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The importance of using tools beyond lifestyle in managing obesity

Making Education Easy 2018

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This publication is a summary of a presentation by Professor John Dixon given in Auckland at the Goodfellow Symposium on Sunday 25th March 2018. The Goodfellow symposium presented a multidisciplinary programme for general practitioners, primary healthcare nurses, urgent care physicians, registrars, specialists and other primary healthcare professionals. Professor Dixon's presentation focused on the importance of tools such as pharmacotherapy, meal replacements and bariatric surgery, as lifestyle enablers, in the management of obesity, a disease he notes should be approached in the same manner as other chronic illnesses. This presentation was sponsored by Radiant Health.

Why go beyond lifestyle?

Why do we have to look beyond lifestyle in the management of obesity? There is no other serious chronic disease where we stop at lifestyle; for diabetes, hypertension, dyslipidaemia, and cancer for example, we go far beyond lifestyle in their treatment, why should obesity be different? Why are we talking about this? Because we have a catastrophic problem.[1,2]

When we look at the global distribution of patients with obesity, looking at those with a body mass index (BMI) of ≥30 kg/m^2, we see that the biggest proportion of obese patients comes from wealthy English-speaking countries, and the same is true for severe obesity (BMI >35 kg/m^2). Notably, there is a big difference between men and women; women absolutely dominate severe obesity everywhere around the globe, making up more than 60% of this category. We have a horrendous problem, we are not preventing obesity and we are not dealing with it very well at all.

The lifestyle changes preached by primary care practitioners produce almost no effective weight change whatsoever, with results of 1-3% weight loss at 6 months and out to 2 years. This is seen repeatedly with intensive combination behavioural programs struggling to achieve 5% or 5kg weight loss. The reality is that only one person in 20 loses weight easily and keeps it off. These people have a physiology that allows them to lose weight and an obsessive-compulsive personality such that they can stick with behaviour change indefinitely; the other 19 out of 20 are not in that category.[3]

Modest sustained weight loss is key

Modest sustained weight loss is incredibly powerful. The first 5-10% weight loss has been shown to provide much of the benefit for anyone who is losing weight, regardless of their starting weight. Five percent weight loss is the best method of diabetes prevention that we have, and many other comorbidities, such as arthritis, liver disease, and sleep apnoea, also benefit from 5-10% weight loss.[4]

Everything that is essential for life is carefully regulated by the brain. If we look at the results achieved by different bariatric procedures, we see they produce sustained weight loss over 20 years, this is because those procedures are altering the regulation in the brain. We regulate our weight and that's why it's so difficult to lose weight. Unfortunately, our bodies carefully defend our fat.

A change in regulation

In obesity, the dose-response relationship between meal size and satiety is shifted to the right (Figure 1). Many of our obese patients never achieve actual satiety, they always feel ready to eat. Effective treatment can slide this relationship across to the left, but treatment needs to be used long-term to have a long-term effect.

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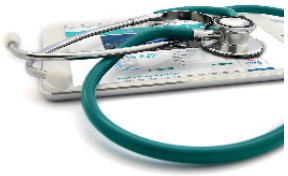

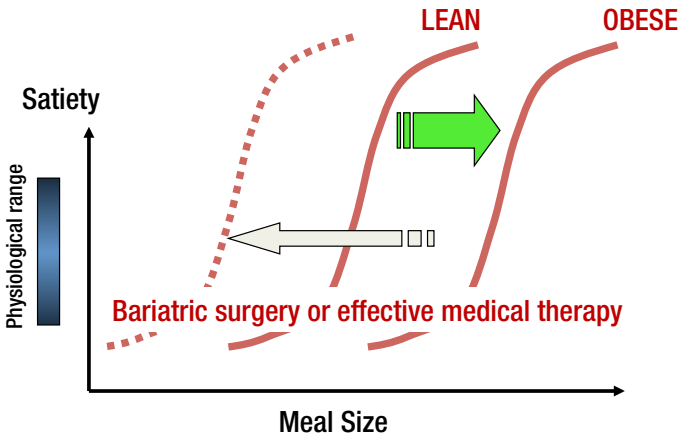

Figure 1. Dose response curve for meal size versus satiety (per, C Le Roux)

If we believe that we are going to rely on lifestyle change, we need to give ourselves a reality check. We must go above the bottom line in the obesity treatment pyramid (Figure 2) to generate significant weight loss and to keep it off. The other tools, medications, meal replacements and surgery, can be considered lifestyle enablers, so that once a person is in control they can then change their lifestyle. This is not a disease of lack of willpower, laziness or lack of adherence, it is a physiological problem of dysregulation in the brain that is largely set up through genes and genetic programming.

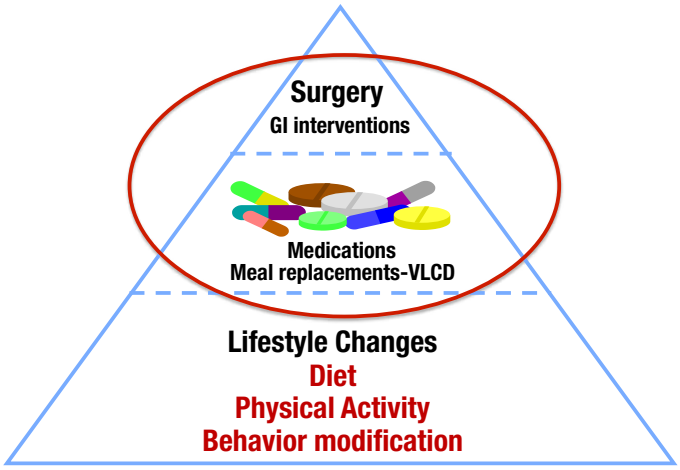

Figure 2. Obesity treatment pyramid

Meal replacements

A meal replacement is a commercially available product that is designed to replace real food. These provide all the essential macronutrients and micronutrients at the same time as reducing excessive calories; they are often in the form of liquids, powders and bars. Meal replacements are regulated but they are not dietary supplements. There are several types of meal replacements, some are simple meal replacements and others have the category of very low-calorie diets (VLCD). The most important thing to understand about meal replacements is that they work.[5,6]

Studies have demonstrated that the best results are achieved by utilising a combination of approaches, with the greatest results achieved with drug therapy, behaviour modification and meal replacements; the addition of meal replacements is associated with dramatic results (Figure 3).

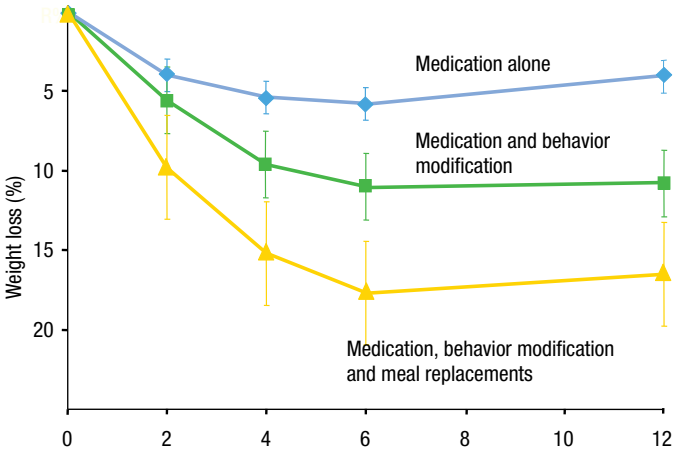

Figure 3. Additive effects of behaviour and meal replacement therapy with pharmacotherapy for obesity.[6]

Very low-calorie diets

VLCD are easy to use and are associated with good adherence. They are low in carbohydrates and cause ketosis, which suppresses hunger. VLCD are very safe, they can be used intermittently, and they provide better long-term sustained weight loss. VLCD have been shown to be associated with 6% weight loss out to 4-5 years, the moderate weight loss that is known to be critical for health benefits.[7] It is important to understand that when people learn to use a tool to manage their weight, they will keep going back to that tool because they know it works. VLCD are suitable for adults with a BMI > 30 kg/m^2 or a BMI >27 kg/m^2 with medical co-morbidities. VLCDs are contraindicated in pregnancy, older age (relative), recent myocardial infarction or unstable angina, organ failure, severe psychological disturbance, alcohol/illicit drug abuse and should be used with caution in those with type 1 diabetes, gout, or impaired renal function. The key to success is learning how to use these meal replacements, and by understanding how they work. It is recommended that you provide an expert in their use to educate and support your patients.

Pharmacotherapy

Pharmacotherapy is a key treatment strategy for obesity, just as it is for any other chronic disease. The general indication for using pharmacotherapy is a BMI over 30 kg/m^2, or over 27 kg/m^2 in the presence of obesity-related risks and complications. Drugs currently available in New Zealand for the treatment of obesity include phentermine (Duromine), orlistat (Xenical), and liraglutide (Saxenda) a glucagon-like peptide (GLP)-1 receptor agonist (Table 1). There are also some off-label options, topiramate (Actavis) approved for prevention of seizures and migraine, and a combination of phentermine and topiramate, which is probably the best combination to date for pharmacotherapy. Other options include a combination of naltrexone and bupropion - there is a combination agent available in the US, but you can use the two separate drugs together off-label, and lorcaserin, which is only available in the United States, the place of which in therapy remains uncertain.

The stopping rule

There is no point in taking a drug that is not effective, that produces unacceptable side effects or that increases net risk of future disease. However, there is also no point in stopping an effective drug if it is well tolerated and reduces risk. Three months of the full dose of a medication is usually sufficient to determine whether it works.

Drug	Starting dose	Available doses	Weight loss versus placebo (% or kg)	Side effects	Contraindications
Phentermine	15 mg	15, 30, 40 mg	3.6–4.5 kg at six months	Dry mouth, insomnia, agitation, constipation, and tachycardia	Severe hypertension, cardiovascular disease, glaucoma, history of drug or alcohol abuse, monoamine oxidase inhibitors, selective serotonin reuptake inhibitor use, pregnancy
Orlistat	120 mg TDS	120 mg	2.9–3.4% at one year	Steatorrhea, oily spotting, flatulence with discharge, faecal incontinence, fat-soluble vitamin malabsorption	Pregnancy
Liraglutide	0.6 mg	0.6–3.0 mg	5.4% at one year	Nausea, vomiting, diarrhoea, constipation Rare: Pancreatitis, cholecystitis	Severe renal or hepatic insufficiency, pregnancy, past history of pancreatitis and major depression or psychiatric disorder
Off-label pharmacotherapy (not approved by Therapeutic Goods Administration for weight loss)					
Topiramate	12.5 mg mane	25, 50, 100 mg	3.4–5.0 kg	Paraesthesia, dry mouth, constipation, altered taste sensation, insomnia, dizziness, cognitive effects Rare: Closed angle glaucoma, depression or suicidal ideation	Glaucoma, renal stones, pregnancy (if used for weight loss)
Phentermine (Phe)/ topiramate (Top)	Phe: 15 mg mane Top: 12.5 mg mane	Phe: 15 mg Top: 12.5, 25, 50, 100 mg	5.0–6.6% at one year	Side effects of phentermine and topiramate	Contraindications to phentermine or topiramate

Table 1. Pharmacotherapy used in obesity management in Australia.[1]

Orlistat

Orlistat inhibits intestinal lipase, reducing fat absorption by 30%. Studies have shown weight loss of approximately 3kg (or 3%) over that achieved with placebo.[8, 9] Of note, in the XENDOS (XENical in the Prevention of Diabetes in Obese Subjects) study, at 4 years, there were more people on Xenical and compliant than there were in the placebo group and compliant, which indicates that people will take this drug long term because it works. With a 3% weight loss over and above the lifestyle intervention, remembering that these interventions are lifestyle enablers, patients should be able to achieve that modest 5% plus weight loss critical for health.

Centrally acting medications

All the other currently available medications act centrally on the brain to reduce energy intake. Patients report that on these agents they feel in control, that they don't need to eat as much to feel a sense of satisfaction, and that they are able to stop eating. When patients feel in control, it is then possible to enable other behaviour change.

Phentermine

Phentermine is the most commonly used weight loss drug in Australia and in the US, and has been for decades, because it works. Phentermine has a sympathomimetic action on the brain, particularly the hypothalamus, that suppresses appetite. While it is an amphetamine derivative, it has almost no serotonergic or dopaminergic effects, and there is almost no risk of addiction. Studies show differences in weight loss at 6 months of 3.6 to 4.5kg over and above placebo; combined with lifestyle, patients actually achieve that 5-10%. A study conducted in the 1960s demonstrates the effect over placebo, with 4.5kg weight loss in patients receiving placebo plus the lifestyle intervention, compared with 9.2kg for patients receiving phentermine 30mg plus the lifestyle intervention.[10] While there are some patients who are unable to take this medication (see Table 1), the more you know about this drug and the more you use it, the more comfort you will have with it.

Start low and go slow

As with all obesity drugs: start low and go slow. Starting at the highest dose of phentermine increases the likelihood of short-term predictable side effects; it is best to start with the 15mg dose and increase if necessary, with most adults able to tolerate the higher 30mg dose over time. It is recommended to take the dose in the morning because of its alerting effects and the sleep disturbances that some people experience, particularly in the first days or weeks. It is important to warn patients of these common early issues, so they understand that these side effects usually abate in the first days or weeks, with early adaptation to the sympathomimetic effects. If a patient does not have side effects and if it's very effective, why would you stop it?

Long-term treatment

Phentermine may be continued on a long-term basis in patients with low to moderate cardiovascular risk, no psychiatric disease or history of substance abuse, and no clinically significant increase in pulse or blood pressure while taking phentermine, with close monitoring during dose escalation and then at least every 3 months thereafter.[1]

Phentermine + topiramate

A low-dose combination of phentermine with topiramate is now available in the US; this is a powerful combination. Topiramate, approved for the treatment of migraine and epilepsy, is used off-label for weight loss at the same doses as migraine prevention (25-100 mg/day). In one extensive meta-analysis of randomised controlled trials, topiramate alone was associated with 5.3% weight loss over that seen with placebo.[11]

It is important to inform patients that use of topiramate in this indication is off-label. It is important that as a clinician you are fully informed about this drug, you must know it well, its contraindications and precautions (see Table 1), and patients must be provided with clear written instructions. When using this agent, we again start low and we go slow; starting at 25 mg/day, best given at night, for at least 2 weeks, and after evaluation for adverse events, cravings and binge eating, the dose can be increased slowly up to a maximum of 100 mg/day.

Combining these two effective drugs gives impressive weight loss, with one 28-week study showing 2.3kg weight loss with placebo, 7.4kg with phentermine, 8.8kg with topiramate and 11.6kg with the combination treatment.[12]

Liraglutide

Liraglutide, a GLP1 agonist used for diabetes management, is very effective in terms of providing significant clinically meaningful weight loss in a wide range of patients, with 8% weight loss in a general population, 6% in patients with type 2 diabetes and 5.7% in patients with obstructive sleep apnoea.[13-15] Treatment with liraglutide should be started low and increased to a maximum of 3 mg/day; it is not necessary to titrate the dose all the way to 3mg, the dose can be adapted to the person based on efficacy and tolerability.[13, 15]

Bariatric and metabolic surgery

There are three main bariatric procedures performed around the world today: adjustable gastric band, sleeve gastrectomy and Roux-en Y gastric bypass. Worldwide, by far the most common is the sleeve gastrectomy.[2] There are differences in the weight outcomes, differences in the advantages and disadvantages, and differences in the nutritional requirements afterwards for these three procedures, but all have been shown to provide excellent results, with all associated with sustained weight loss 20 years post-surgery. These procedures are facilitators, they allow people to change their way of thinking, change their approach to food and their exercise patterns, and achieve much better results.[16] It is up to primary care physicians to learn the key elements of these procedures so that they can counsel patients about them. They are all very safe, we must be very clear that these are not dangerous procedures and they are not things that should be kept as a last resort.

Surgery saves lives

Bariatric surgery reduces the risk of mortality by around 40 to 50%, with a 50% reduction in cardiovascular deaths and a 50% reduction in cancer deaths. These are dramatic results, this is not fringe surgery, this is some of the best evidence-based medicine you can provide.[17]

Indications for bariatric surgery are based on BMI as well as obesity-related risk and contraindications. Eligible patients are those with a BMI > 40 kg/m^2, BMI > 35 kg/m^2 with one or more complication, and BMI 30-35 kg/m^2 with poorly controlled type 2 diabetes.[2] It is recommended therapy in patients with type 2 diabetes if BMI is over 40 kg/m^2 or over 35 kg/m^2 if diabetes is poorly controlled. As physicians, you must be advising your patients with type 2 diabetes and a BMI > 40 kg/m^2, that bariatric metabolic surgery is recommended. There are very few contraindications to surgery, so if in doubt, seek expert advice, and let the experts decide.

Most importantly, surgery is an enabler and we need to understand how to get the best results for a patient. The key thing about bariatric surgery is that it is a lifelong commitment to nutrition and health, and this needs to be considered every single time you see these patients in your practice.

CONCLUSION

Meal replacements, pharmacotherapy and bariatric-metabolic surgery work, that's why we should be using these tools. They are lifestyle enablers. They do not replace lifestyle, but they are necessary. It is dysregulation of weight that is the problem, at the hypothalamus and hedonic centres that work together to make sure we struggle to lose weight. If you are not using these tools, then you haven't started to think about how to treat people with clinically significant obesity.

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