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The safety of incretin based drugs

Latest data on pancreatitis look reassuring, but informed patients will have the final word

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Important concerns have been raised about the impact of incretin based drugs on the risk of acute pancreatitis in patients with type 2 diabetes. Two linked papers by Li and colleagues and Faillie and colleagues could help us decide whether patients and clinicians should consider these concerns when choosing an antihyperglycemic drug.[1 2]

Like all other antihyperglycemic drugs, incretin based drugs have no special ability to reduce the risk of complications of diabetes. Patients might prefer to use these drugs though as they have almost no risk of hypoglycemia, are weight neutral (gliptins) or lead to weight loss (GLP-1 agonists), and have convenient oral (gliptins) or injectable (GLP-1 agonists) dosing. Because of these favorable features, experts recommend them as second line drugs after metformin to help patients achieve glycemic control.[3] Some patients might also need to consider cost, which is about 70 times higher than metformin or sulfonylureas in the United States. Should the possibility of acute pancreatitis with these drugs also affect their decision making?

This evidence should be shared with patients in the context of a shared decision making process

A safety signal suggesting that incretin based drugs could increase the risk of acute pancreatitis, emerged as soon as these treatments entered the market but reached broad notoriety in 2013.[4] Since then, drug regulators have reviewed and conducted toxicological studies in animals and reviewed existing trials and observational studies, finding reassuring but insufficient evidence to reach a conclusion about a causal link.[5] US and European regulators have decided to keep these drugs available with the potential for pancreatitis described in their label.

The first linked paper is a rigorous and comprehensive systematic review and meta-analysis of randomized and observational studies.[1] Most of the summarized evidence comes from 55 randomized trials funded by industry that were at low to moderate risk of bias; none was specifically designed to ascertain and adjudicate episodes of acute pancreatitis. The extent to which patients with known risk factors for acute pancreatitis (such as old age, obesity, duration of diabetes, prior episode of acute pancreatitis, gallstones, alcohol abuse) participated in these trials is unclear. Exclusion of high risk participants and the brevity of the trials can produce an unbiased yet narrowly applicable estimate of effect pertinent to low risk patients taking these drugs for less than six months. The pooled result suggests no significant increase in the risk of acute pancreatitis with incretin based drugs.

The systematic review also included five observational studies that, as expected, included more episodes of acute pancreatitis than the collection of randomized trials and a larger and perhaps more representative population of patients. These studies were judged to be at moderate to high risk of bias, had limited ascertainment of exposure and outcomes, and had limited adjustment for potential confounders. Their results were inconsistent, with most suggesting no significant increase in the risk of acute pancreatitis.

In the other linked paper, Faillie and colleagues report on a large population based cohort drawn from the UK Clinical Practice Research Datalink practice database and the Hospital Episodes Statistics database; its rigor warrants moderate confidence in its results.[2] This study usefully reports on the risk of acute pancreatitis in patients with type 2 diabetes not treated with incretin based drugs: 15 in 10 000 patients per year. This study also reports no significant association between these drugs and acute pancreatitis (hazard ratio of 1.00, 95% confidence interval 0.59 to 1.70). This result, which is consistent with the result of the meta-analysis of randomized trials (odds ratio 1.11, 95% confidence interval 0.57 to 2.17), was robust across several analytical assumptions when incretin based drugs were compared with sulfonylureas, metformin, or insulin, and after adjustment for previous sulfonylurea exposure. Neither here nor in previous studies is there evidence of a relation between the risk of acute pancreatitis and dose or duration of exposure to incretin based drugs or of differential effect of GLP-1 agonists or DPP4 inhibitors on acute pancreatitis.

Best guess: one extra case per 10 000 patients

The available evidence suggests, with low to moderate confidence, that there is no significant increase in the risk of acute pancreatitis with these drugs. There is no question that acute pancreatitis can be severe and even fatal, but it is rare, affecting about 15 out of 10 000 patients with type 2 diabetes each year. If these drugs were truly linked to an increase in this risk, the best guess based on this evidence is that the risk would increase to 16 in 10 000 (95% confidence interval 7 to 23 in 10 000) per year. And theoretically these magnitudes would be lower if incretin based drugs were used only in low risk patients. Ongoing cardiovascular safety trials and new "big data" observational analyses might soon provide additional evidence.

This evidence should be shared with patients in the context of a shared decision making process,[6] with selection of drug treatment reflecting their informed preference rather than a prespecified "next step" after metformin. In essence, patients will be asked to consider the desirability of other drugs against the possibility that incretin based drugs could increase the risk of acute pancreatitis. Patients and their clinicians will uncover the final word on the safety of incretin based drugs for each patient after a careful evidence based discussion, in part supported by the research *The BMJ* publishes today. Given the state of this evidence, however, they would be wise to schedule that decision for review.

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RESEARCH, pp 11, 12

Gila monster saliva: incretin-like properties

Additional work incorporating behavioral and public health strategies to promote "tummy time" and similar positioning strategies should be explored

Helmet therapy for positional plagiocephaly and brachycephaly

Negligible treatment effects in the first randomized evaluation

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Positional plagiocephaly and brachycephaly affects approximately 20% of infants and is the most common reason for referral in many craniofacial centers.[1 2] This reflects an increase in the incidence of the condition after several countries implemented public health campaigns that encouraged parents to position their babies in a supine position for sleep to prevent sudden infant death syndrome.

The advent and marketing of orthotic treatments for positional plagiocephaly and brachycephaly has also likely increased awareness of plagiocephaly among parents and medical professionals. Although the persistence and implications of infant skull deformities are unclear, often parents are concerned about outcomes for their child and are motivated to participate in treatment.

Previous studies showed improvements in head shape after orthotic treatment[3]; however, until the study by van Wijk and colleagues, there were no randomized controlled trials showing the efficacy of orthotic treatment compared with no treatment.

In addition to the sheer number of children affected by positional plagiocephaly and brachycephaly, several factors make van Wijk and colleagues' study important. Earlier longitudinal studies showed that to some extent the head shape of affected children improved with no treatment.[3] Thus at a minimum parents would want to know whether treatment would result in improvements above and beyond what would be expected by doing nothing at all.

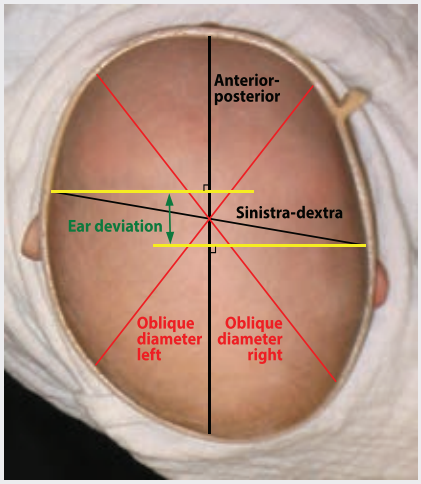
This is particularly true given the burdens of orthotic treatment, including the cost (which is often not covered by insurance) and the requirement that infants wear the helmet for 23 hours a day, seven days a week. For many families these costs would be tolerable if it meant an improved outcome. Unfortunately though, the findings by van Wijk and colleagues suggest virtually no treatment effect.

The authors acknowledge the limitations of this trial, and there are several important next steps for future research. The participation rate (21%) in the randomized controlled trial was low, and in fact limited participation is a barrier that has precluded other groups from attempting a similar study.

Parents interested in their child receiving orthotic treatment for positional plagiocephaly and brachycephaly are understandably reluctant to have that decision randomized. Baseline personal and clinical characteristics were similar in participants and non-participants, suggesting that those who received treatment are similar to the larger population, though differences in unmeasured characteristics are possible. Although statistical power to detect differences was adequate, the sample was too small to examine possible differences between subgroups.

Future studies, including larger samples, would be helpful in determining whether some infants respond more favorably than others. In particular it would be of interest to learn whether children with the most severe positional plagiocephaly and brachycephaly, who were excluded from this trial, show meaningful improvement.

Finally, the measure of compliance with treatment was by parent report after the completion of helmet therapy. Objective measures, ideally provided throughout treatment, would strengthen the argument that parents use the orthotic helmet as intended and provide some insight into any "dosage" effects.



	Oblique diameter difference index (%)		Craniproportional index (%)
Normal shape	<104	and	<90
Mild deformation	104-107	or	90-94
Moderate deformation	108-111	or	95-99
Severe deformation	≥112	or	≥100

All to no avail

No treatment effect, but no "normalization" either

It is worth highlighting that in neither group in this study did head shape "normalize" by the end of the trial. Full recovery was achieved by only 26% and 23% of the treatment and control infants, respectively. The longer term implications of persistent positional plagiocephaly and brachycephaly remain to be shown. However, this finding argues for studies focusing on primary prevention of the condition and novel strategies to ameliorate skull deformation once it develops in early infancy.

Admittedly, such efforts have not been particularly encouraging thus far.[3] However, additional work incorporating behavioral and public health strategies to promote "tummy time" and similar positioning strategies should be explored. Further, in previous papers we have argued that positional plagiocephaly and brachycephaly might serve as a marker for risk of developmental problems.[5 6] Identifying skull deformities early and providing intervention to facilitate development (for example, targeting deficits in early motor function, when present) may have the dual benefit of tackling positional plagiocephaly and brachycephaly and enhancing other areas of development.

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RESEARCH, p 13

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News: Financial crisis is inevitable in the NHS by 2015-16, King's Fund says (*BMJ* 2014;348:g304)

NHS finances: the tanker en route for the iceberg

Will it hit before next year's general election?

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In a report published last week, UK healthcare think tank the King's Fund warned that a financial crisis in the NHS was now "inevitable" by 2015-16 and that, without urgent action to plug the funding shortfall, it could arrive sooner.[1] Such warnings have become increasingly vociferous in recent months, as fears grow that the tanker may be about to hit the iceberg, to coin the phrase used by former NHS Confederation chief Mike Farrar.[2]

Before his departure, the outgoing NHS chief executive David Nicholson warned that the NHS was facing a £30bn (€36.5bn; $50.8bn) funding gap by 2021, which could render it unsustainable without radical change to the way care is delivered.[3] The onus has now fallen on Nicholson's successor Simon Stevens to leverage this change while keeping the ship afloat, amid what Stevens describes as "the longest squeeze on NHS finances in our 65 year history."[4]

Since 2010, there has been an unprecedented slowdown in the growth of NHS funding, as the accelerated investment of the previous decade dried up. The King's Fund's report highlights that, between 1997-98 and 2009-10, NHS spending in England more than doubled in real terms, increasing as a proportion of gross domestic product (GDP) from around 5.2% to just over 8%. But it forecasts that NHS spending as a proportion of GDP will fall back to 6% by 2021—its lowest level since 2003—if the current pace of investment continues.

With the iceberg in sight, the time for a full and frank debate about how much the UK values its health service—both literally and figuratively—is overdue

Falling behind again

The United Kingdom is also falling behind its G7 counterparts, with the Office for National Statistics revealing last week that 9.2% of the UK's GDP is currently spent on healthcare (including NHS and private care), less than all other G7 countries apart from Italy.[5]

Although the NHS has continued to receive modest funding increases since the economic downturn, this has not been sufficient to keep pace with rising costs. To deal with the shortfall, the NHS was set a target of achieving £15-£20bn in efficiency savings between 2011 and 2015[6]—the most ambitious productivity challenge in its history. This has now been extended, with current spending plans anticipating similar squeezes until at least 2021. To date, efficiency targets have been achieved largely through staff pay freezes and management cuts. As the King's Fund highlights, these have been "all but exhausted."

Although further efficiencies can be found in the system, the fund argues that more money will be needed to achieve this, with a specific focus on investing in new models of care in primary and community settings. It has also called for shorter term financial support to be provided to struggling organisations, to prevent "damaging consequences" for patient care. When the escalating cost of providing healthcare for an ageing population with complex needs is factored in, the case for additional investment is compelling.

Only 40% of NHS finance directors recently surveyed by the fund were confident that their organisation would achieve financial balance this year (2014-15), and just 16% expressed confidence for 2015-16.[7] This is partly down to the proposed transfer of a further £1.8bn of NHS funds to local government next year, to support joint working with social care.

The number of NHS foundation hospital trusts in England in financial difficulty has almost doubled in a year from 21 to 39, according to a recent report from health sector regulator Monitor.[8] Having already been squeezed through cuts to their tariffs, hospital providers are bracing themselves to cut emergency and elective work next year.

As he prepares to hold urgent discussions with national and local bodies on how to put the NHS on "a sustainable footing," Stevens must strike a balance between driving change while supporting struggling organisations. Having overseen unprecedented investment in the NHS between 1997 and 2004 during his previous role as a health adviser to former Prime Minister Tony Blair, Stevens will be acutely aware of the need to invest wisely, albeit without the luxuries available in 1997.

He has already indicated that more resources will be directed towards primary care, which would be consistent with the often cited need to shift more services out of hospital and into the community. Addressing MPs at a parliamentary health select committee hearing last week, Stevens said it was out of kilter that a 21% increase in the number of GPs since 2000 had occurred at the same time as an almost 76% increase in the number of hospital consultants. Although this imbalance needs to be rectified, Stevens cannot allow other parts of the service to wither on the vine. With the 2015 general election around the corner, the government should be mindful that an unhealthy NHS equals an unhappy electorate.

When pressed by MPs as to whether the quality of care and breadth of services currently on offer could be maintained without additional funding, Stevens offered a pragmatic response. "If it is the case that strong economic growth returns, then for medical, economic, and social reasons, most independent commentators would predict that the nation will be spending more in real terms on healthcare by 2021 than it is now," he told MPs.

Regardless of the state of the economy, there will be justified pressure on whichever party is in government to ensure that the UK does not slide further behind other developed nations in its investment in healthcare. With the iceberg in sight, the time for a full and frank debate about how much the UK values its health service—both literally and figuratively—is overdue.

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It is vital for healthcare providers and professional groups opposed to the involvement of their members in interrogations to openly support legislation codifying humane policies into law, in the US and abroad

Medical professionalism and abuse of detainees in the war on terror

Time for doctors to stand up for our professional ethics

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"Where were the doctors?" asked physician and bioethicist Steven Miles after the Abu Ghraib photographs became public.[1] A recent task force report from the Institute of Medicine as a Profession (IMAP)/Open Society Foundations provides a disturbing answer.[2]

The report discloses that, among other unethical roles, doctors in Abu Ghraib, Guantanamo, and CIA secret prisons were monitoring oxygen saturations during waterboarding, watching for edema in detainees forced to stand in stress positions, and helping increase psychological distress by sharing prisoners' individual health information with interrogators. Despite criticism, the Department of Defense and the CIA have left in place many protocols that allow, even encourage, this degradation of professional ethics. Given the evidence of the involvement of health professionals in "enhanced" interrogations, we believe that health professionals, international medical societies, and licensing boards should actively oppose this involvement in the abuse of prisoners.

Still in the dark

In 2009, President Obama used his executive authority to end the CIA's detention and interrogation program. But, owing to classification, we still do not fully know the current standards for the involvement of medical personnel, and evidence suggests that abusive interrogations continue today.[3] In addition, the US government has thwarted efforts to make those involved—including healthcare professionals—accountable, by obstructing the release of information and refusing to prosecute potential crimes. This hazy legacy of confronting abuse dilutes the moral authority of the United States to judge the human rights abuses of other countries.

The United Nations Convention Against Torture defines torture as "any act by which severe pain or suffering, whether physical or mental, is intentionally inflicted on a person . . . at the instigation of . . . a public official."[4] The infamous Bush era "torture memos" medicalized the term "severe suffering," redefining it as "equivalent in intensity to the pain accompanying serious physical injury, such as organ failure, or impairment of bodily function, or even death."[5] They also mandated that medical professionals be present during interrogations as "safety officers," flagging suffering as severe enough to merit intervention. These professionals provided protection: if the doctors said no lasting harm would occur, there would be no legal culpability, no matter what harm did occur.

LYNNE SLADKY/PA

Doctors were part of the problem here

These abusive roles represent a dramatic departure from conventional medical ethics, which are anchored in the "do no harm" principle. Many professional societies, including the American Medical Association and the BMA, have issued strong statements condemning any involvement of physicians in interrogations. In pointed contrast, the American Psychological Association allows involvement of members in interrogations as long as cruel treatment is avoided. The IMAP report calls on professional organizations—specifically the American Psychological Association—to strengthen their ethical stances regarding provider involvement in interrogations.

However, organizational policies alone do not provide an adequate framework to protect prisoners or military doctors. The report therefore calls on professional associations to strengthen ethical guidance, to investigate abuses and speak out publicly against them, and to aggressively discipline members found to have participated. Medical societies and licensing boards need to move beyond statements condemning torture to proactively educating members.

The report recommends several steps to change policies allowing healthcare professionals to fulfill intelligence roles that conflict with their professional ethical mandates, many of which are relevant to international medical associations. Specifically, it calls for policies that allow these professionals to serve in roles, such as interrogation support, that are inconsistent with furthering people's welfare, to be rescinded. The report also calls for military approval of abusive measures such as sleep deprivation, prolonged isolation, and exploitation of fears, which are still allowed for certain interrogations, to be recalled.

Importantly, the IMAP report also supports legislation to discourage unethical conduct by health professionals toward prisoners. Several US states have pending legislation directing professional licensing boards to investigate and discipline those guilty of such practices.[6] This legislation would protect prisoners from the involvement of medical professionals in interrogations and provide clinicians with credible justification to decline such involvement. Crucially, it would codify in law that interactions between healthcare professionals and prisoners should prioritize the prisoners' health and welfare. In advocating for these legislative approaches, legislators often ask us why they should take on this issue when health professions are not demanding it. It is therefore vital for healthcare providers and professional groups opposed to the involvement of their members in interrogations to openly support legislation codifying humane policies into law, in the US and abroad.

By adhering to internationally recognized standards and ethical guidelines, healthcare professions can secure our respected position and help safeguard the human rights of all. The IMAP task force report calls on us to reclaim our profession's unflinching ethical rejection of the involvement of physicians and psychologists in abusive interrogations.

We know where the doctors were then. Where are they now?

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