational diabetes had large loss to follow-up[11]
- The DPP discontinued the trial arm because of fear of liver toxicity. Relative risk of diabetes diagnosis after 1 year of troglitazone was 0.25 (P<0.001), but the effect disappeared in the year after drug discontinuation[12]

Angiotensin converting enzyme inhibitors, angiotensin receptor blockers
- Systematic reviews of trials in hypertension, heart failure, and coronary disease that assessed diabetes as a secondary or post hoc outcome found large preventive effects[13]
- DREAM trial failed to confirm the effect[14]

Table 1 | Results of DREAM trial of treatment to prevent diabetes[4]

	No (%) of participants		
End point/side effect	Rosiglitazone (n=2635)	Placebo (n=2634)	Hazard ratio (95% CI)
Primary end point*	306 (11.6)	686 (26)	0.40 (0.35 to 0.46)
Death from all causes	30 (1.1)	33 (1.3)	0.91 (0.55 to 1.49)
Diagnosis of diabetes	280 (10.6)	658 (25)	0.38 (0.33 to 0.44)
Congestive heart failure	14 (0.5)	2 (0.1)	7.0 (1.6 to 30.9)
Oedema	174 (6.8)	124 (4.9)	Not reported

*Composite of death from all causes and diagnosis of diabetes.

Use of a composite end point

The apparent motivation for the use of death and diabetes as the primary end point was fear that death could act as a competing risk (the intervention could reduce the development of diabetes by increasing the risk of dying). Unfortunately, the hypothesis is implausible, and the resulting composite end point is potentially misleading because of a large gradient both in importance to patients and in frequency of events and treatment effects. Rosiglitazone had no effect on all cause mortality, an outcome of great importance to patients.[4]

We have reported previously that readers should beware of trials in which investigators choose composite end points with large gradients in patient importance, event frequency, and treatment effects.[15] An analysis of composite end points in cardiovascular trials showed that end points of least importance to patients often contributed most events.[16] In this situation, readers must focus on the effects of treatment on the components.[17] Thus, considering this trial as showing a 60% reduction in the risk of death or diabetes is a mistake. We should instead consider the apparent benefits of a 62% reduction in diabetes.

Are patients better off taking pills to prevent diabetes?

The biochemical diagnosis of type 2 diabetes is a surrogate end point. From the standpoint of the health system, diagnosis of diabetes is a surrogate for increased use of healthcare resources, at least in the short term. Whether early drug use would reduce long term expenditure is unproved. Equally efficacious lifestyle interventions are far less costly to implement and may well reduce costs in the long run, particularly when applied to populations.

From the standpoint of the patient, the diagnosis of diabetes is a surrogate for challenges with employment and insurability, need for frequent clinic visits and tests, need for self monitoring and drug use, inconvenience, cost, anxiety, and short term (such as hypoglycaemia) and long term complications (such as microvascular and macrovascular complications, depression). For patients to celebrate the finding that taking a pill reduces the risk of receiving a diagnosis of diabetes one key condition needs to apply: patients should be better off.

Table 2 presents the short and long term outcomes important to patients that we might expect in a cohort of 10 000 patients who take rosiglitazone for three years to prevent diabetes, and 10 000 who do not, based on a simplified modelling exercise (see bmj.com for assumptions and estimations).

Downsides of taking pills to prevent diabetes

To show that rosiglitazone has truly prevented diabetes, the DREAM investigators are conducting a discontinuation study to see if the drug has delayed the diagnosis of diabetes after discontinuing treatment. If diabetes is present after rosiglitazone withdrawal, the effect of the drug was actually treatment of diabetes. Tuomilehto and Wareham, in an editorial accompanying the DREAM publication in the *Lancet,* use epidemiological data to show that up to now the glucose lowering effect of rosiglitazone can completely explain the trial's findings.[19]

Table 2 shows that, even under the most optimistic assumptions, patients offered rosiglitazone for prevention will end up taking more pills. Thus, neither patients who value preventing diabetes in order to avoid taking drugs, nor a society concerned with cost minimisation, benefit from early use of rosiglitazone.

Patients at risk of developing diabetes may fear the diagnosis and its consequences. Taking rosiglitazone to prevent diabetes may plausibly reduce this anxiety; alternatively, the daily reminder of the pill may increase anxiety. The finding that one third of patients with screen detected diabetes experienced distressing anxiety when they were exposed to early intensive treatment (compared to one fifth of patients who did not have early intensive treatment) suggests that increased anxiety is a real possibility.[20]

Both DREAM and the prospective pioglitazone clinical trial in macrovascular events (PROactive) trial found

Table 2 | Outcomes important to patients in decision to use rosiglitazone to prevent diabetes

End point	Rosiglitazone (n=10 000)	No rosiglitazone (n=10 000)	Hazard ratio (95% CI)
Drug use			
Patient years of use of ≥1 diabetes drug at end of trial (3 years)	30 000	3 650	—
No of patients with new diagnosis of diabetes at end of trial (3 years)*	1060	2500	0.38 (0.33 to 0.44)
Projected patient years taking ≥1 diabetes drug at 10 years, assuming 3% annual incidence of diabetes	43 637	33 856	—
Projected patient years taking ≥1 diabetes drug at 10 years, assuming 8% annual incidence of diabetes	52 566	33 856	—
Diabetes related outcomes			
Anxiety about diabetes	?	?	?
Costs and inconvenience associated with glucose self monitoring	?	?	?
Costs and inconvenience associated with medical care	?	?	?
Cardiovascular end points (myocardial infarction, stroke, cardiovascular death) at 3 years	120	90	1.39 (0.81 to 2.37)
Cardiovascular end points at 10 years	?	?	?
Heart failure at 3 years	50	10	7.03 (1.6 to 30.9)
Heart failure at 10 years	?	?	?
Retinopathy, nephropathy, or neuropathy	?	?	?
Common adverse effects			
Peripheral oedema at 3 years	680	490	1.4§(1.1 to 1.8)
Weight gain (kg) at 3 years†	2.0	−0.2	—
Peripheral oedema or weight gain at 10 years	?	?	?
Rare adverse effects			
Bone fractures at 4 years‡	632	373	1.7§ (1.3 to 2.2)
Macular oedema	?	?	?

*Assuming that clinicians immediately prescribe diabetes drugs (metformin) to patients who have diabetes diagnosed given that they were already receiving limited lifestyle interventions in DREAM.
†from the DREAM slide set (www.ccc.mcmaster.ca/dream.htm).
‡From the ADOPT trial18
§Risk ratio.

glitazones increased the risk of heart failure.[18] Thus, patients hoping to avoid cardiovascular complications may develop one such serious complication as a result of taking the drug.

Evidence is emerging of other serious side effects of glitazones. These include macular oedema with risk of blindness (probably rare[21]), and bone loss with risk of fracture and loss of independence and death in older women with diabetes. In a community based observational study, Schwartz and colleagues estimated that older women with diabetes taking glitazones for five years could lose 3% of their whole body bone density.[18] Furthermore, a four year trial found the risk of fractures in men and women with a new diagnosis of diabetes was 6.3% in those taking rosiglitazone versus 3.7% in those taking metformin or glibenclamide.[22]

Benefits of diabetes prevention with glitazones

One key issue is whether early drug treatment reduces the risk of developing complications of diabetes. The risk of developing cardiovascular complications in the DREAM cohort with impaired glucose regulation was very low. Thus, although the results seem to favour placebo, the estimates are very imprecise (table 1). This contrasts with many small randomised controlled trials showing that glitazones reduce cardiovascular risk factors and surrogate markers and with the results of the PROactive trial, which found non significant reductions in all cause mortality, non-fatal myocardial infarction, and stroke among patients taking pioglitazone.[23] Consistent high quality direct evidence linking diabetes prevention with glitazones with reduction of complications associated with diabetes remains lacking (table 2).

How can we use our current knowledge to inform patients of the potential benefits of glitazone to prevent diabetes? We can tell patients at 25% risk of requiring a diabetes drug that we are going to give them a 100% chance of receiving that drug for three years in order to reduce their risk of requiring it in the future to 10%. This is a best case scenario. Furthermore, it is unclear how long, if at all, that reduced risk of need will extend.

In general, humans prefer immediate benefits to delayed benefits, prefer to delay inconvenience and adverse events, and prefer certain benefits to speculative benefits. If clinicians offer patients glitazones to prevent diabetes, they are offering certain inconvenience, cost, and risk for largely speculative benefit. Lifestyle changes are clearly at least as effective as glitazones and can be implemented considerably more cheaply.

Conclusion

When drugs are promoted for prevention, and the number of patients at risk of the target condition is very large, the expanded exposure to the drug may lead to important harm. Nevertheless, people at risk may be prepared to tolerate rare serious side effects when the benefits are clear. However, the benefits of rosiglitazone on outcomes important to patients remain speculative.

Because of the risk of harming people with no or minimal symptoms, the threshold for use of drugs in otherwise healthy people must be set high. To get the required data for rosiglitazone requires large and long randomised controlled trials measuring its effect on outcomes important to patients and use of healthcare resources. Clinical use of glitazones to prevent diabetes is, at present, impossible to justify because of unproved benefit on patient important outcomes or lasting effect on serum glucose, increased burden of disease labelling, serious adverse effects, increased economic burden, and availability of effective, less costly lifestyle measures.

SUMMARY POINTS

- Lifestyle changes and certain drugs are effective in preventing the diagnosis of diabetes
- No trial has shown that prevention with drugs improves outcomes important to patients
- Lifestyle changes are equally effective, much safer, and cheaper
- Clinical use of glitazones for prevention cannot be justified

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