Managing obesity could be our biggest challenge

This is the first of three back-to-back papers addressing the problem of obesity in the UK population, which is of undeniable importance to all pharmacists. Here, Paul Grassby outlines the scale of the problem and the NICE recommendations for obesity management.

The 21st Century epidemic

Obesity is now an epidemic[1] and its prevalence continues to rise relentlessly. Within England approximately two thirds of men and half of all women are currently defined as overweight or obese, with one quarter of the population classified as obese. In addition our children are now affected with one third aged 11 years or below overweight or obese.[2,3] It is this fact that should make us concerned, if this trend continues.

The *Oxford English Dictionary* describes an epidemic (adj) as a disease, which is 'prevalent among a people or a community at a special time, and produced by some special causes'. If obesity is indeed a disease in the true sense of the word, what are the special causes of this epidemic and what can we do to eradicate it?

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Definitions of obesity vary, but according to the National Audit Office[3] obesity occurs when a person puts on weight to the point that it seriously endangers health. It has been most commonly defined in terms of an individual's body mass index (BMI), very simply a ratio of weight to height. A BMI of more than 25kg/m^2 is regarded as overweight, and more than 30kg/m^2 as obese.[3] Although an individual's weight in relation to their height is important it has been known for some time that the distribution of fat is also important, the so called android or gynoid fat distribution, more commonly referred to as apple shaped or pear shaped. Men are generally apple shaped with more central fat, which is linked to insulin resistance, dyslipidaemia and cardiovascular disease, while women tend to maintain a pear shape with fat, which is metabolically less harmful on their hips and thighs.[1,4] For this reason measurements such as waist-to-hip ratio, and waist measurements are also used to assess risks associated with obesity. Although no clear cut-off point has been defined a report by the WHO suggests that increased risk is present when the waist measurement exceeds 94 cm (37 inches) for men or 80 cm (32 inches) for women.[5]

The health consequences of obesity

The health consequences of obesity have been postulated for centuries. Despite the Victorian image of the jolly, rotund man, Joe, a young man known for his 'generous build' was described as having 'an uncanny ability to fall asleep anywhere' in Dickens's novel the *Pickwick Papers*. 120 years later we now recognise that he was suffering from alveolar hypoventilation — now called Pickwickian syndrome. [The combination of obesity, somnolence (sleepiness), hypoventilation (under-breathing) and plethoric (red) face.] The health consequences of obesity are now being recognised as being more severe and far reaching with the risks of suffering from a range of chronic conditions being increased significantly (Table 1). For example, a 10-fold increase in the risk of diabetes has been estimated with a BMI of only 27–30kg/m^2 and the previous label of 'essential' given to hypertension of unknown origin is now considered to be a consequence of obesity.[6]

Table 1. The health consequences of obesity

Greatly increased risk (relative risk >3):
- ☐ Diabetes
- ☐ Hypertension
- ☐ Dyslipidaemia
- ☐ Breathlessness
- ☐ Sleep apnoea
- ☐ Gall bladder disease

Moderately increased risk (relative risk about 2–3):
- ☐ Coronary heart disease or heart failure
- ☐ Osteoarthritis (knees)
- ☐ Hyperuricaemia and gout
- ☐ Complications of pregnancy—for example, pre-eclampsia

Increased risk (relative risk about 1–2):
- ☐ Cancer (many cancers in men and women)
- ☐ Impaired fertility/polycystic ovary syndrome
- ☐ Low back pain
- ☐ Increased risk during anaesthesia
- ☐ Foetal defects arising from maternal obesity

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Significant increases in mortality have been demonstrated at any age, but current evidence suggests that for young adults the risk of mortality for someone with a BMI of 30kg/m^2 is about 50 per cent higher than that for someone with a healthy BMI (20–25 kg/m^2), and with a BMI of 35 kg/m^2 the risk is more than doubled.[5] A BMI > 25 kg/m^2 before the age of 20 years is a very strong predictor of obesity and ill health in adulthood.[4]

Size zero it is then?

What is the best weight for us? Should we all strive for the airbrushed images that adorn our newsstands? Some recent US publications[7,8] have demonstrated that the 'simple' association of weight with mortality is complex, and being underweight is also associated with increased mortality. By examination of cause-specific mortality and overall mortality and using 'normal weight' as the reference group, obesity, as expected, was associated with significantly increased mortality from CVD (being associated with 112,159 excess deaths in the USA in the year 2000). However, no other associations could be drawn unless the overweight and obese groups were combined when increased mortality from diabetes and kidney disease (resulting in 61,248 excess deaths) was also demonstrated. Surprisingly, with the exception of increased morbidity from diabetes and kidney disease this overweight group was not associated with increased mortality from cancer or CVD — and their overall all-cause mortality was decreased. In addition, it was observed that being underweight was also associated with increased mortality from non-CVD, non-cancer causes — although most of these cases were aged more than 70 years. This confirms previous studies that have shown that the risk associated with BMI is a U-shaped curve, with the minimum mortality close to a BMI of 25kg/m^2.

Despite these findings, being both overweight and obese can have a strong deleterious effect on the quality of life resulting in physical disabilities, which are again borne disproportionally by younger adults. In terms of economic effects obesity has been estimated to account for 18 million days of sickness annually,[3] and if the present trends continue, the estimates for the annual direct and indirect costs of obesity will be £3.6 billion by 2010.[3]

Tackling the epidemic — 'eat a little less and move a little more'

We do not need to wait for a major scientific breakthrough to treat obesity. Even modest weight reductions are associated with reductions in total mortality, hypertension, cholesterol and the risk of developing type 2 diabetes. In particular, modest weight loss (5–10%) from the intra-abdominal region increases life expectancy 3–4 years for patients with type 2 diabetes.[1]

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The obvious solution to obesity is to lose weight by attacking both sides of the energy equation by improving diet and exercise. In the US the slogan 'move a little more, eat a little less' has been adopted.[11] Indeed only small changes in lifestyle are required for dramatic effects.

By walking an extra 2000 steps a day (around one half mile) and reducing calorific intake by 100 kcal (approximately two chocolate biscuits) 90% of obesity in the US could be abolished.

Eat a little less

NICE[12] recommend that to lose weight patients should be encouraged to make small sustained improvements to daily habits, resulting in a sustained reduction in calorific intake (Table 2).

Evidence for the effectiveness for most commercially available diets is of poor quality. For example a meta analysis of the 'Atkins®' diet, a low carbohydrate regime, revealed no significant difference to a conventional low-fat diet after 12 months, with a mean weight loss of 2.5kg, and the effect of either diets on cardiovascular outcomes are not known.[13] In the BBC diet trials there was no difference seen between the Atkins®, Slim Fast®, Weight Watchers® and Rosemary Conley® diets, with an average weight loss of 5.9kg at six months. Low glycemic index diets (GI) did demonstrate a small (1.1kg) but significant advantage over high GI diets, but the trials are small and of short duration.[14]

Table 2. Dietary strategies to help people achieve and maintain a helathy weight

- ☐ Base meals on starchy foods such as potatoes, bread, rice and pasta, choosing wholegrain where possible.
- ☐ Eat plenty of fibre-rich foods — such as oats, beans, peas, lentils, grains, seeds, fruit and vegetables, as well as wholegrain bread, and brown rice and pasta
- ☐ Eat at least five portions of a variety of fruit and vegetables each day, in place of foods higher in fat and calories.
- ☐ Eat a low-fat diet and avoid increasing your fat and/or calorie intake.
- ☐ Eat as little as possible of:
  - — fried foods
  - — drinks and confectionery high in added sugars
  - — other food and drinks high in fat and sugar, such as some fast foods.
- ☐ Eat breakfast.
- ☐ Watch the portion size of meals and snacks, and how often you are eating.
- ☐ For adults, minimise the calories you take in from alcohol.

Move a little more

In terms of exercise a Cochrane review involving a meta-analysis of 41 RCT's has shown an additional 1.1kg can be lost and a reduction in BMI of 0.4kg/m^2 compared to dieting alone accompanied by reduced diastolic BP, TG's and FBG. High intensity exercise resulted in a 1.4kg increase in weight loss compared to low intensity exercise.[15] Lifestyle changes have also been shown to prevent type 2 diabetes in those with impaired glucose tolerance — perhaps working better than metformin.[16]

A magic bullet for obesity.

A 'Google®' search for 'diet pills' produces seven million hits, which highlights the interest in a treatment for obesity that does not involve lifestyle changes. In recent years three drugs have been approved for obesity, but only as adjuncts to dietary and exercise measures. Whether drug based interventions should also be offered to patients depends on a combination of their BMI classification, waist circumference co-morbidities and other risk factors. In general drugs can be considered in all obese patients with a BMI of 30 kg/m^2, or with lower BMI's in the presence of other risk factors, such as type 2 diabetes or hypercholesterolaemia.[12] In assessing the evidence regarding the effectiveness of these drug interventions, the primary outcome should be at least a 10% reduction of baseline weight, and clinical trial should continue for at least one year, and should consider the maintenance of weight loss.[17] To date most RCT's have been limited by high drop-out rates and no long-term data looking at patient-oriented outcomes (such as mortality and morbidity). NICE state that drug treatment should only be considered after dietary, exercise and behavioural approaches have been started and evaluated.[12] The licensed drugs that can be considered for the treatment of obesity are orlistat and sibutramine — and, until recently, rimonabant.

Table 3. Exercise strategies to help people maintain a helathy weight

- ☐ Make enjoyable activities — such as walking, cycling, swimming, aerobics and gardening — part of everyday life.
- ☐ Minimise sedentary activities, such as sitting for long periods watching television, at a computer or playing video games.
- ☐ Build activity into the working day — for example, take the stairs instead of the lift, take a walk at lunchtime.

Orlistat is a pancreatic lipase inhibitor, and thus prevents the breakdown of dietary triglycerides to free fatty acids, which are normally absorbed. This reduces the amount of triglyceride absorption and it is excreted in the faeces.[18] Its advantage is that only trace amounts are absorbed systemically and this drug has recently been made available over the counter in the US, under the name Alli™. Because of the nature of its action, side-effects are related to the non-absorption of fat and include steatorrhea, faecal incontinence, flatulence and frequent bowel movements which can be unpleasant. Indeed the Alli™ website states 'Until you have a sense of any treatment effects, it's probably a smart idea to wear dark pants, and bring a change of clothes with you to work.'[29] Withdrawal because of side-effects is 4% compared with 1.7% with placebo.[19] Patients should be informed that side-effects can be dramatically reduced when adopting a low-fat diet. NICE recommend that orlistat is prescribed only as part of an overall plan for managing obesity.[12]

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Sibutramine is similar to a traditional tricyclic antidepressant (TCA) in that it inhibits the neuronal uptake of serotonin and noradrenaline. It failed to demonstrate any significant anti-depressant effects in animal studies, but works by increasing satiety and thermogenesis through its action on serotonin and noradrenaline.[20] Because of its pharmacology it is not surprising that anticholinergic side-effects commonly seen with TCA's are observed. It can also increase blood pressure (BP) in some patients, and the Committee on Human Medicines (CHM) have stated that BP and heart rate (HR) should be monitored regularly, every 2 weeks for the first 3 months, every month for the next three months and at least every 3 months thereafter.[21] The treatment must be discontinued if resting HR increases by 10 bpm and a persistent increase in BP of greater than 10mmHg. A meta-analysis of high quality RCT's[22] indicates that after 44–54 weeks diastolic BP increased by an average of 2.8mmHg. It is only licensed for use for one year.

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Rimonabant is a selective cannabinoid antagonist, or more technically an inverse agonist at the CB1 receptor.[23] This receptor is believed to be stimulated by smoking cannabis, which gives rise to the 'munchies', and pharmaceutical folklore suggests this is where the inspiration for its development arose from. This drug was licensed as an adjunct to diet and exercise in obese patients or overweight patients with associated risk factors since June 2006. However on 23 October 2008, the European Medicines Agency recommended suspension of the marketing authorisation of rimonabant, based upon new evidence from post-marketing surveillance and ongoing clinical trials that there was a doubling of the risk of psychiatric disorders in patients taking the drug. Because of its mechanism of action it is not surprising that use of the drug can result in psychiatric

side-effects, such as depression (3.2% of patients).[23] Previously, pooled data from studies had indicated that almost twice as many patients (13.8%)[24] discontinued the treatment compared to placebo. In addition all studies had excluded patients with pre-existing psychiatric conditions.

Do the drugs work?

The Cochrane review[19] on the efficacy of long-term pharmacotherapy for obesity examined 16 orlistat, 10 sibutramine and four rimonabant studies. They were all affected by high drop-out rates (30–40%). Compared to placebo over one year orlistat modestly reduced weight by 2.9kg, sibutramine by 4.2kg and rimonabant by 4.7kg. In addition, patients were more likely to achieve 5% and 10% weight loss thresholds. Other meta-analyses have yielded similar results. In terms of disease prevention, only orlistat has demonstrated a reduction in the incidence of type 2 diabetes from 9% in the placebo group to 6.2% in the orlistat group.[25] In terms of longer studies, treatment with orlistat has shown a similar degree of weight loss (2.2kg), with 67% maintaining a greater than 5% weight loss compared to a placebo rate of 56%.[26] New cases of diabetes were also reduced from 10.9% to 5.2%. With regards to rimonabant there was no extra weight loss after an additional year of treatment.[27] After one year of treatment there was also a 40% drop-out rate.[28]

NICE guidance

NICE stresses that drugs should only be prescribed for obesity as part of an overall strategy, which includes support and counselling on diet and exercise. In addition treatment should be regularly reviewed, providing an additional opportunity for reinforcing the messages of diet and lifestyle. NICE recommends that orlistat or sibutramine treatment beyond three months should only be considered if the patient has lost 5% of their initial starting weight. If treatment is continued, orlistat can be prescribed for more than one year, provided risks and benefits are discussed with the patient, but treatment beyond a year is not recommended for sibutramine.[12]

Conclusions

We do not have to wait for a 'magic bullet' treatment for obesity because lifestyle intervention and education should underpin our efforts to manage this epidemic. It is important to stress that even modest weight loss is associated with reductions in mortality, the risk of developing type 2 diabetes, hypertension and cholesterol. It is also sensible to target those with the highest risk — those with a family history and children who are obese who tend to reside in areas of the greatest deprivation. The effect of using drugs that are currently available is only modest and must be integrated with lifestyle changes. In addition drop-outs through side-effects of these medications are significant, and monitoring is required. ✣

Declarations of interest

The author has no interests to declare.

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