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FEATURE

DIABETES DRUGS

Has pancreatic damage from glucagon suppressing diabetes drugs been underplayed?

Incretin mimetics have been called "the darlings of diabetes treatment" and they may soon also be licensed for treating obesity. But a *BMJ* investigation has found growing safety concerns linked to the drugs' mechanism of action. **Deborah Cohen** asks why patients and doctors have not been told.

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They've been touted as the "new darlings of diabetes treatment"—the biggest breakthrough since the discovery of insulin nearly a hundred years before. The so called incretin therapies—glucagon-like peptide-1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors—looked as if they might change the face of type 2 diabetes. Their dual action of switching on insulin and suppressing glucagon to help control blood glucose was the ultimate in diabetes care.

The promise of a Nobel prize for the investigators loomed large. Scientists had discovered a treatment that could potentially modify disease progression. Studies in experimental animals showed that GLP-1 caused a proliferation in new insulin producing β cells. The hope was that these new cells might be able to replace those that died off in the course of human diabetes.

Nor did the promise end there. GLP-1 acts on the brain to makes people feel less hungry and the more powerful drugs aid weight loss—rather than weight gain like many antidiabetic drugs before them.

It's an effect companies are seeking to market in its own right. Spurred on by the US Food and Drug Administration's willingness to license new obesity treatment, Novo Nordisk's chief science officer Mads Krogsgaard Thomsen said last year that the "political establishment in the US now knows that behaviour change alone is not enough."[1]

His company's drug, liraglutide, is in the process of late stage clinical tests, which Thomsen says show promising results.

But an investigation by the *BMJ* suggests Thomsen's confidence might be optimistic. Concerns held by some specialists about the potential side effects of GLP-1 drugs have emerged into the mainstream after both the FDA and the European Medicines Agency announced in March that they would launch a review into whether the drugs may cause or contribute to the development of pancreatic cancer.

As yet neither agency has reached any conclusions, but they are meeting to discuss the matter later this month. And, as this investigation has found, for the regulators it is not a new

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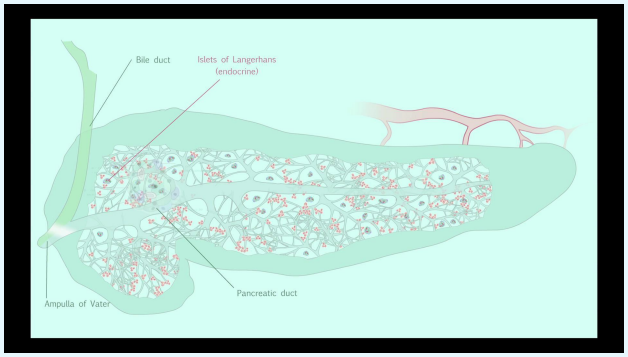

Edwin Gale and Deborah Cohen discuss the science behind the story

concern. Over the years, drug assessors have become increasingly concerned that the incretin drugs have the potential for unwanted proliferative effects.

Expert concerns

Concerns long held by some experts about the potential side effects of incretin mimetics have gathered momentum with three publications this year. An independent analysis of health insurance data published in February found that people taking exenatide and sitagliptin were at twice the risk of hospital admission for acute pancreatitis compared with people taking other antidiabetic drugs[2]—the absolute risk 0.6%. And in April an analysis of data from the US Food and Drug Administration's adverse event reporting system showed an increase in reports for pancreatitis and pancreatic cancer in people taking incretin mimetics compared with those taking other antidiabetic drugs.[3]

The FDA and EMA have both confirmed to the *BMJ* that their own analyses also show increased reporting or signals of pancreatic cancer with incretin mimetics. But they emphasise that this does not mean the relation is causal.

Both agencies announced in March that they will review data from a study just published showing pre-cancerous and dysplastic changes to the pancreas in organ donors exposed to incretin mimetics.[4]

The evidence is fiercely contested, with manufacturers stoutly defending the safety of their products. Merck, for example, told the *BMJ* that independent observational studies and a meta-analysis of clinical trials involving 33 881 patients found no association between DPP-4 inhibitors and pancreatic cancer. Bristol-Myers Squibb says that "post-marketing data does not confirm a causal relationship between saxagliptin or exenatide and pancreatitis and/or pancreatic cancer" (see bmj.com for full questions and answers with manufacturers).

But a "Dear Doctor" letter from Bristol-Myers Squibb and AstraZeneca on the UK Medicine and Healthcare Products Regulatory Agency's website says: "A review of reports of pancreatitis from post-marketing experience revealed that signs of pancreatitis occurred after the start of saxaglitpin treatment and resolved after discontinuation, which is suggestive of a causal relationship. Moreover, pancreatitis has been recognized as an adverse event for other DPP-4 inhibitors."[5] A spokeswoman for Boehringer Ingelheim told the *BMJ*: "Pancreatitis has been reported in clinical trials and spontaneous post marketing sources. Guidelines for the use of linagliptin in patients with suspected pancreatitis are included in the prescribing information of the treatment."

The increasingly fractious debate among scientists and doctors was played out last month in the specialty journal *Diabetes Care*.

Experienced GLP-1 investigator, Professor Michael Nauck, head of the Diabeteszentrum in Bad Lauterberg, Germany, and a consultant to many of the manufacturers, argued that the published evidence against the drugs is weak. "The potential harms and risks typically refer to rare events and are discussed in a controversial manner," he wrote.[6] But a team of four academics from the US and UK (one an expert witness in litigation against one of the manufacturers) suggested that neither the safety nor the effectiveness of the class can be assumed. "The story is familiar. A new class of antidiabetic agents is rushed to market and widely promoted in the absence of any evidence of long-term beneficial outcomes. Evidence of harm accumulates, but is vigorously discounted," they wrote in their response. [7]

In the course of this investigation, the *BMJ* has reviewed thousands of pages of regulatory documents obtained under freedom of information and found unpublished data pointing to unwanted proliferative or inflammatory pancreatic effects.

The *BMJ* has also found that, despite published reports that indicated safety concerns, companies have not done critical safety studies; nor have regulators requested them. And access to raw data that would have helped resolve doubts about the safety of these drugs has been denied.

On their own, the individual pieces of unpublished evidence may seem inconclusive — increases in size and abnormal changes in animal pancreases, raised pancreatic enzyme concentrations in humans, reports of thyroid neoplasms, and pancreatitis in early clinical trials.

But when considered alongside other emerging and long standing evidence—such as concerns about the effect of GLP-1agonists on α cells first published in 1999[8]; the presence of the GLP-1 receptor on cells other than the target pancreatic β cell; and increasing signals from regulatory databases[2 9]—a more coherent and worrying picture emerges, posing serious questions about the safety of this class of drug.

Problems in diabetic rats

These controversies might have stayed behind closed doors for much longer if Merck hadn't approached the Larry L Hillblom Islet Research Centre at the University of California in Los Angeles (UCLA) in 2007.

Merck offered to fund Professor Peter Butler, chair of the laboratory, and his research team to study the effect of the DPP-4 inhibitor, sitagliptin on the β cells of rats that have been bred to develop diabetes similar to that in humans. Butler's team designed the study; Merck provided the drug and advised them what dose to use. "I think they felt our [animal] model was nearer to type 2 diabetes than some of the other models they had studied and had available to them," Butler said.

He agreed to take on the work, and his team, led by biologist Aleksey Matveyenko, gave the rats sitagliptin, metformin, or a combination of both drugs. During the 12 week study, the rats all seemed well. So Matveyenko was surprised to find abnormalities in the pancreases of the rats given sitagliptin. All were enlarged; one showed acute pancreatitis; and three out of 16 had acinar to ductal metaplasia, a pathological change thought to be a potential precursor of pancreatic cancer.[10]

As agreed, Matveyenko and Butler reported the results to Merck in a series of meetings in June 2008 before publishing their data the following year.[10] In the course of these meetings, Butler told the company he was concerned about the safety implications of the animal studies. He offered to re-examine histological slides of pancreases taken from monkeys treated with sitagliptin, which Merck had collected as part of their preclinical study package, to see if these showed similar problems. His offer was not taken up.

The company and others did, however, act on Matveyenko's rat study. The *BMJ* has learnt of a closed door meeting in June 2009, shortly after the study's findings were published. It was held at the American Diabetes Association's annual conference in New Orleans, which was supported by Merck. Delegates included regulators, doctors, and manufacturers with GLP-1 and DPP-4 drugs either on the market or in the pipeline. The meeting was sanctioned by the FDA, which sent Mary Parks, the director of the Division of Metabolism and Endocrinology Products, among others.

The *BMJ* has seen notes from the meeting, as well as one of the Powerpoint presentations. In it, a professor of digestive diseases (not named here to protect a source) said that the acinar to ductal metaplasia and chronic pancreatitis seen in the Matveyenko study could suggest an increased risk of pancreatic cancer. If the results turned out to be true, he said, the future of the drugs was in doubt; chronic pancreatitis can be subclinical for years before it shows up clinically. But this concern had to be balanced against the lack of data indicating similar effects in humans, he said.

The fact that the UCLA rats had diabetes might be seen as a strength of the research. But several speakers at the meeting dismissed Butler and Matveyenko's rat model as being unreliable and, as reported in documents seen by the *BMJ*, suggested privately that their study should be aggressively pursued to show that the results were spurious.

Despite having collected the data under discussion and being at that time the editor of *Diabetes* (a journal owned by the American Diabetes Association), Butler was not invited to the meeting. Unaware that it had taken place, he contacted Robert Elashoff, a UCLA biostatistician and cancer epidemiologist, to discuss his concerns about the human relevance of their findings. Because companies control their clinical trial data, Elashoff thought the best way to see if there were any relevant safety issues would be to consult the FDA's adverse event reporting system—where doctors and patients can log cases.

Regulator's response

So with the help of Elashoff's son, Michael, a former FDA drug reviewer, they checked the FDA's adverse event reporting system for evidence of pancreatitis and pancreatic cancer in patients taking the drugs. They found an increase in the number of reports of pancreatitis and pancreatic cancer with sitagliptin and exenatide. They also found increased reports of thyroid cancer with exenatide. Up until this point, the FDA had notified doctors only about exenatide and pancreatitis—there had been no warnings about exenatide and thyroid cancer or pancreatic cancer, nor any warnings at all about sitagliptin and pancreatic disease. So they decided to contact the FDA to share their concerns.

On 14 September 2009, Butler, Robert Elashoff, and Matveyenko held a teleconference with Mary Parks and others at the FDA. They discussed the findings of the rat study and raised their concerns about the safety signals coming from the FDA's database. They offered to work with the agency to try to find out more.

But the FDA did not seem enthusiastic. "The [response of the] FDA was quite surprising. They seemed to be defending the companies and defending the drugs. They were giving the exact same sound bites that the companies were giving," Butler told the *BMJ*. "When we talked about the database showing a signal for pancreatic cancer, at that point the conversation was ended by the FDA."

Shortly afterwards, on 25 September 2009, the FDA put out a safety alert for pancreatitis for sitagliptin. Others outside healthcare had taken swifter action. In October 2006, investment analysts from Bear Stearns had spotted the reports of pancreatitis associated with exenatide in the FDA's database and warned investors.[11] And in May 2009, London based pharmaceutical market analysts at Sanford Bernstein alerted its clients to safety concerns, based on its own review of the FDA database.[12]

What the manufacturers knew

Manufacturers too had spotted early signs of a link. In September 2008, Lilly convened a pancreatitis working group. Its aim was to establish the company's "core medical beliefs for exenatide and pancreatitis" to get their external messaging correct. A presentation pointed to the mounting reports of pancreatitis in patients taking exenatide and the strengthening biological plausibility of exocrine pancreatic effects. While noting that diabetes itself increases the risk of pancreatitis, it drew attention to raised pancreatic enzymes and the fact that "several strong positive-rechallenge cases had been reported" (when a patient is taken off the drug and then put back on it gets the same symptoms).

It concluded, "While it is difficult to prove causal association between exenatide and pancreatitis, a causal association is likely." An amended version seen by the *BMJ*, downgraded these concerns, taking out the words "causal" and replacing "likely" with suspected.

In a statement to the *BMJ*, Lilly said that it "evaluated data on an ongoing basis to ensure it adequately communicated the risks of Byetta [exenatide]. Lilly concluded that the FDA-approved labeling for Byetta appropriately communicated the potential risk of acute pancreatitis to health care providers."

A month after the meeting with Butler, in October 2009, the FDA asked Merck to conduct a three month safety study in diabetic rodents treated with sitagliptin. The FDA had to repeat the request several times before Merck complied. The company eventually sent its results to the FDA earlier this year. These have not yet been published.

A spokesperson for Merck said it "shares data on an on-going basis with regulatory agencies around the world." The FDA has told the *BMJ* that it deems this regulatory requirement to have been "fulfilled" and that "no regulatory recommendations were made based on our review of the study."

The FDA also asked other companies with GLP-1 based drugs to do further safety studies, and the agency has provided the *BMJ* with copies of the resulting publications.

Amylin and Lilly published their results in 2012. Both articles state in their titles that there was no drug induced pancreatitis, and the companies use them to suggest an absence of harm from the drugs. However, both papers reported pancreatic changes.

In the Novo Nordisk study, the rats treated with liraglutide showed increased ductal proliferation and acinar to ductal metaplasia. One rat treated with exenatide had a "hemorrhagic pancreas" at necropsy with "moderate apoptosis-like necrosis, minimal inflammatory infiltration and slight hemorrhage/edema."[13] Although the pancreases did not increase in weight, the incretin treated rats had "significantly higher" levels of pancreatic amylase. Three of the liraglutide treated animals died from a "single erroneous dosing."

A spokeswoman from Novo Nordisk told the *BMJ*, "Importantly, the study did not find any abnormalities in the pancreas associated with liraglutide treatment."

In the Amylin study, amylase levels increased in the exenatide group but dropped back to the level seen in the control animals when the drug was stopped—a finding the company said was not toxicological [a damaging effect of the drug]."[14]

Effects of GLP-1

Meanwhile, Butler and his team wanted to understand what might be behind the safety signals they had detected. Their persistence has earned them a reputation for having an agenda

against the drugs. Butler denies this allegation and says he has participated in teams to investigate both the potential benefits and unintended adverse effects of incretin mimetic drugs.

They suspected that GLP-1 receptors occur on pancreatic duct cells as well as pancreatic β cells—a fact the regulatory documents support and the medical literature confirms[8 15]—and that the hormone might have a proliferative effect.

To understand more about how GLP-1 agonists might affect people with diabetes, who are predisposed to pancreatic disease, they studied mice genetically predisposed to developing chronic pancreatitis and pancreatic cancer. The work was led by biologist Belinda Gier, who has since started working for Bristol-Myers Squibb.

These mice were given exenatide for 12 weeks. The researchers observed rapidly accelerated chronic pancreatitis and pancreatic dysplasia with an increase in lipase levels in those that had been treated compared with the controls. They found that the dysplastic areas (PanIN lesions) had the GLP-1 receptor.

In another study, Gier treated non-diabetic rats with the drug to examine the effects in the absence of pancreatic disease or diabetes. The pancreases of treated rats increased in weight compared with those of the untreated controls and showed hyperplasia in the exocrine pancreas. The researchers studied human tissue in vitro too. They found that GLP-1 induced proliferative signalling pathways.

According to Butler, this is the only study to look at the effects of the drugs in chronic pancreatitis. Proponents of the drugs question Gier's methods, however, and companies have told the *BMJ* that they found no abnormalities in their preclinical studies. However, Gier's work suggests that the way the pancreas is sectioned can affect the results. She found that, in healthy animals treated with the drugs, the histology was normal in the most accessible portions of the pancreas, the body and tail. "Methodological analysis of the entire pancreas . . . is necessary," she wrote.

For the UCLA team, these findings suggested that the drugs have a proliferative effect, causing problems when superimposed on underlying disease. Its results were published in 2012.[16]

The team also published its review of the FDA adverse event database.[9]The paper presented data from 2004-09 on the frequencies of adverse event reporting associated with sitagliptin or exenatide for pancreatitis, pancreatic and thyroid cancer, and all cancers compared with those associated with four other diabetic treatments. It showed a sixfold increase in cases of pancreatitis with both exenatide (reporting odds ratio 10.68; 95% confidence interval 7.75 to 15.1; P<0.0001) and sitagliptin (6.74; 4.61 to 10.0; P<0.0001). It also showed a roughly threefold increase in reports for pancreatic cancer (exenatide: odds ratio 2.9; P<0.0001; sitagliptin: odds ratio 2.7; P=0.008) and a roughly fourfold increase in thyroid cancer with exenatide (odds ratio 4.73; P=0.004).

The authors highlighted the limitations of their study and advised that it should be interpreted with caution. Their methods were heavily criticised by industry representatives and medical societies—for example, for the lack of information about confounding factors such as obesity, alcohol consumption, smoking, and concomitant medications.[17]

But in April 2013, the US Institute for Safe Medication Practices published its own analysis, which reached similar conclusions. The institute reviewed data from the nationwide FDA Adverse Event Reporting System for patients taking incretin mimetics in the year ending 30 June 2012 and found 831 cases of pancreatitis, 105 of pancreatic cancer, and 32 of thyroid cancer.[3]

All five incretin mimetics, taken together, had rates of pancreatitis that were more than 25 times higher than in diabetic patients on other drugs (95% CI 15.9 to 41.8). For pancreatic cancer, results were mixed, with the GLP-1 agonists showing rates 23 times higher than for other anitdiabetic drugs (95% CI 5.7 to 95.1) and the DPP-4 inhibitors frequencies 13.5 times higher (95% CI 3.11 to 58.5). For the two other oral drugs, linagliptin and saxagliptin, there was only a single case each, with reporting ratios that were not significant.

Other independent sources have also corroborated the UCLA team's FDA database analysis. Michael Elashoff presented the analysis at an American Statistical Association meeting in August 2012. Also presenting was William DuMouchel, chief statistical scientist at Oracle Health Sciences—a company that sells sophisticated computer analysis tools to regulatory authorities. Representatives from the FDA and some of the manufacturers attended too.

The *BMJ* has seen a copy of the Oracle presentation and spoken to DuMouchel. He reported a strong signal for pancreatitis for exenatide, sitagliptin, and liraglutide. For sitaglptin and exenatide there was also a signal for pancreatic cancer.

The *BMJ* also contacted WHO's Uppsala Monitoring Centre—an independent foundation for the safe use of medicines—which collects adverse event reports from around the world.

Chief medical officer Pia Caduff told the *BMJ* that the centre had identified disproportionate reporting on pancreatic cancer with sitagliptin, exenatide, and liraglutide between 2009 and 2011 and for thyroid cancer with exenatide and liraglutide. However, there were only a handful of cases.

"Reports on these combinations have since then increased and together with the "human tissue study" hint at a possible causal association," she said.

Legal action

Concerns about a link with pancreatitis has led to a lawsuit in California. Patients who have developed acute pancreatitis while taking exenatide are suing the drug's manufacturer Amylin, now owned by Bristol-Myers Squibb. The lawsuit now includes relatives of people who have died from pancreatic cancer, and part of the case revolves around the interpretation of unpublished animal data. Lawyers acting for the plaintiffs asked to see pancreas histology slides from monkeys treated with exenatide in preclinical studies for market authorisation. The manufacturer refused: the slides were a commercial secret and had to be reserved for FDA access, it said.

However, a judge overruled the company, and Professor Clive Taylor, a pathologist from the University of Southern California, was asked to study the slides, though he was given only brief access under close supervision by staff at Charles River laboratories, the contract research organisation that conducted the monkey studies on Amylin's behalf. Taylor looked at 96 slides from 48 animals. He pre-specified an algorithm for scoring the slides, was unaware of the doses received, and was handed the slides randomly one by one.

When Taylor returned home and analysed his findings, he found pancreatic intraepithelial neoplastic lesions in the treated animals, indicating chronic pancreatitis and pancreatic disease. The amount of pathological change in the treated animals was about twice that in the control animals.

"Well, if we were looking at human pancreas and saw those changes, I would say yes it's a concern," Taylor said in an interview with the *BMJ* and Channel 4's *Dispatches*. "These

changes are associated with pancreatitis and even, perhaps, with pancreatic [neoplasia], pancreatic tumours," he said.

The company's pathologists disagree with Taylor's interpretation—although they did not have a systematic way of scoring the slides. Taylor says the best way to resolve the difference of opinion is to make the slides available for further independent scrutiny. "As new information and new methods become available for looking at things, it seems to me that the right thing to do is apply that new information and those new methods to the material," Taylor says. "There are other analyses that could be done. So far they have not, as far as I'm aware, been done."

The company has refused to release the slides, and the judge has ruled that release would have to be at the request of the FDA.

The *BMJ* asked Bristol-Myers Squibb if it should allow independent experts access to the material for further analysis. It did not respond to this question.

Neither did it answer questions about whether it agreed with Taylor's findings. A spokesman told the *BMJ*: "The available data from these [preclinical and clinical] studies, including the 91-day and 273-day monkey studies, were shared with regulators, including the FDA and EMEA [EMA]."

Neither the FDA nor the EMA has seen the Amylin monkey slides—they told the *BMJ* that they usually rely on the overall pathology report provided by the drug sponsor.

The FDA stated that the "pathology slides are the property of Amylin, and the FDA has not requested that Amylin have the slides re-evaluated by a pathology working group." Taylor has sent the FDA his report and an agency spokesman has confirmed that it has received it. "The FDA has read Dr Taylor's report and agrees that Dr Taylor's interpretation differs from Amylin's and the veterinarian pathologists that originally read the slides, but that the two parties are seeing the same type of histological changes." The agency has not decided if an independent review would help. EMA has said it is able to request an additional review of the slides if it has concerns.

Taylor told the *BMJ* that the company pathologists who re-examined the slides had noted more pancreatic disease in those on the drugs but used different terminology for the changes.

Liraglutide in monkeys

The *BMJ* has learnt of other unpublished and disputed evidence from industry studies in monkeys. A study by Novo Nordisk reported results from monkeys treated with liraglutide for 52 weeks.[18] The study, published in *Diabetes* in 2012, concluded an "absence of pancreatic structural changes in three species."[18]

The paper has been used by the company to downplay concerns of pancreatitis and proliferative changes associated with their drug both at conferences and to the *BMJ* when asked. However, it does not seem to present a complete picture of the 52 week study's findings.

Through freedom of information requests, the *BMJ* has found that results that were not included in the published paper led regulators to raise concerns at the time of licensing the drug in 2008 and 2009. One of the EMA reviewers had noted that liraglutide had the "possibility of increased neoplasia perhaps through growth promotion (rather than a genotoxic effect)." The regulator also asked the company about a statistically significant increase in pancreatic weight in young healthy monkeys treated with liraglutide.

"Further investigations of the pancreatic tissues collected in the 52-week monkey study showed that the increased pancreatic weight was due to a 67% increase in absolute duct cell mass and 64% increase in exocrine cells when compared to the vehicle group," an EMA reviewer said in 2008." Considering that concerns have been raised regarding the potential induction of acute pancreatitis following treatment with GLP-1 receptor agonists, the applicant is requested to evaluate the clinical relevance of this finding."

In reply Novo Nordisk said the findings were due to the control monkeys having smaller pancreases. They also offered reassurance from a longer 87 week study, which they said did not show any effect on pancreas weight or any changes suggestive of inflammation or pancreatitis.

However, the pathology report obtained by the *BMJ* suggests that only the thyroid was processed for histology. The pancreases in the treated animals were also bigger. But the study was not set up to analyse organ weights and a source close to EMA said it was underpowered to detect anything but a large change given the spread of weights and the small numbers involved.

But the company disagree. A spokeswoman for Novo Nordisk stressed that a biological finding has to be reproducible and that is not the case with the 87 week study. "No dose-dependent significant increases [occurred] in any study but the 52 week [study]," she said.

Adding to the confusion a "human error" by a Novo Nordisk employee meant a graph to answer EMA's concerns contained the wrong data so that it appeared to show no change at all. The EMA accepted the company's explanation and did not ask to see the 52 week slides. It has since told the *BMJ* that its "interpretation of the 52 week monkey study is that there is no effect of liraglutide on pancreas weight."

However, the FDA also had concerns about the 52 week study. Reviewers noted increased pancreatic weight in monkeys after 28 days of treatment. The toxicology reviewer believed these changes to be treatment related and suggested that the safety margin was low. An FDA spokesperson told the *BMJ*: "An expanded mass of exocrine and/or endocrine structures is also not equivalent to evidence of toxicity, but would merit investigation of causality if shown to be drug-related and dose-dependent."

In fact the *BMJ* has uncovered an apparent dose-response relation in the Novo Nordisk data, which were obtained from the EMA. With increasing dose, the pancreatic weight and the exocrine component increased—although at the end of a four week recovery period (a period of not taking the drug), the pancreatic weights of treated monkeys were similar to those of control monkeys. Readers of Novo Nordisk's publication in *Diabetes* were not given this information.[18] The paper did make it clear that the sections were assessed unblinded to treatment.

A spokeswoman for Novo Nordisk said that the company thought the paper fairly represented its animal studies but noted that space constraints had prevented inclusion of some findings. "When publishing non-clinical data in a scientific journal, limitations on the article length do not allow for the inclusion of all study results," she said, adding: "No macroscopic or microscopic changes were noted in any cell type in any of the monkey studies in the pancreas."

Human pancreases

Even though the companies used a breed of monkey that is the closest proxy to humans, animals do not always accurately predict what will happen in humans. So earlier this year, a team

of researchers from UCLA and the University of Florida decided to analyse the pancreases of human organ donors. Their findings, published in *Diabetes*, have prompted both US and European regulators to issue public statements about precancerous changes[19] and to do further analyses. The FDA has confirmed that it has sent the team questions and plans to meet up.

Eight of the organ donors had type 2 diabetes and had been taking an incretin mimetic for at least a year (seven sitagliptin and one exenatide). Twelve other diabetic organ donors had been taking other classes of treatment. Fourteen non-diabetic organ donors were used as controls. The researchers matched the donors in the two treatment groups for sex and body mass index.

The pancreases in those who had taken incretin mimetics were on average 40% larger, with more precancerous changes. In addition, seven of the eight patients who had been treated with a mimetic had α cell hyperplasia, three expressed α cell derived microadenomas, and one had a grade 1 α cell derived neuroendocrine tumour that was "not appreciated in life." These findings did not occur in the diabetic patients treated with other drugs or in the non-diabetic patients.

The researchers were not overly surprised. They viewed these findings as being entirely consistent with the drugs' mode of action, glucagon suppression. Nor were they the first to find α cell hyperplasia associated with GLP-1 treatment. Long before the first incretin mimetic came on the market, published reports showed increased numbers of alpha cells in animals treated with a GLP-1 agonist.

In 1999, GLP-1 researcher Joel Habener and a team at Harvard found that exendin-4 (exenatide) induced an increase in α cells in rats. "It will be interesting to determine how sustained this increase in alpha-cell mass is during even longer-term administration of exendin-4," they concluded.[8] The *BMJ* asked Bristol-Myers Squibb about this finding. It did not answer the question.

At the behest of their ethics review board the UCLA/Florida team wrote to notify the FDA of the results of their study on human pancreases. The agency replied, "As you are aware, FDA shares your concern over the potential role these drugs may have on causing pancreatitis and/or pancreatic cancer and multiple nonclinical and clinical assessments have been required of sponsors of these drugs, including postmarketing requirements for those already on the market."

However, the study has been criticised. A spokeswoman for Novo Nordisk told the *BMJ*: "The number of patients included in the study is small, and the groups are seemingly not well matched in relation to age at diagnosis, duration of diabetes, BMI [body mass index], and concomitant medication."

Adverse event reporting

Many also argue that the value of evidence from regulatory databases is limited. Both the regulators and manufacturers point to ongoing post-marketing studies that will resolve the questions in years to come. Medical societies, such as the American Diabetes Association and the American Association of Clinical Endocrinologists, say that even the link to pancreatitis is controversial and question the evidence underpinning the safety concerns. In a recent statement, they said that patients should consult their doctor and that only adequately powered randomised controlled trials can really resolve this impasse.[20] "New [randomised controlled trial] data [will be] available relatively soon which will allow physicians to definitively assess risks and benefits of this class of medicines," a recent statement said.

But critics point out that the trials are done by the drug companies themselves. And Sonal Singh, assistant professor of medicine at Johns Hopkins University and drug safety researcher, whose database study published this year found increased rates of pancreatitis in exenatide and sitagliptin treated patients[2] wonders what harm may be done while we wait for this level of evidence. "Safety signals can be dismissed on one limitation or another or you can find some other study which shows no risk. The other option is you can place a high bar for absolute certainty of risk or ask for such a long term study that years fly by and the patent expires," he says. "The fundamental question is who bears the burden of the passage of time while these debates are settled?"

Responding to questions from the *BMJ,* the FDA said that adverse event reporting was most useful for detecting rare, serious, and unknown events but of limited value for assessing a known event or detecting events that have a high background rate in the population, such as pancreatitis or thyroid cancer.

However, the FDA has acted on such evidence before. It issued a safety alert in 2007 about pancreatitis linked to exenatide on the basis of 30 cases. In 2008 this was updated to include six cases of necrotising pancreatitis. In 2009, a similar warning for pancreatitis was issued for sitagliptin and, more recently, one for liraglutide—which also carries a black box warning for c cell originating thyroid tumours.

The EMA too has produced safety guidance for the incretin mimetics based on small numbers of cases of pancreatitis. But given that there are now hundreds of reports of pancreatic cancer—and the case reports have remained consistent or increased over many years— why no alert for this? Could it be because this class of drugs would not survive such a warning?

The *BMJ* asked the FDA about this seeming inconsistency. "Because of the time required for cancer to develop, it will always be difficult to apply spontaneous reports of cancer (any cancer) to drug exposure that began or occurred years before," a spokesman said, adding that spotting disproportional reports in its safety database was not sufficient in isolation.

"FDA has conducted several reviews of pancreatic cancer in association with incretin mimetics and has not advanced a recommendation for labeling. It is important to note that neither a mechanism nor human cases need to be identified for labeling. For example, liraglutide and Bydureon [long acting exenatide] both have a warning for the potential for C-cell thyroid cancer based on rodent studies," he said.

FDA official Curtis Rosebraugh said to an FDA committee convened to discuss the licensing of liraglutide that even if the drugs do cause pancreatitis the FDA would not remove them from the market but would "encourage awareness and early diagnosis." He concluded that, "while many sponsors may responsibly introduce a drug into marketing, theirs is a profit-based business and the pressures to generate revenue are strong. Also, with most classes of drugs, there are similar drugs in development from competitors which places even more pressure to generate profit before there is more competition."

Both the EMA and the FDA now acknowledge there is increased reporting of pancreatic cancer with incretin mimetics. But in a statement to the *BMJ*, the FDA said: "There has been no causal relationship established between exposure to incretin mimetics and pancreatitis, pancreatic cancer, and thyroid cancer."

EMA said that it did not consider that current data support an increased risk of pancreatic or thyroid cancer with the products

in question. “However the issue is under review at CHMP [EMA’s regulatory committee] and outcomes will be communicated when available,” a spokeswoman said.

While the debate continues about pathophysiology and mechanisms of action, questions remain about whether the companies and regulators have done enough to get to the bottom of these safety concerns. And have doctors and patients been adequately warned?

For Michael Elashoff, a former FDA drug reviewer who was part of the team expressing safety concerns in the recent journal debate, the implications are clear.

“These drugs are being used by hundreds of thousands or millions of patients and if the safety hasn’t been adequately studied then there’s a lot of people at risk of some very serious side effects of the drugs.”

Competing interest: I have read and understood the BMJ Group policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Provenance and peer review: Commissioned; externally peer reviewed. (Editorial note: this statement has been amended since the article was originally posted. The original statement said that the article had not been externally peer reviewed, which was incorrect.).

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What's going on in the pancreas?

In a world where the prevalence of type 2 diabetes is increasing rapidly, finding new targets for therapy is a high priority for drug companies. The discovery by scientists in the 1970s and the then publication in 1993 by Michael Nauck of the double action of GLP-1 (glucagon-like peptide-1) provided just such a target.

GLP-1 is a hormone-like peptide released by the intestine in response to a meal; its functions include regulating insulin and blood glucose and slowing gastric emptying. In his study, Nauck found that GLP-1 both increased the insulin made in the pancreas and, by inhibiting the secretion of glucagon, reduced the glucose released by the liver. Excessive glucose release by the liver underpins the high circulating glucose that defines type 2 diabetes. Following secretion, GLP-1 is quickly inactivated by an enzyme, dipeptidyl peptidase-4 (DPP-4). The GLP-1 drugs are either analogues that are not inactivated by DPP-4, taken by injection (exenatide, liraglutide) or oral drugs that inhibit DPP-4 (sitagliptin, saxagliptin, and linagliptin).

The saliva of the desert dwelling Gila monster was the source for the first GLP-1 analogue on the market, exenatide. A heavy slow moving lizard, it eats once or twice a year, and uses the secretion of its salivary hormone exendin-4—which displays similar properties to GLP-1—to induce proliferation of its pancreas and gut to assimilate a meal. Some say this should have provided a valuable clue to the unwanted effects of raised circulating levels of a hormone that usually lasts for only minutes before it is broken down.

But now that most of the other treatments for type 2 diabetes are off patent, these are valuable drugs. Merck's market leading drug sitagliptin generated about $4.1bn (£2.6bn; €3bn) in sales in 2012 with liraglutide's 2012 sales of $1.7bn coming in behind. The profit margins mean there is much at stake for the companies and the organisations and doctors who depend on their support.

However, serious doubts about the wisdom of basing treatments on GLP-1 agonists have existed since the beginning. And the companies and regulators have, on reflection, had in their hands ample warning signs—and chance to resolve some of the emerging controversies.

In 2005, the *New England Journal of Medicine* published a study that showed pancreatic changes in patients who had a type of gastric bypass surgery called Roux-en-Y. The authors noted hypertrophy and hyperplasia of the islet cells, also affecting the cells in the pancreatic ducts. They thought this might be due to raised levels of the hormone GLP-1, which were known to occur after this type of procedure.[21] (A later study on this type of surgery also showed a "pronounced" increase in α cell mass[22]).

Senior executives from Amylin and Lilly wrote to the New England Journal to distance their drug from the paper and to stress the lack of evidence of a pathological effect on the islets in animal studies. "A study of nine months' duration in healthy cynomolgus monkeys at doses of more than 400 times those used in humans showed minimal-to-mild islet hypercellularity with no increase in islet size (data on file, Amylin Pharmaceuticals)," they said.

The suppression of glucagon by incretin mimetics was highlighted by companies in their drug licensing applications and was noted by regulators. Billions of dollars of sales later, after concerns have been raised about the safety of glucagon suppression and its effect on glucagon producing α cells, the extent to which they do this is being contested.

Butler and colleagues' finding of α cell hyperplasia in humans taking GLP1 based drugs[4] was not the first. In 1999 GLP-1 researcher Joel Habener and a team at Harvard found that exendin-4 (exenatide) induced an increase in α cells in rats.[8]

But evidence of α cell hyperplasia has come from multiple models and sources—including the companies themselves. Whether this is applicable to GLP-1 based treatments is subject to fierce debate.

Only last October, Professor Dan Drucker, a long standing consultant to many of the companies, gave a keynote lecture at European Association for the Study of Diabetes conference. "The therapeutic window for reduction of glucagon action to manifest beneficial effects for glucose control while avoiding enhancement of hepatic lipid storage, dyslipidemia, hepatocyte injury, and α-cell proliferation in diabetic subjects is unclear," the official conference journal reported.[23]

Others in industry have previously highlighted the important role of glucagon suppression in the control of diabetes. In 2005 at a session entitled "GLP-1s: the new darlings of diabetes treatment" Jens Holst, scientific director of the Novo Nordisk Foundation for Metabolic Research at Copenhagen University and a long standing consultant to the company, told the American Diabetes Association annual conference that GLP-1 agonists were a powerful inhibitor of glucagon secretion, adding that he thought this would be "a very important action to diabetes patients."

A spokesperson for Novo Nordisk acknowledged an effect on α cells but only from full not partial glucagon suppression. She told the *BMJ*: "Complete removal or blocking of the glucagon receptor, or important signalling components, have caused α cell hyperplasia. This is separate from the relatively modest lowering of glucagon secretion induced by GLP-1."

The *BMJ* asked Drucker about this. In response he sent a copy of an article he had written in *Cell Metabolism*, but this did not describe α cell effects.[24] Yet the *BMJ* has found that the companies were aware of the unwanted effects of the full and partial suppression of glucagon before the incretin mimetics came onto the market.

At the turn of the century, Holst, working with scientists from Novo Nordisk, reported that glucagon suppression in mice resulted in massive enlargement of the pancreas and the proliferation of α cells (α cell hyperplasia).[25] They concluded that α cells appear not just in the islets but in the pancreatic ductal epithelium—something that Butler and colleagues found. Importantly, this effect did not require complete blocking of glucagon receptors or the stopping of glucagon production. Even a partial reduction in the hormone signalling resulted in α cell hyperplasia, as shown by Eli Lilly in 2004.[26] The Lilly team acknowledged that they hadn't seen any neoplasia; the studies up until that point had been short—only four months long. They suggested that both glucagon and its receptor must be functional in order to maintain a feedback loop that restrains α cell growth "but the exact nature of this feedback loop is unclear."[26]

Over the years, evidence of the effects of modifying glucagon signalling has mounted. In 2009 Run Yu, codirector of the carcinoid and neuroendocrine tumour programme at Cedars Sinai Hospital in Los Angeles, published a report in patients with a rare condition causing deficiencies in glucagon signalling.[27] He found α cell hyperplasia and neuroendocrine tumours.

"In type 2 diabetes glucagon plays a role but there is a price to pay with reducing it," he told the *BMJ*.

Yu said that he had shared his view with certain companies after the study came out. Because of agreements with the companies, he was unable to say which they were.

He then did a study in mice with decreased glucagon signalling that was far longer than any conducted by the companies. He found that neuroendocrine tumours invariably developed after formation of α cell hyperplasia and eventually led to death. Yu concluded that glucagon suppression was not a safe way to treat diabetes.[28] But whether this applies to GLP-1based therapies is still uncertain.

In the course of this investigation, the *BMJ* has looked at thousands of pages of regulatory documents from both the FDA and the EMA. There seems to be little discussion about the potential adverse effects of interfering with glucagon signalling on the α cell, even though the manufacturers spelt out —and the regulators noted—that glucagon suppression was one of the effects of the drugs. Michael Elashoff, a former FDA reviewer who has analysed the safety of the drugs, believes the regulators should have been more cautious in approving them.

"If some of the side effects can be anticipated in advance, then it seems incumbent upon the FDA to really force the companies to do real significant investigation of these potential side effects before the drug goes on the market and not leave it to experiment with actual patients taking the drug," he said.

The FDA maintains that: "Long-term studies of incretin mimetics in rodents, dogs, and monkeys failed to demonstrate adverse pancreatic pathology or other toxicology reflective of a glucagon deficit that could be interpreted as a clear risk to human subjects."

The *BMJ* asked the five companies who market incretin mimetics if they have ever studied the effects of glucagon suppression on the proliferation of α cells. Only Novo Nordisk responded to the question. It stressed that it had never seen α cell hyperplasia in any of its studies.[29-31] "Alpha-cell hyperplasia is not mediated by the GLP-1 receptor," a spokeswoman said. Behind the scenes, concerns also started to emerge about the potential inflammatory effects on the pancreas. Effects on pancreatic enzymes: Internal industry documents show that in 2005, one industry key opinion leader reported "extremely high" lipase levels in a patient taking exenatide. He was concerned that the company had missed signs of potential inflammation in its clinical trials.

Dennis Kim, then executive director at Amylin, wrote in an email that the doctor's report was a "bit concerning" and confirmed that pancreatic amylase and lipase were not measured systematically in the company's clinical trials.

The *BMJ* has found that companies have measured these enzymes for "safety issues," but in many cases the data have not been reported in the published studies.

For example, in one Lilly funded trial comparing weekly exenatide with sitagliptin and two other diabetes treatments—insulin and pioglitazone—enzyme levels increased in a higher percentage of people taking incretin mimetics after 26 weeks of treatment.

Regulatory documents show the mean (SD) lipase concentration in the exenatide group increased from 42.0 (23.77) U/L on day 1 to 60.8 (38.39) U/L at week 26. Sitagliptin also increased lipase from 40.3 (21.3) U/L to 48.7 (30.7) U/L. The levels in the pioglitazone control dropped. However, when the trial was published in the *Lancet*, these data did not make the final cut.[32] The company did not say why when the *BMJ* put it to them. Neither did lead author, Richard Bergenstahl, answer the *BMJ's* queries.

Earlier this year, the *Lancet* published another study funded by Eli Lilly and Amylin in which enzyme levels were measured but not reported.[33] "Routinely measured concentrations of pancreatic lipase and total amylase varied in both groups and were not predictive of gastrointestinal symptoms," the paper said.

The FDA says that the clinical value of routine amylase and lipase monitoring in asymptomatic patients is not clear. But pancreatologists, have told the *BMJ* that reporting enzyme levels is important because they may reflect a subclinical effect of the drug.

"Many large phase III trials report findings of significant biochemical abnormalities, even though the clinical significance may be uncertain at the time, and in this case where the drug is known to exert effects on the pancreas, I would find such information of value," Thor Halfdanarson, a pancreatic surgeon, at the Mayo Clinic in Arizona said.

Indeed, writing in support of incretin mimetics in *Diabetes Care* last month, Michael Nauck said that the effect on pancreatic enzymes may be important.[6] "Effects of GLP-1 receptor stimulation on pancreatic enzyme synthesis, potential leakage into the circulation rather than direct secretion into pancreatic digestive juice, and a potential induction if a chronic inflammatory response need to be studied," he said.

What happens to those who raise safety concerns

Those who have attempted to publish evidence on the possible harms of GLP1-based drugs have found that it can be difficult.

Butler and colleagues' FDA database paper in *Gastorenterology*—which showed a sixfold increase in reports of pancreatitis with both exenatide and sitagliptin as well as increased reports of pancreatic and thyroid cancer[4]—was met with anger against the authors, particularly Butler. This was despite the paper being clear that their methods had limitations and should be interpreted with extreme caution. After the paper was published online, senior executives from Merck, manufacturer of one of the drugs in the study, and Novo Nordisk wrote to the editor of *Gastroenterology* to express their strong views.

Mads Krogsgaard Thomsen, the chief scientific officer for Novo Nordisk, likened the paper to the fraudulent *Lancet* paper by Andrew Wakefield and colleagues linking MMR vaccine to autism, in that it risked creating an unwarranted public health scare. He said that Novo Nordisk had drawn different conclusions from the data and asked the journal to "withhold the publication of Elashoff et al until it has been confirmed by an independent statistical analysis."

Even attempts to discuss the *Gastroenterology* study and alert doctors of any potential implications proved problematic. Shortly after the paper was published online, the German Diabetes Society issued a statement written by Thomas Danne, a paediatric diabetologist in Hannover, on behalf of the society's executive board.

It stated that new patients should be started on GLP-1 receptor agonists and DPP-4 inhibitors only in special circumstances and that all patients currently treated with these drugs should be informed about the findings to appear in *Gastroenterology*.

But three days later the statement disappeared from the society's website, only to be replaced by another. This said that Novo Nordisk's letter to the editor of *Gastroenterology*—which the journal hadn't published—said there was a "reporting bias," which drew the quality of the published results into question. The executive board rescinded their initial recommendations and advised doctors not to change their current practice.

The *BMJ* has also learnt that Novo Nordisk has sent out scientific liaison officers to those who have raised concerns about their drug—although there is no evidence of intimidation. But now several of Peter Butler's UCLA team and Michael Elashoff have been subpoenaed by Lilly in the relation to the lawsuit it is fighting with patients who have developed pancreatitis and pancreatic cancer while taking exenatide.

The request by Lilly's lawyers for documents from Butler is particularly wide ranging. He has been asked for all published and unpublished data; all correspondence with authors pertaining to incretin mimetics when he was an editor; reviews he has done; and letters to journal editors. The subpoena also includes any communications to any media about GLP-1 studies.

Butler declined to talk about the subpoena when asked.

Novo Nordisk told Danish newspaper *Berlingske* that it has not been directly involved in the subpoena. However, a spokeswoman said that "it may be an industrial organisation (like Pharma) that is behind [it]."