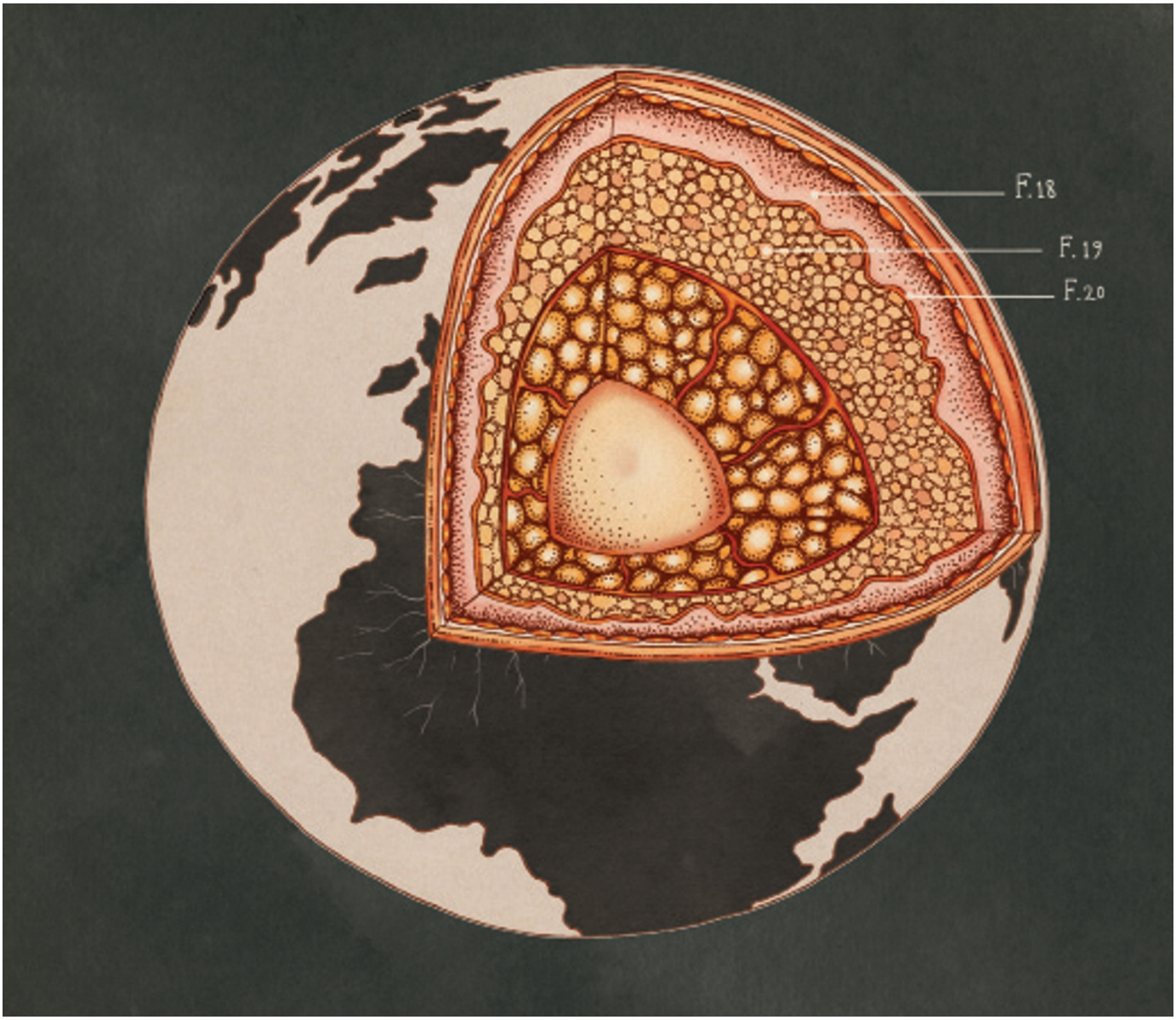

KATIE SCOTT

TREATMENT

Marginal gains

Behavioural interventions work, but not for everyone, and weight regain is common. Are there better ways to treat obesity?

BY EMILY ANTHES

In Providence, Rhode Island, researchers are teaching overweight adults how to get more sleep. The patients are learning the importance of developing regular night-time routines, avoiding alcohol and caffeine before bed, and other basic 'sleep hygiene' strategies as part of a study investigating whether getting more shut-eye can lead to healthier eating habits and weight loss. In San Francisco, California, clinicians are sending overweight, low-income, pregnant women to a course in mindfulness, in the hope of reducing stress-related overeating. In New York City, scientists are asking overweight African-American and Latino adults to make one small change in their eating behaviours, such as using smaller plates.

These small-scale trials are all part of Obesity Related Behavioral Intervention Trials (ORBIT), a US$37-million programme at the US National Institutes of Health, based in Bethesda, Maryland, designed to target some of the major drivers of weight gain and to translate insights from basic behavioural science research into innovative treatments for obesity.

Despite years of research and countless clinical trials, there is no clear strategy for treating obesity at the population level and reversing the

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obesity epidemic. Comprehensive behavioural programmes, designed to get patients to eat less and exercise more, can yield significant weight loss. But they do not help everyone. Certain segments of the population, such as those with low incomes, remain especially difficult to reach, and many patients have trouble maintaining their hard-earned weight loss once a study ends.

"We need to work on ways to help people initiate these changes in their lives and stick to them."

"We have developed some good interventions for weight control, and those can be very effective in helping people achieve clinically significant weight loss," says Susan Czajkowski, a research psychologist at the National Heart, Lung, and Blood Institute in Bethesda, Maryland, and the lead project officer of ORBIT. "But we need to work on ways to help people initiate these changes in their lives and to stick with them."

TAKE A LOAD OFF

The first-line treatment for obesity is getting a patient to change his or her behaviour: eat fewer calories and exercise more. If obese and overweight patients lose 5–10% of their body weight, they show significant clinical improvements, including reductions in various cardiovascular risk factors. Over the years, studies have shown that lifestyle changes can yield this amount of weight reduction, at least in the short term.

In late 2013, the American College of Cardiology, based in Washington DC, the American Heart Association in Dallas, Texas, and The Obesity Society in Silver Spring, Maryland, jointly issued a new set of guidelines for treating overweight and obese adults based on an evaluation of peer-reviewed research by an expert panel[1]. Among other treatment strategies, the panel looked at the effectiveness of comprehensive behavioural interventions that included three components: a low-calorie diet, increased physical activity, and some sort of structured behavioural programme in which patients learn strategies that can help facilitate weight loss (such as goal setting or regular monitoring of calorie intake and activity). The programmes also tended to include weekly meetings with health professionals.

After 6 months, such interventions produce an average weight loss of up to 8 kg, a figure that represents a 5–10% weight loss for many patients. But participants' weight tends to level off at 6 months. And the panel found that after a year, even with continued regular contact with professionals, patients begin to put the weight back on, at an average rate of 1–2 kg per year. "We can get a lot of weight loss," says Catherine Loria, a nutritional epidemiologist at the National Heart, Lung, and Blood Institute and a co-author of the new guidelines. "The main challenge there is still keeping the weight off long term."

CREEPING BACK

The slow regain of body fat, which scientists have documented again and again, reveals how difficult it can be to change long-term habits. New skills that people learn in behavioural programmes can easily break down in the face of real-world environments that are saturated with calorie-dense foods. "We've got these sort of tepid behavioural interventions — 'Do this diet for a little while' or 'Learn these few skills' — but meanwhile we have a culture that sanctions junk as a food group," says David Katz, director of the Yale-Griffin Prevention Research Center in Derby, Connecticut. "The modern world conspires against weight control."

Helping people maintain their weight loss in a society with an abundance of cheap convenience foods and oversized portions may require long-term, ongoing support. In a study of more than 1,000 people who had lost an average of 8.5 kg in 6 months, researchers found that individual monthly counselling sessions — which were conducted primarily by telephone and gave patients a chance to report on their progress, set future goals and discuss challenges they faced — helped participants maintain some of their weight loss[2]. At the 3-year mark, participants who had personal contact with counsellors had regained 4 kg, on average, whereas those who participated in an online maintenance programme had put 5.2 kg back on, and patients receiving neither treatment regained 5.5 kg. "We've started to think about it as a chronic disease which needs continual intervention," Loria, who co-authored the study, says of obesity. "The more involvement you have, the more contact you have, probably the better a person will do long term."

Comprehensive behavioural programmes have also shown promise in children. A 2012 review of randomized controlled trials of lifestyle interventions for obese children concluded that such treatment programmes led to significant reductions in body-mass index (BMI) — a standard ratio of weight to height that is commonly used to determine whether people are overweight or obese — and improvements in cholesterol levels, glucose metabolism and blood pressure[3].

Particularly for school-age children, "we have a treatment approach that can produce effective changes," says Chantelle Hart, a clinical psychologist at the Center for Obesity Research and Education at Temple University in Philadelphia, Pennsylvania. However, she adds, "Not all children who participate in behavioural interventions achieve a healthy weight status, so we need to look at innovative strategies that we can add as an adjunct."

Hart is developing one such approach. Epidemiological studies have revealed a connection between sleep habits and body weight. Children and adults who sleep less tend to weigh more, and sleep deprivation can alter the levels of hormones involved in metabolism and appetite. Last year, Hart published the results of the first experimental study on sleep duration and weight in school-age children. She found that when these children were assigned to increase their sleep duration — spending an extra hour-and-a-half in bed — they ate 134 fewer calories a day, on average, than when they were asked to spend less time than usual in bed[4]. After a week on the enhanced sleep schedule, the children had lost an average of 0.22 kg.

At the University of Buffalo in New York, clinical psychologist Leonard Epstein is developing a programme to enhance the ability of overweight children and adults to delay gratification. "So far, at least in the laboratory, we've been very successful," he says. In a paper published in 2013, he showed that overweight women who were asked to think about positive events in their future — such as vacations, birthdays or holiday celebrations — consumed fewer calories during a 15-minute snacking session[5].

Obesity is increasingly an issue of economic class. Although obesity rates have begun decreasing among adolescents of high socioeconomic status, no such improvement is evident in poorer and minority populations. In March 2014, headlines trumpeted a study finding that the proportion of 2- to 5-year-old children who are obese in the United States dropped from 13.9% in 2003–2004 to 8.4% in 2011–2012 (ref. 6). However, the data also showed that obesity remained more common among the Hispanic and African-American children in that age group.

The prevalence of obesity among those without financial resources means that we need inexpensive treatments. "What we do to intervene in that group has to be low cost and has to be something that's attainable and feasible in a lower household income," says Elsie Taveras, a paediatrician and obesity researcher at the Massachusetts General Hospital in Boston.

In a randomized trial published in 2013, Taveras showed that she could reduce

MEASURING WEIGHTS

How do we define obesity?

Obesity is typically assessed by using the body-mass index (BMI), a standard ratio of weight to height. The BMI is calculated by dividing someone's weight, in kilograms, by the square of his or her height, in metres. Patients who have a BMI between 25.0 and 29.9 are considered to be overweight, and a BMI of 30.0 or higher indicates obesity.

children's BMIs by helping their families make small, no-cost changes in basic home routines[7]. In her "Healthy Habits, Happy Homes" study, Taveras and her colleagues dispatched health coaches to work with low-income families with children between the ages of 2 and 5. (Approximately 60% of the families had annual incomes of US$20,000 or less.) The coaches encouraged families to eat more meals together, reduce television watching and increase children's sleep duration — all behaviours that have been linked with reduced obesity risk. After 6 months, children in families that had received the intervention were sleeping longer and spending less time watching TV; their BMIs had also decreased by an average of 0.18, whereas those of children in the control group had increased by 0.21, on average.

Different patient populations have different needs, and obesity researchers are moving away from the 'one size fits all' idea, says Czajkowski. ORBIT is funding trials focusing on groups ranging from African-American teens to menopausal women. "We've learned that there are different motivations, different challenges, different barriers for different groups of people, and so by focusing in on subgroups and their unique needs, you get a better chance for success," Czajkowski says.

DRUG DIETS

Some experts believe that the marginal gains seen with behavioural interventions indicate that the only practical solution to the obesity problem will involve drugs. The use of anti-obesity drugs peaked in 1996, when approximately 8,500 prescriptions for the medications were filled for every 100,000 people in the United States. Then, in 1997, two popular medications, the drugs fenfluramine and dexfenfluramine, were linked to cardiovascular problems and removed from the market. In 2011, there were about 2,500 prescriptions filled per 100,000 people and 2.74 million total users of anti-obesity drugs[8].

At that time, there was just one drug available that the US Food and Drug Administration (FDA) had approved for long-term use against obesity: orlistat (Xenical), which interferes with the body's ability to absorb fat. When taken at high doses, and in conjunction with a low-calorie diet and increased exercise, orlistat yields weight loss of about 3% beyond what patients achieve with a placebo, as well as an improvement in several cardiovascular risk factors and a reduction in the risk of diabetes[9]. In 2012, the FDA approved two drugs for the long-term treatment of obesity: lorcaserin (Belviq), which promotes satiety (the feeling of being full) by activating a certain kind of serotonin receptor in the brain, and a phentermine/topiramate combination (Qsymia), which combines an amphetamine that suppresses appetite with an anti-epileptic drug associated with weight loss (see 'Weighing up the options').

"There's no question that there are many people who lose more weight when they take medication."

Like most drugs, however, these medications can sometimes have serious side effects. Qsymia, for instance, can cause an elevated heart rate and, when taken during pregnancy, birth defects. And over the past two decades, six weight-loss compounds have been withdrawn from the market due to safety concerns, most recently in 2010 when sibutramine (Meridia) was pulled after research linked the drug to an increased risk of heart attacks and strokes.

WEIGHING UP THE OPTIONS

Weight-loss drugs approved by the US Food and Drug Administration for long-term use.

Drug	Approved	Average placebo-adjusted weight loss	Percentage losing at least 5% of body weight
Xenical (orlistat)	1999	3%	57%, compared with 31% of those taking a placebo
Belviq (lorcaserin)	2012	3.0–3.7%	47%, among patients without type 2 diabetes, compared with 23% of those taking a placebo
Qsymia (phentermine and topiramate)	2012	6.7–8.9%, depending on the dose	62–69%, depending on the dose, compared with 20% of those taking a placebo

Pregnant mothers participated in a study to reduce stress-related overeating.

Such side effects may be unavoidable. The pathways that are involved in metabolism and obesity are so ubiquitous in the body that it is difficult to alter them in ways that lead to weight loss without unwanted consequences, says Tamas Horvath, a neurobiologist at Yale University in New Haven, Connecticut. "You are interfering with autonomic regulation of body tissues, which in the long run may not be beneficial for those tissues or the body at large," he says.

But that does not mean that weight-loss drugs cannot be useful, says Horvath. He believes that regulators need to be more willing to tolerate their side effects, at least in the morbidly obese, for whom the benefits of losing weight may outweigh potential risks.

Obesity drugs can also be useful for kick-starting weight loss and helping patients stick to low-calorie diets. Researchers have found, for instance, that patients who take a weight-loss drug while participating in lifestyle interventions lose 3–9% more weight than those who get a placebo[10]. "There's no question that there are many people who lose more weight when they take medication," says Louis Aronne, director of the Center for Weight Management and Metabolic Clinical Research at New York-Presbyterian Hospital and the Weill Cornell Medical Center.

For now, though, with much left to learn about the long-term effects of these drugs, most experts recommend that patients try diet and exercise first and that weight-loss medications be used only in conjunction with behavioural approaches. As Loria puts it, "I don't know that we can be on weight-loss drugs for 60 years, and so at some point, I think people need to make sustainable changes in what they eat and the activity they get."

Ultimately, the only effective, sustainable solution — on a large scale over the long term — may be to change the culture. "The issue to me is not whether or not behavioural interventions work," Katz says. "There's absolutely no question to me that they are the thing that we have to depend on." But even the most comprehensive programme, he says, is no match for a culture built around calorie-dense foods and sedentary lifestyles. "Behavioural interventions are a very slow march forward on a moving walkway that's going in reverse." ■

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1. Jensen, M. D. *et al. J. Am. Coll. Cardiol.* http://dx.doi.org/10.1016/j.jacc.2013.11.004 (2013).
2. Svetkey, L. P. *et al. JAMA* **299**, 1139–1148 (2008).
3. Ho, M. *et al. Pediatrics* **130**, e1647–e1671 (2012).
4. Hart, C. N. *et al. Pediatrics* **132**, e1473–e1480 (2013).
5. Daniel, T. O., Stanton, C. M. & Epstein, L. H. *Psychol. Sci.* **24**, 2339–2342 (2013).
6. Ogden, C. L. *et al. JAMA* **311**, 806–814 (2014).
7. Haines, J. *et al. JAMA Pediatr.* **167**, 1072–1079 (2013).
8. Hampp, C., Kang, E. M. & Borders-Hemphill, V. *Pharmacotherapy* **33**, 1299–1307 (2013).
9. Rucker, D. *et al. BMJ* **335**, 1194 (2007).
10. Yanovski, S. Z. & Yanovski, J. A. *JAMA* **311**, 74–86 (2014).

MATERNAL ADIPOSITY, METABOLISM AND STRESS (MAMAS) STUDY