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Incretin therapy: should adverse consequences have been anticipated?

Transparency is what we need

Edwin Gale emeritus professor of diabetic medicine, Department of Diabetes and Metabolism, Southmead Hospital, Bristol BS10 5NB, UK
Edwin.Gale@bristol.ac.uk

In a linked investigation, Cohen shines a spotlight on the safety of the incretins—drugs for the treatment of diabetes that mimic or enhance the biological effects of glucagon-like peptide-1 (GLP-1).[1] Her investigation raises important questions as to the nature of the dialogue between drug companies and the regulators, and the extent to which potentially harmful effects of these drugs have been hidden from prescribers and patients.

The drugs that have transformed the modern treatment of chronic illness—β blockers, angiotensin converting enzyme inhibitors, and statins—are typically inhibitors of defined molecular pathways, with consequences that are relatively predictable. By contrast, the incretins are agonists that act on multiple targets with multiple effects. They are "magic shotguns" rather than "magic bullets."

The thiazolidinediones—nuclear receptor agonists that modulate the activity of numerous genes—are good examples of this. They were introduced with great fanfare, but unwanted effects such as weight gain, fluid retention, and osteopenia have limited their use in the management of diabetes. Troglitazone, the first in class, was withdrawn because of hepatic injury; rosiglitazone was withdrawn from most countries in 2011 because of cardiovascular problems; and pioglitazone has been implicated in bladder cancer.

In each case the potential problem was spotted early in development but the regulatory response was disconcertingly slow. Troglitazone eventually came off the market because of the "termites"—Food and Drug Administration officials who alerted members of Congress to the problem (and were disciplined for doing so)—and because of the work of a Pulitzer prize winning journalist.[2] Rosiglitazone was brought down by a cardiologist who published an independent analysis of clinical trials that the drug's manufacturer was fortuitously obliged to make public in the wake of an unrelated misdemeanour.[3] If the clinical trials had not been made public, would we still be using this drug?

GLP-1 is a short acting gut peptide that interacts with receptors in tissues including the brain, cardiovascular system, renal tubules, thyroid, and pancreatic exocrine and islet cells. GLP-1 deficiency does not seem to be an intrinsic feature of type 2 diabetes,[4] and the therapeutic actions of the incretins are achieved at pharmacological doses that are much higher and more prolonged than in the physiological situation. The long term consequences of this exposure are unknown. GLP-1 has both neurocrine and endocrine effects and is also an enterogastrone (an agent that affects stomach motility). Another important effect is proliferation of cell growth.

The first GLP-1 agonist to reach the market was exenatide, first identified as exendin-4 in the venom of the Gila monster, *Heloderma suspectum*, a North American species of poisonous lizard. Few have paused to wonder why this predator should produce a non-toxic peptide in its saliva. The answer is that *H suspectum* is a desert lizard that goes for weeks or months between meals and conserves energy during the intervals by involution of its digestive apparatus, including its intestinal epithelium and exocrine pancreas. Production of exendin-4, a human GLP-1 agonist, causes rapid proliferation of intestinal tissue and a 50% increase in the size of the pancreas when it feeds.[5]

The growth stimulating effects of the incretins have long been known, and it was initially hoped that they would stimulate regeneration of pancreatic β cells and reverse the progression of diabetes. However, duct cells in the mammalian exocrine pancreas also carry the GLP-1 receptor and proliferate in response to GLP-1 receptor stimulation. Pancreatic enlargement has been noted in several species, and ductal hyperplasia offers a plausible mechanism for the occurrence of acute pancreatitis, an increasingly undeniable class effect of the incretins.[6 7]

Postmortem studies in people who have been taking incretins confirm that the use of exenatide or sitagliptin is associated with pancreatic enlargement and morphological change.[8] Regulatory documents unearthed by Cohen's investigation provide further evidence that the incretins produce greater subclinical fluctuations in pancreatic enzymes than other treatments for diabetes. Increased concentrations of pancreatic enzymes do not prove subclinical pancreatic inflammation but are consistent with it, and silent pancreatic inflammation is associated with the development of pancreatic cancer.[9] Signals that the use of the incretins may be associated with pancreatic and thyroid tumours are now clearly present in regulatory databases.[10]

Marked α cell and β cell hyperplasia, as well as exocrine expansion, has been seen in pancreatic tissue obtained at autopsy from people taking incretins. Hyperplasia of α cells was associated with microadenomas in three of eight pancreases examined, one of which also contained a neuroendocrine tumour.[12]

It has taken eight years from the introduction of exenatide for all this to come to light. What went wrong? It is always easy to blame the regulators—they can't answer back. I was an adviser to the European Medicines Agency for several years and can testify to the high quality, motivation, and training of the people who work there. Nor is big pharma the evil empire. The problem lies in a system that subordinates the public interest to commercial secrecy and allows the perceived need for such secrecy to define the legal, administrative, and cultural limits of the interaction between the mirror bureaucracies of the regulators and companies. Regulatory documents released to the *BMJ* under the Freedom of Information Act make it abundantly clear that the European Medicines Agency raised the right questions at an early stage, but the agency took each one off the agenda when plausible responses were supplied by the applicants. Each concern was treated in isolation rather than as another clue to an emerging pattern of biological effect.

The fate of the incretins has yet to be determined, but it has once again been shown that current regulatory procedures are inadequate to deal with the challenges presented by drugs that act on many targets. Similar scenarios will play out again while secrecy rules and the companies control access to the data. Safety requires more than tidy paperwork or the performance of yet more clinical studies. Cohen's investigation has shown us—if further proof is needed—how much we need transparency.

Competing interests: I have provided expert testimony in litigation concerning exenatide.
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EDITORIAL, p 8; FEATURES, p 16

Data from studies from all developmental phases should be available to the regulatory authorities and the scientific and safety advocacy community

Helping patients make sense of the risks of taking GLP-1 based drugs

Tough when benefits and harms are unclear

Victor M Montori professor of medicine, Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, MN 55902, USA
montori.victor@mayo.edu

There are three reasons to lower glycaemia in patients with type 2 diabetes: to treat the symptoms of hyperglycaemia; to prevent symptomatic hyperglycaemia; and to reduce the risk of developing complications associated with diabetes. Regulatory agencies approve antihyperglycaemic agents because they prevent and treat hyperglycaemia. The US Food and Drug Administration now requires drug companies to show that their antihyperglycaemic drugs do not increase a patient's risk of developing cardiovascular disease. Currently, however, no regulatory agency requires evidence of a drug's efficacy in reducing the risk of developing complications of diabetes.

Does the use of antidiabetic drugs have any benefits in patients with asymptomatic type 2 diabetes? It is possible that lowering glycaemia, regardless of the approach, reduces the risk of microvascular and cardiovascular complications, but this remains uncertain, despite testing in contemporary trials that have enrolled tens of thousands of patients.[1] Furthermore, comparative effectiveness studies have shown no antihyperglycaemic drug to be more beneficial in this regard than any other.[2] Evidence from long term follow-up of patients in the UK Prospective Diabetes Study suggests that cardiovascular complications might be reduced by preventing hyperglycaemic symptoms.[3] Considerable uncertainty exists, however, in applying this evidence to patients who are at risk of cardiovascular complications but who quit smoking and adhere to low dose aspirin, standard or high dose statins, and antihypertensive treatment. The residual modifiable risk might be too small to justify expensive, inconvenient, and risky antihyperglycaemic drugs, let alone inform the selection of a particular agent. Therefore, the clearest indication for the use of antihyperglycaemic drugs in asymptomatic patients with type 2 diabetes remains the prevention of symptomatic hyperglycaemia.

If we are satisfied that this is justification enough for treatment how might we choose antihyperglycaemic agents? In the absence of any clear indication that one agent is better than another, the choice will depend on their unfavourable features, which include costs of treatment, particularly out-of-pocket costs, inconvenient administration, and adverse effects. Although some serious adverse events are rare, they will still play an important role in making a choice, particularly if patients at risk cannot be reliably identified or when the adverse event is severe or lethal.

Pancreatitis and pancreatic cancer are associated with high morbidity and mortality; their risk is increased with obesity and diabetes,[4 5] and with conditions associated with these disorders, such as hypertriglyceridaemia or gallbladder disease.

Metformin has been estimated to reduce the risk of pancreatic cancer by 24% (although not statistically significant); sulfonylureas and insulin have been associated with a 70% (significant) and 59% (not significant) increased risk, respectively.[6] But these estimates arise from observational studies with important limitations, such as potential for reverse confounding. Other factors such as incomplete adjustment for risk factors and the potential association of a risk factor for cancer (such as age) with a higher chance of being prescribed an antidiabetic drug further impair interpretation of these observational analyses.

As noted by Cohen and others, there is a compelling biological rationale linking GLP-1 based treatments with pancreatitis and pancreatic cancer.[8-12] Faced with emerging data, regulators have added warnings to product information leaflets.

Meta-analyses of observational studies and randomised trials have found no significant association between GLP-1 based treatments and pancreatitis or pancreatic cancer. However, many factors bring the reliability of the evidence into question. Observational studies have lacked sufficient numbers of patients using these agents who were followed for a sufficiently long period and accrued enough instances of adequately ascertained pancreatitis or pancreatic cancer. Careful selection of participants, co-interventions, and comparisons have also affected the results of trials of these agents.[13] A recently published population based case-control study based on a large US administrative dataset found a twofold increase in the odds of hospital admission for pancreatitis in patients exposed to GLP-1 based treatments, after accounting for important confounders.[14] Taken together, it seems plausible that GLP-1 based treatment can cause pancreatitis and pancreatic cancer, but the causal link is far from established.

So how can clinicians and patients work together to decide on a drug regimen that reflects the available evidence and the patient's context and values?

Shared decision making tools (such as the Diabetes Medication Choice Decision Aid; http://diabetesdecisionaid.mayoclinic.org) can be used to support this process.[15] Patients will have to consider carefully their predisposition to diabetes complications and drug side effects, taking into account their personal and family history of diabetes complications and risk factors for pancreatitis and pancreatic cancer in light of their life expectancy. They will also need to think about how well they are likely to tolerate adverse drug effects (such as hypoglycaemia and drug induced weight changes). After careful reflection, most patients and clinicians may opt to avoid GLP-1 based drugs or to avoid using them early in the disease course, alone, or for a prolonged period of time.

Colouring these discussions is the concern that the evidence is corrupt. The public record about drug safety and the opinion of experts, particularly of those with financial ties to drug manufacturers, have often been found to be untrustworthy.[16]

Big pharma has behaved poorly in the past two decades by hiding safety signals, skewing the evidence and debate in favour of its products, and attacking those who raise concerns. The work of investigators, regulators, and advocates who make it their business to look carefully at the safety of drugs may go unrecognised and is often vilified. Yet, such work helps us to moderate our expectations about innovations and to be thoughtful in prescribing, so that the patient's best interests are to the fore. The effects of antidiabetic drugs should be tested independently of the manufacturers, and all data from all studies from all developmental phases should be made available to the regulatory authorities and to the scientific and safety advocacy community. In turn, government and civil society actors must fulfil their duty to protect the health of those who are most vulnerable.

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Commissioners need evidence of long term outcomes, what works for whom, under what circumstances, and at what cost to families and health services

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News: Government welfare cuts are hitting children, says BMA (*BMJ* 2013;346:f3129)

Growing up in the UK: can we deliver a healthy future for our children?

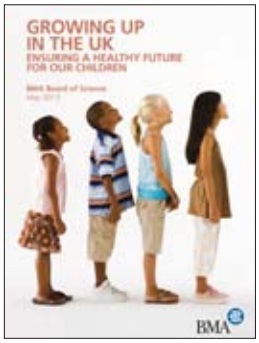
Implementation of the BMA's recommendations will be challenging

Janis Baird senior lecturer in public health, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton SO16 6YD, UK jb@mrc.soton.ac.uk
Andrew Mortimore director of public health, Public Health, Southampton City Council, Southampton, UK
Patricia Lucas senior lecturer in early childhood, School for Policy Studies, University of Bristol, Bristol, UK

The health and wellbeing of children growing up in the United Kingdom are worse than is seen for children in most of the UK's European counterparts.[1] In May 2013, the BMA report *Growing up in the UK: Ensuring a Healthy Future for our Children* set out an ambitious agenda for improving child health and reducing inequalities.[2] Central to its message is greater advocacy on behalf of children from all people involved in their care and better representation of the views of children and families.

The report argues powerfully for prevention—a public health approach that acts on risk factors at all levels to deliver a whole population shift. It cites many examples of where this makes compelling economic sense, with early intervention preventing high costs later on. Local authorities, which now have responsibilities for public health leadership, currently face the most challenging budget reductions in living memory. Services are being severely cut back, and all authorities are searching for a sustainable delivery model that protects essential services such as child protection, while allowing for the promotion of health and wellbeing. Clinical commissioning groups and public health teams must lead the way in making the case to preserve and build on successful early years programmes by working in genuine partnership with the communities they serve. Implementing the report's recommendations will be challenging in many ways.

There have been only modest improvements in child health since the last BMA report on child health in 1999,[3] despite a succession of initiatives. This relative lack of progress can, in part, be attributed to high persisting rates of child poverty: one in four children in the UK lives in poverty.[4] Rates of child poverty in the UK fell slightly between 2007 and 2010 owing to a tax benefit system that favoured families with children. But this system is currently undergoing major restructuring, and families will be affected by the introduction of universal credit and changes to child benefit, disability living allowance, and council tax benefit. These changes will restrict, reduce, or remove benefits from many families, and forecasts from the Institute of Fiscal Studies suggest that child poverty will rise slightly in 2013-14.[5] Many vulnerable families will probably do badly under these changes—those with one resident parent, families headed by vulnerable adults (for example, people with mental health difficulties), larger families, and those where anyone has a disability. The report calls for professional bodies to lobby for action to reduce the impact of benefit reform on children, and for the introduction of a minimum income for healthy living. This assumes that doctors will observe and report the impact of poverty on families in their care and advocate on behalf of children.



Maintaining a focus on early intervention, the report recommends a life course approach to improving child health. It is well established that the nutrition of mothers influences the lifelong health of their children.[6] The health behaviours of parents also have a major influence on the health and development of their children. Mothers' diet is a strong predictor of infant diet, and growth during infancy predicts later risk of obesity.[7 8] The government response to the current epidemic of obesity and chronic disease emphasises the need for people to make healthy choices and calls for action at community level to bring about population improvements in diet and physical activity.[9] But although government initiatives, such as Change4Life, have led to a decrease in unhealthy behaviours, recent evidence shows that reductions have mainly been among more advantaged groups and unhealthy behaviours continue to cluster in disadvantaged groups.[10] The latest BMA report calls for upstream action to tackle societal and environmental constraints on health behaviour. Such actions would include making outdoor spaces more accessible and safe; discouraging car use; and changing the food environment. Everybody has a duty to promote the wellbeing of children, and communities should be encouraged to provide networks of support for children and the adults who care for them.

Improving the health of children with complex needs—including those with disabilities, emotional and behavioural problems, and those who are maltreated—will require integrated and coordinated working from health and social care agencies, according to the report. Implementation of the Health and Social Care Act 2012 will lead to greater competition for the provision of services and increased numbers of providers. Delivering integrated and coordinated care will be more challenging as a result.

Few current services and interventions for children are informed by evidence of effectiveness. The report calls for urgent action to improve the evidence base. A shift away from universal services to targeted ones potentially threatens early interventions, such as parenting support. Healthy Start provides a mechanism for vitamin supplementation among pregnant women and young children in low income families, yet evidence on the ground shows that after seven years less than 10% of the target population are taking vitamins; this suggests that the targeted approach has failed. A universal offer of vitamin D supplements is relatively cheap and has improved health in some areas,[11] but procurement and distribution obstacles are considerable and increasing.[12] Sure Start, a key setting for delivery of early interventions,[13] is already experiencing loss of staff and services. Effective measures such as these should not be allowed to fall by the wayside.

Most interventions that can improve child health involve collaboration between a range of agencies and settings. Assessing their effectiveness will require studies that are complex in design and costly to conduct. Commissioners need evidence of long term outcomes but also of process—what works for whom, under what circumstances, and at what cost to families and health services. This is a challenging research agenda, particularly given recent cuts to public spending.

We welcome the BMA's report, its scope and ambition, and its focus on putting children first in services and policies. We fear that the climate for adopting its recommendations may not be favourable, but the medical profession must rise to the challenge.

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News: Israel amends law forcing adult cyclists to wear helmets (*BMJ* 2011;343:d4530)

2011 poll: Should it be compulsory for adult cyclists to wear helmets? Yes: 462 (32%) No: 978 (68%)

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Bicycle helmets and the law

Canadian legislation had minimal effect on serious head injuries

Ben Goldacre Wellcome research fellow in epidemiology, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
ben.goldacre@lshtm.ac.uk
David Spiegelhalter Winton professor for the public understanding of risk, University of Cambridge, Cambridge, UK

We have both spent a large part of our working lives discussing statistics and risk with the general public. We both dread questions about bicycle helmets. The arguments are often heated and personal; but they also illustrate some of the most fascinating challenges for epidemiology, risk communication, and evidence based policy.

With regard to the use of bicycle helmets, science broadly tries to answer two main questions. At a societal level, "what is the effect of a public health policy that requires or promotes helmets?" and at an individual level, "what is the effect of wearing a helmet?" Both questions are methodologically challenging and contentious.

The linked paper by Dennis and colleagues investigates the policy question and concludes that the effect of Canadian helmet legislation on hospital admission for cycling head injuries "seems to have been minimal."[1] Other ecological studies have come to different conclusions,[2] but the current study has somewhat superior methodology—controlling for background trends and modelling head injuries as a proportion of all cycling injuries.

This finding of "no benefit" is superficially hard to reconcile with case-control studies, many of which have shown that people wearing helmets are less likely to have a head injury.[3] Such findings suggest that, for individuals, helmets confer a benefit. These studies, however, are vulnerable to many methodological shortcomings. If the controls are cyclists presenting with other injuries in the emergency department, then analyses are conditional on having an accident and therefore assume that wearing a helmet does not change the overall accident risk. There are also confounding variables that are generally unmeasured and perhaps even unmeasurable. People who choose to wear bicycle helmets will probably be different from those who ride without a helmet: they may be more cautious, for example, and so less likely to have a serious head injury, regardless of their helmets.

People who are forced by legislation to wear a bicycle helmet, meanwhile, may be different again.

The current uncertainty about any benefit from helmet wearing or promotion is unlikely to be substantially reduced by further research

Firstly, they may not wear the helmet correctly, seeking only to comply with the law and avoid a fine. Secondly, their behaviour may change as a consequence of wearing a helmet through "risk compensation," a phenomenon that has been documented in many fields.[4 5] One study—albeit with a single author and subject—suggests that drivers give larger clearance to cyclists without a helmet.[6]

Even if helmets do have an effect on head injury rates, it would not necessarily follow that legislation would have public health benefits overall. This is because of "second round" effects, such as changes in cycling rates, which may affect individual and population health. Modelling studies have generally concluded that regular cyclists live longer because the health effects of cycling far outweigh the risk of crashes.[7] This trade-off depends crucially, however, on the absolute risk of an accident: any true reduction in the relative risk of head injury will have a greater impact where crashes are more common, such as for children.[8]

The impact on all cause mortality, and on head injuries, may be even further complicated if such legislation has varying effects on different groups. For example, a recent study identified two broad subpopulations of cyclist: "one speed-happy group that cycle fast and have lots of cycle equipment including helmets, and one traditional kind of cyclist without much equipment, cycling slowly." The study concluded that compulsory cycle helmet legislation may selectively reduce cycling in the second group.[9] There are even more complex second round effects if each individual cyclist's safety is improved by increased cyclist density through "safety in numbers," a phenomenon known as Smeed's law.[10] Statistical models for the overall impact of helmet habits are therefore inevitably complex and based on speculative assumptions.[11] This complexity seems at odds with the current official BMA policy, which confidently calls for compulsory helmet legislation.

Standing over all this methodological complexity is a layer of politics, culture, and psychology. Supporters of helmets often tell vivid stories about someone they knew, or heard of, who was apparently saved from severe head injury by a helmet. Risks and benefits may be exaggerated or discounted depending on the emotional response to the idea of a helmet.[12] For others, this is an explicitly political matter, where an emphasis on helmets reflects a seductively individualistic approach to risk management (or even "victim blaming") while the real gains lie elsewhere. It is certainly true that in many countries, such as Denmark and the Netherlands, cyclists have low injury rates, even though rates of cycling are high and almost no cyclists wear helmets. This seems to be achieved through interventions such as good infrastructure; stronger legislation to protect cyclists; and a culture of cycling as a popular, routine, non-sporty, non-risky behaviour.

In any case, the current uncertainty about any benefit from helmet wearing or promotion is unlikely to be substantially reduced by further research. Equally, we can be certain that helmets will continue to be debated, and at length. The enduring popularity of helmets as a proposed major intervention for increased road safety may therefore lie not with their direct benefits—which seem too modest to capture compared with other strategies—but more with the cultural, psychological, and political aspects of popular debate around risk.

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