FAT BUSTERS

The next generation of weight-loss drugs is on its way. Will their side effects be hard to swallow? **Asher Mullard** investigates

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IN THE 1800s, commonly sold diet pills had ingredients ranging from soap to lard and even arsenic. To be fair to the arsenic pedlars, the chemical would certainly have made those who consumed it lose weight – as well as causing diarrhoea, vomiting and convulsions.

These days, although medicines only reach the clinic after extensive studies in animals and people, we still lack an appealing weight-loss pill. Over the next year or two several new types of diet drugs are set to reach the clinic. But we have been here before, and dozens of apparently promising diet pills have had to be scrapped due to dangerous side effects. So will the next generation of fat busters be different, or are safe and effective diet drugs an impossible dream?

For most of human history, the biggest challenge in life was getting our hands on enough calories to meet our daily energy requirements. Now, many in the west face the opposite problem: one of the biggest threats to health is overeating. In the US at least 1 in 3 adults is obese, and the figures are almost as bad in the UK and Australia.

Being overweight raises the risk of diseases like heart attacks, strokes and cancer, and takes a financial toll in terms of healthcare costs and lost work days. "The consequences of obesity, at a personal and a societal level, are staggering," says Susan Yanovksi, co-director of obesity research at the National Institutes of Health in Bethesda, Maryland.

People battling their weight are constantly told it boils down to a simple equation: energy in has to equal energy out. They just need to eat less or exercise more, and preferably both.

So why is it incredibly hard to put this advice into practice? Part of the problem, says obesity doctor David Lau at the University of Calgary in Alberta, Canada, is that we have evolved to gain weight to survive long famines. As a result we are fantastic at fattening up, and terrible at slimming down. Given how hard it is to lose weight, new solutions are needed, says Lau. "We have to stop the blame game."

Amphetamine craze

The long and chequered history of diet pills is laid bare in *Calories & Corsets,* a book about 2000 years of diet fads by Louise Foxcroft, a medical historian in Cambridge, UK. Based on the track record, she says, "diet drugs are more likely to help you lose pounds from your pocket than pounds from your hips".

Any weight-loss medicine needs minimal side effects, especially since unscrupulous diet clinics hand drugs out to people wanting to lose weight for purely cosmetic reasons. "Healthy young 15-year-olds are going to take it, and we can't afford to make them ill," says Stephen Bloom, a hormone researcher at Imperial College London.

Arsenic is not the only diet drug to have failed on that score. In the 1930s the craze began for amphetamines, a broad class of stimulants that curb appetite and boost activity levels, but they have serious side effects, including heart problems. They are also highly addictive. In the US there is just one amphetamine-like drug on the market now. Called phentermine, it is only supposed to be taken for a few weeks at a time because of the health risks.

Only one weight-loss drug can be taken long-term: orlistat, which works by blocking fat absorption in the gut. Made by the Swiss firm Roche, it causes modest weight loss, but has an off-putting side effect: the fat slides all the way through the bowel, which can lead to flatulence and incontinence – sometimes simultaneously.

Over the past few decades various other kinds of diet pill have been and gone, most recently two called sibutramine and rimonabant. "We've been left with very little to help us," said Caroline Apovian, an obesity doctor at Boston University in Massachusetts. Let-downs are to be expected with drugs such as these, which bind to receptors distributed widely in the brain, says Bloom. This is because their pathways affect so many bodily processes, from managing emotions to motor function. "Blanket blocking is really a bananas approach," he says.

Will the next crop of weight-loss drugs prove more successful? The next to reach the clinic is likely to be a drug called Qnexa, made by Vivus of Mountain View, California. This is a combination of the amphetamine-like phentermine with a second drug called topiramate, which is used to treat epilepsy but has also been found to curb appetite.

Neither drug is considered safe enough for long-term weight loss on its own – phentermine can cause changes to the heart rhythm, and topiramate has been linked with memory loss, and birth defects if taken by pregnant women. Vivus argues, however, that by combining the two drugs, each can be given ›

at a lower dose, thereby reducing side effects.

Assuming that argument holds, the firm looks as if it is on to a winner: in one large year-long trial, people lost on average 9.3 per cent of their body weight (about 11 kilograms), after adjusting for the placebo effect (*Obesity*, vol 20, p 330). That looks impressive considering the rough benchmark for approval is 5 per cent. "This is by far the most potent anti-obesity drug we've ever seen," says Lau, who has worked with various

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pharmaceutical firms, including Vivus.

Although concerns about side effects linger, the US medicines regulator, the Food and Drug Administration, looks set to approve Qnexa next week. Its drug review committee has already passed the medicine as safe and effective, which usually (although not always) leads to a thumbs-up.

In fact a makeshift version of this medicine is already in use. Because both components are available individually, some doctors are willing to prescribe them together at the correct dose. That may continue whatever the outcome is next week, as the do-it-yourself version uses unbranded drugs and so is bound to be cheaper than Qnexa.

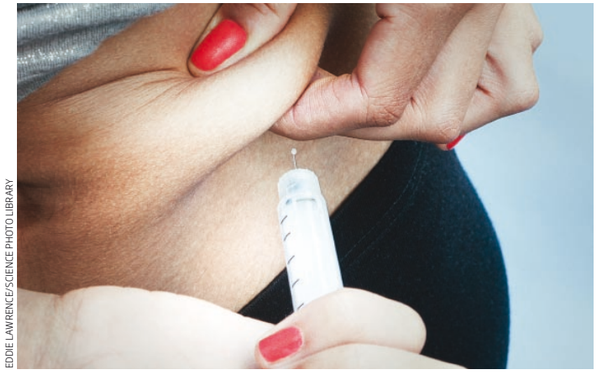
Then there is lorcaserin, made by Arena Pharmaceuticals of San Diego, California, which reduces appetite by binding to serotonin receptors in the brain. While they have not been compared head to head, lorcaserin seems to cause less weight loss than Qnexa: 3.6 per cent of body weight after allowing for the placebo effect in one large year-long trial (*The New England Journal of Medicine*, vol 363, p 245). Arena argues that the drug is very safe, which outweighs its modest effect on weight. The FDA is likely to give its verdict on lorcaserin in June.

While those two drugs could be first to reach the clinic, waiting in the wings is a batch of compounds that work through a different mechanism altogether. Unlike drugs that have broad effects on the brain, the next group mimic gut hormones that have evolved to regulate how much we eat.

Work on these hormones began decades ago, when it was realised that chemical signals from the gut prompt the pancreas to release insulin, the hormone that deals with raised blood sugar levels after eating. Called incretins, these mysterious substances were viewed as a potential treatment for people with type 2 diabetes, who respond too weakly to insulin and may also fail to release enough of the hormone. Type 2 diabetes can be treated with regular insulin injections, but this approach has several drawbacks and so new diabetes drugs are sorely needed.

One of the incretins, discovered in the 1980s, is a small protein molecule called GLP-1. The protein itself would make a poor drug because it only lasts for a few minutes in the bloodstream before being broken down by enzymes or cleared by the kidneys. But several longer-lasting mimics have been developed, and are now used to treat type 2 diabetes.

The GLP-1 mimics have to be injected, twice a day, once a day or once a week. Many people feel nauseous during the first weeks of use, although most battle through this stage. More worryingly, the GLP-1 mimics might cause inflammation of the pancreas, and studies in rats suggest a risk of thyroid cancer.



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People with type 2 diabetes often improve if they lose weight

MOLLY RILEY/REUTERS/CORBIS

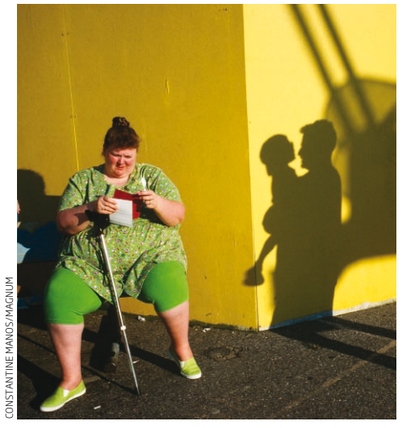
Over 20 years, portions in US restaurants have doubled or tripled

Yet many users put up with these risks for the sake of another "side effect": they lose weight. This is a key benefit as obesity and type 2 diabetes are intimately entwined. Being overweight is big risk factor for developing diabetes, and losing weight helps to improve control of blood sugar. Frustratingly, though, most other diabetes medicines, including insulin, make people put on weight.

That is undoubtedly why sales of the GLP-1 mimics as diabetes treatments have soared; the first two to reach the clinic have become so-called "blockbuster" drugs, that is to say they earn more than $1 billion a year in sales.

Why would incretins cause weight loss? In addition to triggering insulin release, GLP-1 also binds to receptors in the gut and the brain to slow the speed with which food moves through the gut and dampen appetite – all fairly logical for a hormone released after eating. Crucially, though, the receptors in the brain are not widely distributed but are only present in select circuits that control appetite, which should in theory make for better targeted, safer medicines.

More evidence comes from those who have had stomach bypass surgery; although they can only eat minuscule portions, these people tend not to feel ravenous. This might be because the surgery results in more nutrients being delivered to the lower end of the gut more quickly, and it seems this tricks the gut into ramping up production of the hormones that are normally released after eating, including GLP-1 (*New Scientist*, 5 September 2009, p 30).



CONSTANTINE MANOS/MAGNUM

Besides heart disease, obesity causes joint and mobility problems

After the operation many people lose their cravings for sweet foods, and some suspect that may also be due in part to GLP-1. Reports from people taking the GLP-1 mimics support this theory. "Patients come in and tell us that they have completely lost their interest in milk chocolate and candies," says Arne Astrup, an obesity researcher at the University of Copenhagen in Denmark, who helped unravel the effects of GLP-1 and now advises Novo Nordisk, based in Bagsvaerd, Denmark, and other drug developers.

No surprise then that the GLP-1 mimics are being tested as weight-loss drugs in people who are not diabetic. A participant in one of the studies is Phyllis Klepic, a retired healthcare worker from Calgary who has struggled with her weight all her adult life. When she saw the poster in her doctor's office advertising a trial of one such drug, liraglutide, she signed up right away. Eight months on and Klepic does not know whether her injections contain the drug or a placebo. Encouragingly, though, she has lost 18 kilograms, from a starting weight of 122 kilograms. "I'm doing things I haven't been able to do for years," she says. "For a while I couldn't bend over and tie my shoes, and now I can do that."

A previous large clinical trial of this drug in people who were obese but not diabetic gave encouraging results, with participants losing around 6 per cent of their body weight over a year, with placebo adjustment. "The prospects for liraglutide are good," Lau says. A GLP-1 mimic with a once-monthly injection schedule is also in the pipeline.

Liraglutide will not be licensed for another year or two for people who are not diabetic, but some people are not willing to wait. Internet forums are abuzz with stories of those who have secured it "off-label", in other words, outside the terms of its licence. Some are willing to travel to get the prescription. "Here in Canada, we had patients go down to the US to get the drug," says Lau.

Other gut hormones are being investigated as aids to weight loss. And at an even earlier stage of development is a third broad class of possible drugs that takes another approach – boosting metabolic rate. The furthest-along of these is beloranib, originally developed as a cancer treatment, which makes the body blaze through its fat stores, resulting in weight loss.

With so many new diet drugs on the way, is life about to get easier for people trying to slim down? The two medicines with any chance of going on sale this year will garner their share of attention, but it will take a couple more years before the first of the more promising new weight loss drugs – the GLP-1 mimics – gets the official green light. And even then, this group will stand and fall by their side effects; they will not last long if suspicions are further raised they cause inflammation of the pancreas, or thyroid cancer.

"Each of the dozens of drugs previously proposed initially carried great excitement, before their limitations became clear," points out David Ludwig, an obesity doctor at Harvard Medical School in Boston. Until longer-term data is in, he will remain sceptical.

If the new drugs prove safe and effective, there are still other unanswered questions. Many doctors are unsure if such drugs even have a place in the pharmacy. Lifestyle changes can be effective when pushed properly, says Ludwig, and diet drugs offer none of the advantages of exercise and healthy eating.

Even among doctors who agree with the use of weight-loss drugs, there is disagreement over how widely to roll them out. "We should be restrictive and use these drugs only for obese patients who have complications," says Astrup. It is not a question of weight-loss pills replacing diet and exercise, he adds, but using them on top of lifestyle changes.

If so, Klepic would be his ideal patient. Taking part in the trial may (or may not) have given her a pharmaceutical boost, but she is also using her will power, she says. She is choosing smaller portions and walking every day. As far as Klepic is concerned, it's win-win whatever she has been injecting herself with. "If it is the drug, I think it's excellent," she says. "But if I've done it on my own, I'll feel really good about it." ■

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