Letter to the Editors

Obesity: weighing the risk before prescribing

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There is no doubt about the current pandemic of obesity and its diverse consequences for health. The list of complications is long, particularly the increase in the incidence of Type 2 diabetes mellitus [1]. Drug therapy can reduce the increased mortality associated with hypertension, hypercholesterolaemia and diabetes. Could advances in clinical pharmacology tackle the growing problem of obesity? To answer this question, it is useful to compare the increased risk of obesity with other risks, such as hypertension or hypercholesterolaemia. Surprisingly large amounts of excess weight need to be shed to increase longevity and at present there are no long-term outcome studies to show weight loss drugs reduce the risks of obesity.

Most adults in England are overweight and one in five is obese with a body mass index (BMI) >30 [2]. BMI is defined as weight in kg divided by the square of height in metres, a calculation not kind to those used to non-metric units. Using a height of 1.73 m (5 ft 8 in) as a guide, as it squares to three and also lies conveniently between average adult male and female heights, overweight is defined as 75 kg and obese as 90 kg. The risk of the extra 15 kg, or 33 lb, is modest when compared with other risk factors. Epidemiological data suggest that such a difference of 5 in BMI increases the risk of mortality by 20% [3].

This risk can be placed in context by comparing it with the risk of raised blood pressure or cholesterol. For those on the borderline of overweight and obese, as in the example above, 15 kg of weight is approximately equivalent to only 5 mmHg in diastolic blood pressure, or 0.5 mmol l⁻¹ in total cholesterol, in terms of mortality risk [3]. More recent estimates of the risk of blood pressure suggest that even a 2-mmHg lowering of systolic blood pressure might reduce stroke mortality by about 10% and ischaemic heart disease mortality by about 7% [4].

At higher values, the mortality curves for weight, cholesterol and blood pressure are semilogarithmic, becoming steeper as the risk factor value increases, but the comparative difference in importance between these three factors remains about the same. This relative risk does not hold true at lower values as, unlike cholesterol, and to a lesser extent blood pressure, there is a marked J- or U-shaped curve for weight. Lower than average weight is associated with increased mortality and recent large-scale US studies found a nadir for risk at a BMI of 27, for both men and women [5, 6]. A larger Norwegian study, of two million men and women followed for an average of 22 years, found the nadir lower at a BMI range of 22–26 [7].

For very large increases in weight, the risk of obesity is still small when compared with the risk of raised cholesterol or blood pressure. A normal person of 70 kg with a healthy BMI would need to gain approximately 35 kg to increase their mortality risk by 50% [3]. In contrast, the same 50% increase in mortality risk is associated with an increase in total cholesterol from 5.5 mmol l⁻¹ to 6.5 mmol l⁻¹, or an increase in diastolic blood pressure from 90 mmHg to about 107 mmHg [3]. Whereas drug therapy can readily reduce such increases in cholesterol or blood pressure, reducing weight by 35 kg is far outside the capability of pharmacological intervention.

So can intervention lower risk? Lowering blood pressure reduces the incidence of stroke, and to a lesser extent heart attack [8]. Reducing total cholesterol with a statin reduces the risk of ischaemic heart disease, and to a lesser extent stroke [9]. In contrast, there are no data at present, nor are there likely to be in the foreseeable future, to show pharmacological intervention can reduce the mortality associated with obesity. It is important to recall the lessons learnt with cholesterol and not assume that reducing a known risk factor will automatically translate into clinical benefit. The first substantial pharmacological intervention trial to test the cholesterol hypothesis with adequate power used clofibrate and showed an increase in overall mortality of 47%, despite

a fall in cholesterol [10]. It is likely that intentional weight loss decreases mortality, but the data available are far from compelling [11].

As obesity is the major cause of Type 2 diabetes, it would be reasonable to suppose that this is a population that would gain particular benefit from weight loss, but when risk factors for coronary heart disease were analysed in non-insulin-dependent diabetes, the top five in order of importance were high LDL, low HDL, hypertension, HbA_{1c}, and smoking. Increased BMI did not appear to be a risk, which makes weight reduction a less convincing treatment goal compared with reducing the risk from the other five factors [12].

An additional hurdle for weight loss drugs is the impact they make long-term. Whereas antihypertensives or cholesterol-lowering drugs can be taken for many years, antiobesity medication is usually prescribed short-term and weight gain on cessation of treatment is unfortunately to be expected [13]. For this reason, the impact of such drugs over a lifetime will be diluted by long periods off treatment.

Despite these concerns, it has been recommended that antiobesity drugs may be used in adult patients at medical risk of obesity (BMI 30 or greater), or overweight patients with established comorbidities (BMI 27), if the drug licence permits and other measures have failed [14]. Drug-induced weight loss is modest. In clinical trials orlistat reduced weight by about 2–5 kg over a year [15], and sibutramine by about 4–5 kg [16], when compared with placebo. Whether such weight loss is beneficial is doubtful, particularly when such small changes are compared with the risk reduction that is possible with therapeutic interventions for raised cholesterol or blood pressure. One editorial suggested that ‘...neither we nor our patients should be deceived into thinking that these drugs lower an adverse medical event rate’. [17] These reductions in weight are not achieved without risk. For orlistat adverse events are mostly gastrointestinal; for sibutramine, sympathomimetic symptoms predominate [18]. The sympathomimetic effects of sibutramine on blood pressure and heart rate may negate any benefit from a loss of weight. Sibutramine may increase blood pressure significantly in some patients and even changes in blood pressure that are too small to detect in an individual in clinical practice may be detrimental to cardiovascular morbidity and mortality [4]. The increase in heart rate with sibutramine might also be detrimental, as increased heart rate is an independent risk factor for both cardiovascular and noncardiovascular mortality [19, 20].

Lifestyle changes are effective modulators of weight, as such changes have accounted for a dramatic increase

in obesity over the past 50 years, but reversing such lifestyle changes in practice is difficult [21]. For this reason there will always be interest in pharmacological intervention as a treatment for obesity. However, severe diets for the very obese are effective [22] and more modest primary care-based advice can prove effective long-term over many years [23], even if for most in clinical practice such results are hard to achieve.

On present evidence, prescribing current weight loss agents is unlikely to reduce the mortality risk of obesity. Other benefits of the small reductions in weight have not been shown to improve the quality of life in long-term trials. Before prescribing, it is important to consider if these drugs improve health, particularly as they are not devoid of adverse events. At present, there is a lack of evidence that available antiobesity agents will help us to deal with the consequences of the obesity pandemic. Drug-induced weight loss appears insignificant when compared with the amount of weight many obese individuals would need to shed should they opt for a healthier life style.

Competing interests

The author works for the UK Medicines and Healthcare products Regulatory Agency. The views expressed are the author's personal ones and are not those of the Agency.

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