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Glucagon-like peptide-1 agonists

Cannot be recommended strictly for weight reduction until their benefits and risks are clarified

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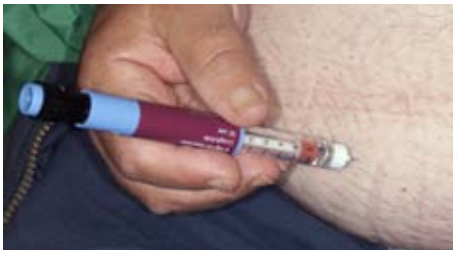
Over the past century, considerable progress has been made in understanding the role of enteroendocrine signals in regulating glucose. One substantial advance was the delineation of the "the incretin effect," which refers to the ability of orally administered glucose to stimulate pancreatic insulin secretion to a greater extent than glucose administered intravenously.[1] Glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide are the two key enteroendocrine factors responsible for the incretin effect.[2] GLP-1, secreted from the lower gastrointestinal tract L-cells after nutrient ingestion, stimulates endogenous insulin secretion in a glucose dependent manner, inhibits postprandial glucagon release, delays gastric emptying, and increases satiety.[3] However, GLP-1 is of limited therapeutic use because it is rapidly degraded by dipeptidyl peptidase 4, an enzyme produced at epithelial and endothelial membranes.

In the linked systematic review and meta-analysis, Vilsbøll and colleagues assess the effect of GLP-1 receptor agonists on weight loss, blood pressure, plasma concentrations of cholesterol and liver enzymes, and glycaemic control.[4] The two currently approved GLP-1 analogues, exenatide and liraglutide, mimic the action of GLP-1 but are resistant to the proteolytic effects of dipeptidyl peptidase 4 and are administered subcutaneously once or twice daily, or less often, depending on the specific drug and formulation.[2] Compared with placebo, GLP-1 agonists reduce mean glycated haemoglobin (HbA_{1c}) values by 1.0% (95% confidence interval 0.8% to 1.1%) and are approved for type 2 diabetes as adjunctive treatment to metformin and other agents.[5 6] Vilsbøll and colleagues' meta-analysis comprised 21 randomised controlled trials (n=6411) with follow-up periods of 20-52 weeks, in which the primary objective was to examine the effect of exenatide and liraglutide on body weight.[4] Compared with placebo or active comparators, GLP-1 agonists reduced weight by 2.9 kg (2.2 to 3.6) in all studies, 3.2 kg (2.1 to 4.3) in three studies of people without diabetes, and 2.8 kg (2.1 to 3.2) in 18 studies of people with diabetes. Small, statistically significant improvements in blood pressure and total cholesterol were also found.



DR P MARAZZI/SPL

Subcutaneous injection of GLP-1 agonist

Body weight was a secondary, not primary, end point in 18 of 21 trials. Furthermore, these pooled weight loss estimates were associated with substantial heterogeneity and are difficult to interpret because they combine the results of trials using placebo and active comparator arms. Of the comparator drugs, insulin, sulphonylureas, and thiazolidinediones increase weight and dipeptidyl peptidase 4 inhibitors are weight neutral. In a subgroup analysis of 10 placebo controlled trials, GLP-1 agonists reduced weight by 1.9 kg (0.9 to 2.9), which is probably a more accurate estimate of the weight reductions that would be expected in clinical practice.

Patients with type 2 diabetes are consistently less responsive to weight loss interventions than those without diabetes.[7] This is partly because of the weight increasing effects of conventional antidiabetic agents other than metformin. In this respect, the comparative weight reducing benefits of GLP-1 agonists are beneficial. However, the overall mean reductions in weight (and reductions in blood pressure and cholesterol) associated with GLP-1 agonists are modest, they are costly (£70 (€82; $112) to £80 a month in the United Kingdom), and prospective data showing reductions in clinically important end points, such as cardiovascular events or mortality, are lacking.

Given that other antidiabetic and antiobesity agents—most recently thiazolidinediones and sibutramine—have been withdrawn from the market because of unfavourable cardiovascular risk profiles, caution is warranted until studies with hard end points are available (expected after 2015). A meta-analysis of 20 randomised controlled trials (n=10 485) found no evidence of cardiovascular risk with GLP-1 agonists, but it was based on only 114 major cardiovascular events.[8]

Thus, although Vilsbøll and colleagues' meta-analysis highlights the weight reducing benefits of GLP-1 agonists, it should not alter current clinical practice. Modification of diet and lifestyle remains the cornerstone of the treatment of type 2 diabetes.[9] Treatment with statins and antihypertensive drugs to achieve guideline concordant reductions in cardiovascular risk factors is vital.[9] Metformin should be the first line drug for glycaemic control and HbA_{1c} targets should be individualised.[9 10] If indicated, glycaemic control can be further improved by the addition of other agents, including GLP-1 agonists, with the expectation that microvascular but not necessarily macrovascular complications will be reduced.[10] On the basis of current evidence, off label use of GLP-1-agonists for weight loss in people without diabetes cannot be recommended at this time. Studies evaluating the weight reducing efficacy of GLP-1 agonists in obese people without diabetes and those with prediabetes are ongoing.

Several questions require further clarification in future studies, including delineation of the mechanisms that underlie weight reduction, which seem to be mainly related to a centrally mediated reduction in food intake[11]; examination of the efficacy and safety of longer acting once weekly and once monthly preparations; and elucidation of the clinical relevance of a possible β cell mass preserving effect seen in animal models.[2]

However, the most important unanswered question relates to the safety of GLP-1 agonists. Animal studies have raised concerns of an increased risk of pancreatitis, pancreatic metaplasia, and thyroid C cell tumours.[12] The clinical relevance in humans is unknown and may take decades to assess fully, although data from post-marketing surveillance studies and meta-analyses of the (admittedly) highly selected patient populations enrolled in randomised controlled trials have been reassuring.[12] Nevertheless, continued and close surveillance of these new agents using all available data sources is warranted.

Competing interests: The author has completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: no support from any organisation for the submitted work; he is currently a site investigator for a Novo Nordisk GLP-1 agonist study; no other relationships or activities that could appear to have influenced the submitted work.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2011;343:d7282
RESEARCH, p 14

Unicef distributes around 1.5 billion vitamin A capsules a year in more than 70 countries, and this is thought to prevent about 350 000 child deaths a year

Vitamin A supplementation in children and hearing loss

Long term follow-up suggests a potential benefit only in children with otitis media

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For most clinicians, vitamin A is first and foremost associated with eye disease. Vitamin A deficiency causes a range of ocular manifestations including xerophthalmia, night blindness, Bitot's spots, and keratomalacia. Indeed, vitamin A and the eye provide a well known example of the importance of micronutrients for health, and many children have been told to eat their carrots because it is good for their eyes. In the linked long term follow-up of a randomised controlled trial, Schmitz and colleagues assess a different effect of vitamin A—whether vitamin A supplementation in the preschool years can reduce hearing loss.[1]

Vitamin A has many important functions in the human body, and its role in resistance to infectious diseases has been known for almost 100 years.[2] However, interest in vitamin A waned with the appearance of antibiotics, to return in the 1980s when a study in Indonesia showed that half yearly high dose vitamin A supplementation dramatically reduced child mortality.[3] This brought vitamin A back on to the international public health agenda, with an estimated 600 000 deaths in children each year attributed to vitamin A deficiency.[4] Half yearly high dose vitamin A supplementation was embraced as a "golden bullet" against child mortality. Unicef distributes around 1.5 billion vitamin A capsules a year in more than 70 countries, and this is thought to prevent about 350 000 child deaths a year.[5]

Schmitz and colleagues report on a long term follow-up of preschool children in Nepal who received five doses of a high dose vitamin A supplement or placebo.[6] The trial was terminated early owing to a strong beneficial effect of vitamin A on mortality. Hence, all subjects received vitamin A supplements after the first 16 months of the trial. Sixteen years later, about 51% of the participants were traced for hearing assessment. Although overall vitamin A supplementation had no effect on failing the hearing test, in the subgroup of children (20%) with a history of ear discharge, vitamin A supplements significantly reduced the risk of hearing loss by 42% (OR 0.58, 95% confidence interval 0.37 to 0.92). Unfortunately, a weekly recall of ear discharge was recorded during five visits only, hence morbidity data were available for only five of 64 weeks, and many cases of ear discharge were probably missed.

SANJIT DAS/PANOS

Vitamin A administered to a child in a Keralan clinic

The effects of vitamin A on morbidity are far from clear. Recent meta-analyses point to a reduction in diarrhoeal disease after vitamin A supplementation, but no effect on, or even an increase in, the incidence of respiratory infections.[7 8] The current study adds another piece to the big puzzle of how vitamin A may affect morbidity. The authors speculate that vitamin A supplements reduced the severity of ear infections because they had no effect on their incidence. Thus, vitamin A might have led to a more controlled immune response, with less oxidative stress, so that an episode of otitis media caused less damage.

Vitamin A is a strong modulator of the immune reaction, certainly when given in high doses. Because vitamin A modulates the balance between T helper 1 and T helper 2 type immune responses,[9] the type of pathogen causing the infection is important. For example, vitamin A given to Mexican children reduced the duration of *Escherichia coli* associated diarrhoea but increased the duration of *Giardia lamblia* associated diarrhoea.[10] The modulating effects also depend on the age and sex of the subject and factors such as whether the vitamin A is given together with vaccination, whether other nutritional deficiencies are present, and whether the subject is vitamin A deficient. The results of the study are therefore difficult to extrapolate to other settings.

Although the study's findings are intriguing and original, they will probably not result in a change in practice. More direct evidence for a role of vitamin A in otitis media will be needed before vitamin A is used as a treatment. The modest long term impact on hearing loss in a population that is more severely vitamin A deficient than most is unlikely to result in high dose vitamin A supplementation being taken up by national public health bodies, especially in view of current concerns about sustainability, overall effectiveness, and possible adverse effects of such programmes.[11 12] Other more immediate outcomes, such as mortality, should guide vitamin A interventions, and other more direct interventions, such as access to adequate antimicrobial treatment, would be more appropriate for reducing hearing loss.

Instead, the study should inspire further investigations that will help in understanding the role of vitamin A in immune function and how it affects health outcomes. The study underlines the importance of micronutrients in early childhood for health outcomes in the long term and points to a beneficial long term adjuvant effect of vitamin A supplements in certain populations.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2012;344:d7603
RESEARCH, p 15

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Identifying women with suspected ovarian cancer in primary care: derivation and validation of algorithm (*BMJ* 2012;344:d8009)

Computer assisted diagnosis of ovarian cancer in primary care

Moving closer, but still some way off

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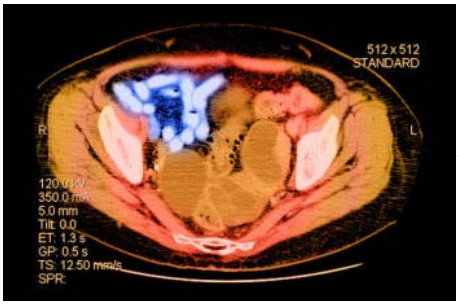
More than 6500 women are diagnosed with ovarian cancer each year in the United Kingdom. This cancer has a relatively poor prognosis—five year survival is 41%.[1] Screening is not available, although a large UK trial is due to report in 2015, so this may change.[2] Currently, the diagnosis is made almost entirely as a result of women reporting symptoms to primary care.[3] However, several factors make the diagnosis of ovarian cancer difficult. The cancer is relatively rare—full time general practitioners (GPs) will encounter it once every five years on average, so they build up little personal experience of diagnosing the disease. Many of the symptoms, such as urinary frequency or abdominal pain, are non-specific, with causes other than ovarian cancer more likely.[4] Furthermore, women are not as knowledgeable about the symptoms of ovarian cancer as they are about other cancers.[5] This encourages late presentation, with women unlikely to mention the possibility of ovarian cancer in the consultation. Contrast this with breast cancer, where most women finding a breast lump will report it swiftly and will expect the possibility of cancer to be discussed at the consultation.

In the linked study, Hippisley-Cox and Coupland look at a different aspect of the diagnosis of ovarian cancer—that of computer assisted diagnosis.[6] They identified the symptoms of ovarian cancer in a large electronic database, created a predictive algorithm, and then tested it in a different subset of the database. The algorithm performed well, with an area under the receiver operating characteristic curve of 84%. The authors hope that their algorithm could be used routinely to identify women at high risk of harbouring ovarian cancer who could then be offered testing. How realistic is this?

There are several stages before computerised support for a diagnosis of cancer can become a reality. Creation of an algorithm is generally the first one—they have been created for several other cancers, such as colorectal cancer.[7] Ideally, such algorithms should be validated in a different dataset from the one in which they were created because their performance is generally worse when tested in a second environment. Some of this



MEDICAL BODY SCANS/SPL

Axial cross sectional pelvic CT scan showing an ovarian cystadenoma

poorer performance reflects coding idiosyncrasies peculiar to each dataset. Several computer and coding systems are in use in UK general practice, with the Hippisley-Cox algorithm derived from one of the most common ones. However, primary care record keeping is far from standardised, especially for symptoms. Variation between GPs in recording styles would have a considerable impact on the algorithm. For example, loss of appetite was recorded in 0.5% of patients in both the derivation and validation cohorts yet was recorded in 1.5% of controls in a similar study that examined both written and computerised records.[4] This difference probably reflects "hidden" information that cannot be extracted by simple computer searches.[8] A change of this size may invalidate the algorithm. Furthermore, GPs do not record every symptom that is mentioned in the consultation—much of the time they document only diagnoses and treatment. Once GPs knew that their records of symptoms were being incorporated into an algorithm, their style of record keeping would probably change, again weakening the current algorithm, although it could be updated.

We also need to know if these algorithms can easily be integrated into general practice software. An early attempt put several computers out of action in a practice in Sheffield.[9] Various teams are working on incorporating diagnostic software into practice computers, so this aspect can probably be solved satisfactorily, for the popular general practice computer systems at least. There is also good evidence that GPs are willing to use algorithms to improve clinical care. Cardiovascular risk assessment is standard practice in primary care. GPs have also shown that they are willing to use scoring systems to identify possible colorectal cancer.[10] Several hundred English GPs are currently piloting a paper based risk scoring system aimed at identifying lung or colorectal cancers that would not qualify for urgent investigation under National Institute for Health and Clinical Excellence (NICE) recommendations.[11]

Once these hurdles are overcome, it will be important to select an "action level" for patients identified by any cancer diagnostic algorithm. False positives—patients in whom the algorithm identifies possible cancer but who do not have the disease—will be common. In cancer diagnostics, the action level with the highest possible sensitivity is usually selected to ensure as few cancers as possible are missed. The upper limit is then set when the false positive rate becomes unacceptably high. The disadvantages of false positive results can be minimised by having a simple "second level" test that can refine the risk further before undertaking more invasive tests. This is particularly important if an algorithm is used away from the consultation room. For instance, GPs could run regular sweeps of their electronic records for patients with symptom patterns that might represent cancer and invite patients who test "positive" for additional testing.

Despite its rarity, ovarian cancer may be a sensible choice for field testing an algorithm. Measurement of Ca 125 is now thought to be useful in primary care, although it too has false positives and false negatives.[12] Furthermore, GPs in England now have improved access to transvaginal ultrasound, which provides a reasonably rapid mechanism for confirming or rebutting the diagnosis.

Hippisley-Cox and Coupland's study has taken us one step closer to computer assisted diagnosis of cancer, although several steps remain. One final step must take place outside the GP's surgery. All systems that aim to improve identification of cancer in primary care will lead to increased demand for definitive tests. There is no point in increasing public awareness, as with recent TV campaigns for bowel cancer, or increasing the willingness of GPs to investigate, unless additional investigative services can be provided—and paid for.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2012;344:d7628
RESEARCH, p 17

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Successful delivery of information technology in the NHS

Chief clinical information officers are needed to lead the information revolution

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In a time of austerity it might be unpopular to suggest that every NHS organisation needs a new high level post: a chief clinical information officer (CCIO). Yet it is an idea that is gathering support and leading to action in some quarters.

A campaign was recently launched (www.ehi.co.uk/campaign/ccio) to encourage NHS organisations to appoint a CCIO. Organised by eHealth Insider, a news and information channel on healthcare information technology, with the British Computer Society and the Royal College of Physicians as partners, the campaign has attracted many supporters. Five royal colleges; NHS medical director, Bruce Keogh; health minister, Lord Howe; 27 IT firms; and numerous individual clinicians and IT professionals have endorsed it to date.

One of the drivers behind this campaign is unfortunately a negative one. Although the NHS can be proud of some of its achievements in IT, there have been too many failures, particularly in secondary care. In many cases, commercial complications and a lack of engagement with doctors and nurses, the primary users of clinical IT systems, have been cited as factors.

The need for clinical engagement and leadership were highlighted by Frank Burns in 1998.[1] However, the NHS never promoted the importance of this, and ten years later the health informatics review again referred to the need for strong clinical and management engagement, and the development of informatics capacity and capability within the NHS workforce.[2] This was re-emphasised in the NHS operating framework 2010-11 and associated documents.[3 4] Even Aidan Halligan, appointed to the NHS National Programme for IT in March 2004 as director general for benefits realisation, came to the conclusion that in the absence of serious engagement of frontline staff, resistance to change was too big an obstacle to the successful implementation of the IT strategy.[5] The National Audit Office, which has completed three reviews of the NHS National Programme for IT, warned in its second 2008 report that successful implementation of new systems depends on the support of staff.[6] However, in its most recent report the need for trusts to take charge of their own system planning was acknowledged, but there was no mention of clinical engagement whatsoever,[7] perhaps reflecting the ongoing lack of clinicians' influence over NHS IT strategy. This is especially true in secondary care, whereas analysis of successful healthcare IT deployments, such as in primary care practices—95% of which are computerised—shows that clinical staff had process and economic incentives to become involved in informatics.[8]

There are positive drivers for introducing CCIOs. In the United States the role has developed over the past two decades, usually in the form of chief medical information officers, who often work with a counterpart from within the nursing staff. One study found that these officers had been able to set project expectations, support the selection of vendors, recruit other champions for IT enabled clinical projects, contribute to design meetings and training programmes, and direct deployments and support.[9] In the United Kingdom, the British Computer Society has recommended the appointment of CCIOs as part of its solution to the challenge of making the behavioural changes needed to make IT enabled developments work.[10]

An NHS in which clinicians have access to all the information they need to deliver integrated care along pathways made up of a diverse range of providers . . . is quite a challenge in information terms

Several insights have been gained from previous rudimentary information systems and how these could transform patient care. For instance, the electronic requesting and results service launched in the mid-1970s at the Royal London Hospital—now part of Barts and the London NHS Trust—was invaluable and the only way tests could be ordered for inpatients. The prescribing information and communication system developed with close participation of clinicians in the liver and renal units of Birmingham's Queen Elizabeth Hospital in the 1990s was the forerunner of the system now used across the University Hospitals Birmingham NHS Foundation Trust. Experience worldwide has shown that the benefits of such systems become tangible only after users achieve key "tipping points." In a small number of NHS secondary care settings (but many more outside the UK) clinicians are beginning to rely more on the digital health record than the paper one—an experience that most relish because they are able to make clinical decisions with all of the necessary information at their fingertips.

All of these successes are associated with the CCIO role being performed by strong clinical leaders, who can engage with clinical and non-clinical staff to show them the full benefits and ignite enthusiasm for transformation yet impart a common sense approach to problem solving. They must be able to interpret between the frontline user and the software engineer, who often misunderstand one another. Untrained clinicians may not understand the psychology of good user interfaces and other aspects of good software design, which sometimes means that well intended projects fail to deliver value. These skills will be essential to fulfil the new agenda set for the NHS.

The coalition government has abandoned the centralised approach embodied in the NHS National Programme for IT. However, its ambitions for the NHS will require considerable investment in IT and radical changes in the way clinicians work. The proposed reforms that flow from the government's Liberating the NHS white paper envisage an NHS in which clinicians have access to all the information they need to deliver integrated care along pathways made up of a diverse range of providers.[11] This is quite a challenge in information terms, and even harder when the needs of the secondary use services, commissioners, and of course patients are considered, as discussed in the NHS information revolution consultation.[12]

With the policy shift to local ownership, NHS trusts will depend increasingly on their own clinical leadership to deliver informatics-enabled transformation. Failure to embrace the digital opportunities jeopardise improvements in quality, productivity, and efficiency of patient care and service delivery. For the right clinicians to be attracted into the CCIO role, the NHS must support a career path for clinicians interested in informatics and develop opportunities for clinically trained health informaticians to help harness the power of informatics to modernise the NHS.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2011;343:d6663