Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Background Paper 6.18
Obesity

By Veronika J. Wirtz
Update on 2004 Background Paper, BP 6.18 Obesity

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Executive summary

Obesity is a chronic and multi-factorial disease and one of the most important causes of morbidity and premature mortality worldwide.

Currently, over a billion people are overweight and half a billion are obese. In more than half of the EU countries one in two individuals are overweight or obese. The epidemic is still increasing in many European countries, whereas in some it seems to have slowed down. In the United States, obesity has been declared the number one health threat.

Non-surgical and non-pharmacotherapeutical treatment options include diet, exercise, behaviour modification and psychological support. The effect size has been reported with a single digit weight loss in kilograms which can be maintained. In contrast to experimental settings, implementing life-style interventions in routine primary care that reduce morbidity at population level have proven to be difficult.

There are only very limited pharmacotherapeutic treatment options. Overall, pharmacotherapy has played a minor role in the treatment of obesity. Only one medicine is currently available in most European countries (orlistat). No current pharmacotherapy possesses the efficacy needed to produce clinically significant weight loss (at least 5 to 10% weight loss) in a large proportion of morbidly obese patients in the long-term. More research is needed on whom to treat, adherence factors and the regain of body weight after discontinuation of pharmacotherapy to more adequately evaluate the cost-effectiveness of pharmaceutical therapy. It has been challenging to develop pharmacotherapy that has gained acceptance by medicines regulatory authorities or remained available for a long time due to their adverse benefit/risk profiles that have emerged with use.

Bariatric surgery is currently the only intervention providing significant and long-term weight loss for the morbidly obese (approximately 20% weight loss after ten years) which improves diabetes, hypertension and quality-of-life. However, it is associated with surgical risks (mortality less than 1%), long-term digestive problems and nutritional deficiencies. Savings might be achieved six years after the surgery for the health care systems but whether there are savings after ten years is unclear.
1. **What is the size and nature of the disease burden?**

Obesity is a chronic and multi-factorial disease which is characterized by an excess of body fat. The Body Mass Index (BMI) is most commonly used to define what is regarded as an “excess” (see Table 6.18.1).

<table>
<thead>
<tr>
<th>BMI</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>Normal weight</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>Class I obesity</td>
</tr>
<tr>
<td>35.0-39.9</td>
<td>Class II obesity</td>
</tr>
<tr>
<td>40 and above</td>
<td>Class III obesity</td>
</tr>
</tbody>
</table>


Note: the BMI is calculated as the weight in kilograms of a person divided by the square of his/her height in meters (kg/m²). The BMI is highly correlated with body fat.

The World Health Organization (WHO) classifies adults as overweight when the BMI is equal or greater than 25 and obese when the BMI is equal or greater than 30.1

In 1980, fewer than one in ten people were classified as obese. Since then, the global numbers on obesity have doubled, and in some countries it has tripled. In 2008, worldwide more than half a billion adults were obese (205 million men and 297 million women).2 In 2008, the highest mean BMI for adults over 20 years of ages both sexes were found in the Oceania region (33.9 BMI for males and 35.0 BMI for females in Nauru) and the lowest in sub-Saharan Africa (21.5 BMI) and some countries in East, South and South-East Asia.2 The USA is the high income country with the highest mean BMI for adults over 20 years old, where 35% of the population within this group is obese. Japan is the high income country with the lowest mean BMI.2 Even though there is a positive relationship between BMI and GDP, wealth and its related changes in behaviours namely in diet and physical activity can only partly explain the variation in prevalence of overweight and obesity among countries.3 Prevalence rises with age and in certain ethnic populations, such as American Indians, Hispanic Americans and Pacific Islanders.4

The new Global Burden of Disease 2010 data presented in 2012 shows that risk factors, such as underweight children, dropped from first place to eighth position on the ranking of attributable risk factors for the burden of disease and high body mass index jumped to sixth rank from tenth globally between 1990 and 2010.5 High body mass index is ranked third in Western Europe and fourth in Central and Eastern Europe as an attributable risk factor for the burden of disease.
In more than half of the member states of the EU one in two people are overweight or obese (Figure 6.18.1). Countries most affected by obesity are the United Kingdom and Malta and least affected are Italy and Bulgaria.

Figure 6.18.1: Percentage of population with Body Mass Index (BMI) above 30 (defined as obese), age-standardized estimate, based on available data for Member States of the European Union in 2008/2009

Source: Author’s own elaboration based on Eurostat data Nov 2011 (Eurostat Press Office, 2011)
Note: According to Eurostat there was not recent data available for Denmark, Ireland, Lithuania, Luxembourg, Netherlands, Portugal, Finland, and Sweden.

In some countries such as Italy the obesity epidemic has come to a halt over the last decade. In some countries, such as France and Spain, only a modest increase in the magnitude of obesity was recorded (2 to 3% increase).

1.1 Adult obesity

More women than men are obese, and the obesity rate has increased faster in men than women. There is not only a difference in the prevalence of obesity between men and women but also a large disparity which has been remarkably stable over the last decade in high income countries: less educated and lower-income individuals are more likely to be overweight and obese. Women with little education are two to three times more likely to be overweight than more educated women, but smaller or no disparities exist for men. For low- and middle-income countries (LMIC) a reverse relationship has been found: more wealthy middle-aged adults in urban areas are obese than are those from lower socio-economic backgrounds. For some middle income countries it has been documented that...
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these patterns change with increasing gross domestic product, where more individuals living in rural areas and belonging to lower socio-economic households are increasingly affected.13

Urbanisation might also play a major role in the development of obesity. In China, the overall rate of obesity is less than 5%, but in some cities it is more than 20%.11 It is expected that obesity will further increase globally. Rates are rising faster in low- and middle-income than in high-income countries.

According to global projected trends it is expected that in 2030, one billion people will suffer from obesity.12 Projected trends of obesity in the EU27 countries between 2005 and 2020 indicate an increase of an average of 3.8% in prevalence (Figure 6.18.2).13 For the United Kingdom, a 10% increase in obesity is expected between 2010 and 2020.7 There are some exceptions in which no increase in obesity is expected based on current data: Estonia, Hungary, Latvia, Lithuania, Poland and Romania.13 Updated figures on projected trends in obesity are expected to be published later in 2013 by the WHO.1

Figure 6.18.2: Future projection of obesity range in Europe


1.2 Child obesity

Since the bodies of children and adolescents undergo a number of physiological changes as they grow, developing a simple body mass index is difficult. Hence, the WHO has developed growth charts to measure for overweight and obesity in infants and young children up to age
five and for individuals between five and 19 years.\textsuperscript{14} Globally, the rate of childhood obesity has increased dramatically over the past two decades and is still rising in some countries (e.g. Canada, Mexico, China and India).\textsuperscript{15} The proportion of obese children in Canada has increased from 10\% in the 1980s to 30\% in 1990s, and in Brazil from 4\% to 14\% during the same period.\textsuperscript{16} Also in India and China, childhood obesity continues to rise.\textsuperscript{15} It has been estimated that nearly every other child in North America (40\%) and Eastern Mediterranean WHO regions is overweight or obese; in Europe 38\%, in the western Pacific 27\%, and in South-East Asia 22\%.\textsuperscript{16} Recent data published in 2013 from the Childhood Obesity Surveillance Initiative 2008 shows a high variation of the prevalence of obesity (6.0 to 26.0\% for boys and 4.6 to 17.3\% for girls) between 12 European countries with the highest level of overweight in southern European countries and the lowest in northern European countries.\textsuperscript{17}

There are some indications that the epidemic of child obesity is slowing down in some countries; for instance, in the last 20 years child obesity in France has been relatively stable at around 6 to 8\%.\textsuperscript{8} A series of biological and environmental factors have been identified that contribute to higher food intake in children such as longer working hours of parents, lack of cooking skills, limited money to buy healthier food and very successful marketing campaigns for unhealthy food targeting not only children but also adults.\textsuperscript{18} There is an increased risk for overweight children and adolescents to become obese adults.\textsuperscript{15} Adulthood obesity seems to be more severe if it has developed since childhood.\textsuperscript{19} Childhood obesity has been associated with higher mortality in adulthood and with a higher risk of nutritional deficiencies such as Vitamin D and iron deficiency.\textsuperscript{18}

### 1.3 Morbidity and mortality related to overweight and obesity

Obesity is an important risk factor for hypertension, dyslipidaemia, diabetes, cardiovascular diseases, obstructive sleep apnoea, fatty liver disease, osteoarthritis and asthma; It has been estimated that the global burden attributable to increased BMI were 12\% for colon cancer, 8\% for postmenopausal breast cancer and 32\% for endometrial cancer in women.\textsuperscript{20} In terms of diabetes, it has been estimated that 64\% of cases of diabetes in men and 77\% of cases in women can be attributed to excess weight gain. The same is true for 33\% of ischaemic heart disease and ischaemic strokes, 50\% of hypertensive disease and 25\% of osteoarthritis.\textsuperscript{13}

Overweight and obesity are also associated with a higher mortality risk, see Figure 6.18.3.\textsuperscript{19} Severely obese people die 8-10 years sooner than those with normal weight; for every additional 15 kilogram of excess weight the risk of an early death increases by 30\%.\textsuperscript{8} In 2004, the estimated disability due to obesity and its effects was estimated with more than 36 million disability-adjusted life-years (DALYs).\textsuperscript{20} In the USA alone, obesity kills more than 100 000 adults per year.\textsuperscript{21} In the European Region, obesity is responsible for about 10 to 13\% of deaths according to the WHO regional office in Europe.\textsuperscript{22}

Many of the health consequences (among them cardiovascular diseases) that are observed in adult-onset obesity are often preceded by abnormalities manifested during childhood.\textsuperscript{15} Health consequences of childhood obesity are similar to adults; cardiovascular diseases, diabetes, breathing problems such as sleeping apnoea and asthma, joint problems, fatty liver disease, gallstone, gastro-oesophageal reflux.\textsuperscript{16} A systematic review found that blood pressure, cholesterol and triglycerides, fasting insulin and insulin resistance were higher in overweight and obese than in normal weight children.\textsuperscript{23}
Overweight and obesity also have psychological and social effects which are often difficult to quantify; many obese individuals suffer from depression and eating disorders. It has been found that elevated BMI adversely effects quality of life in adult. In children, obesity has been linked to sadness, loneliness and nervousness.

Figure 6.18.3: Mortality risk as estimated hazard ratio associated with being under- and overweight

![Graph showing estimated hazard ratio vs BMI range](image)

Source: Constructed by author using data provided by Berrington de Gonzalez. Note: Hazard ratio calculated with age as the underlying time scale, stratified by study and adjusted for alcohol (g/day), education, marital status and overall physical activity.

A project funded by DG SANCO - Dynamo-HIA (Dynamic Modelling for Health Impact Assessment)- has modelled the health impact of obesity (see also [http://www.dynamo-hia.eu/](http://www.dynamo-hia.eu/)) in Europe with respect to a series of diseases. For instance, it calculated an increased risk in ischaemic heart disease of 1.35 for men and women who are classed as being overweight and 2.0 for obese individuals. Overweight men and women have an estimated relative risk of 2.30 for diabetes which increases to 5.50 for obese men and 7.0 for obese women. Overall, over a million deaths in the EU region annually are due to diseases related to excess body weight.

1.4 The costs associated with overweight and obesity

Together with the associated diabetes and cardiovascular diseases, obesity is becoming the greatest health care burden affecting European society. An obese person incurs 25% more health expenditure than a person of normal weight. Obesity alone is consuming 1 to 3% of the total health expenditure in most OECD countries (estimates of direct costs of obesity alone in the EU in the 1990's ranged from 1% of health care expenditure in the Netherlands,
up to 3.1-4.2% in Germany and 6% in Belgium.\(^8\) In the United States, 5 to 10% of the total health expenditure is estimated to be spent on prevention and treatment of overweight and obesity and their related health consequences.\(^8\)

It is important to consider that much of the cost of obesity falls outside the health sector. For instance, it has been estimated that obesity costs the United Kingdom two billion GBP, out of which only 24% (479.3 million GBP) are related to the health sector; the rest is attributed to the loss of productivity and costs that individuals, households and carers incur.\(^26\) In 2007, the Wanless Report from the King’s Fund in the United Kingdom\(^27\) argued that obesity could cripple the NHS if no further action was taken. In the USA, the annual economic costs (comprising medical costs, loss in productivity and additional economic impacts) associated with obesity has been estimated to be US$ 215 billion.\(^28\) In 2012 the OECD reported that obesity accounts for an estimated 1% of the GDP.\(^8\)

2. **What are the control strategies?**

There are control strategies at individual and population levels, some aimed at preventing further overweight and obesity, and others at treating those already affected. In the following sections we will first briefly describe preventative strategies at population level and individual non-pharmacotherapeutic treatment. The main focus of the background paper will be on pharmacotherapeutic interventions that are currently available.

2.1 **Population measures for the prevention of overweight and obesity**

There is widespread agreement that the obesity epidemic is a “normal response of normal people to an abnormal environment”.\(^29\) Control strategies require the leadership of governments and international organizations. The World Health Organization with the member states in the EU agreed in 2006 on the European Charter on Counteracting Obesity\(^30\) and the European Action Plan for Food and Nutrition Policy 2007–2012.\(^31\) The Charter stresses the need to align health goal with those in other areas such as economy, society and culture and defines nine principles which should guide the action of member states; the first three include the call for political will and leadership, the action against obesity should be linked to wider strategies to prevent non-communicable diseases, and governments need to take responsibility, as well as individuals.\(^30\)

The European Action Plan for Food and Nutrition Policy 2007 to 2012\(^31\) identified six fields of action: supporting a healthy start; ensuring a safe, healthy and sustainable food supply; providing comprehensive information and education to consumers; carrying out integrated actions to address related determinants; strengthening nutrition and food safety in the health sector; monitoring and evaluation. As a key indicator for progress, the Member States chose prevalence of obesity, particularly in children and adolescents. Along with the Action Plan, a structure for its implementation was created which includes (1) the High Level Group on Nutrition and Physical Activity, (2) promotion of concrete stakeholder-driven action, and (3) ensuring reliable, comparable and regularly updated data.\(^32\) The Action plan 2012 to 2016 for the implementation of the European Strategy for the Prevention and Control of Non-
Communicable Diseases (NCD), highlights that obesity requires special attention as it is a result of common risk factors and a cause of many NCDs.

There are a variety of policy measures (voluntary or statutory) that governments can use to promote the consumption of healthier food. For instance, in Denmark a tax on food rich in saturated fats was introduced in 2011; as a result, consumer prices of those products have increased. For instance, butter prices were higher by an average of 0.29 euros per 250 g (this tax was abolished in 2013; see Section 6.0 “What are the opportunities for research into new pharmaceutical interventions?”). Other examples include Hungary, where a tax on pre-packed products with high salt and sugar content was introduced and Finland, that has a tax on sugary products such as soft drinks, ice cream, and chocolate. The literature on the effects of fiscal measures to promote healthier food choices indicates that taxes are likely to shift consumption in the desired direction and that the tax would need to be at least 20% to have a significant effect on population health.

There is also an increasing interest in combining soft (voluntary) measures with hard (statutory) policy measures such as fiscal measures to influence consumer choices. Apart from fiscal measures, governments have been encouraged to consider putting a ban on the sales of certain products: The City of New York put a sales ban on sweetened beverages in containers of more than 480 ml (16 Oz). Three recently published studies show an association between the consumption of sugar sweetened beverages and the development of overweight and obesity. The intake of sweetened beverages was found to determine body weight indicating that the excess in calorie intake from beverages results in higher body weight rather than consumption of specific foods.

Analysis of the cost-effectiveness of a series of interventions to prevent and treat obesity in Australia showed a series of measures that are cost-savings and are currently recommended (see also Appendix 1) including tax on sugar sweetened beverages, traffic light labeling of food and reducing junk food and beverage advertisement to children.

2.1.1 Prevention of adult and childhood obesity

Population interventions to prevent adult obesity include promoting lifestyle changes, healthier diets and increased physical activity. However, changes in diet habits and increased physical activity are very challenging for most people, although achievable through either community support or strong motivation; for instance, it has been estimated that with dietary and lifestyle modification around 80% of highly motivated patients are unable to achieve weight loss long-term. Around 60% of the world’s population are getting insufficient exercise. This is primarily due to mechanized transportation and labour-saving technology at home. For instance, in both children and adults there is an association between hours of viewing television and the risk of obesity.

Many population interventions to prevent childhood obesity have targeted schools. One common strategy is to ban vending machines that dispense snacks and sugary beverages, while reducing calories in school meals and increasing the children’s physical activity. Public policies in the United Kingdom have introduced mandatory screening in schools of children and reporting results to parents about their children’s body weight.
Ensemble, prévenons l’obésité des enfants (Together, let’s prevent obesity in children, or EPODE) has been developed in France and implemented in many cities across various countries in Europe to prevent childhood obesity. It aims at modifying behaviour and the environment which includes the development of public transport, the promotion of physical activity, strengthening food and non-alcoholic beverage labelling, restricting food and non-alcoholic beverage promotion and removing vending machines from schools. It has shown encouraging results for small cities in lowering childhood obesity and more studies are underway to test whether it also worked in larger urban or very rural areas.

2.2 Non-pharmacotherapeutic treatment options

The goal of obesity treatment is to achieve an individual negative energy balance. As in prevention, dietary changes in combination with increased physical activity are defined as first-line therapy in adults and children. Due to the benefit-risk balance, pharmacological and surgical treatments are considered second- and third-line treatments.

2.2.1 Dietary changes and increased physical activity in adults

Diet changes and increased exercise are the first-line treatments combined with behaviour modification and psychological support. Weight loss in overweight and obese participants of about 5% to 10% of initial body weight is associated with an improvement in cardiovascular risk factors and a reduction in the incidence of type 2 diabetes in high-risk individuals. However, the effect size is very modest with a long-term weight loss of less than 10kg over time. Regaining weight over time is very common.

A health technology appraisal found that a fall in systolic blood pressure of 6.1 mmHg was associated with weight loss of 10% and a 10 kg weight loss with an average fall in total cholesterol of 0.25 mmol/l and a fall in diastolic blood pressure of 3.6 mmHg. Even though some studies report clinically meaningful reduction in cardiovascular risk, maintenance of weight loss over time remains a major challenge.

A meta-analysis of studies analysing the long-term effect of low calorie diets (which included 600 kcal/day deficit diets) demonstrated weight reduction of -5.31 kg (95% CI -5.86 to -4.77 kg) after one year and weight loss continuing for three years. Low-fat diets were associated with the prevention of type 2 diabetes, and improved control of hypertension. Effect size increased with adding an exercise programme and behaviour therapy programmes to the low calorie diet. A Cochrane Review published in 2009 on psychological interventions for overweight and obesity concluded that with increasing intensity of behavioural interventions more weight loss was achieved. Combining cognitive-behaviour therapy with a diet/exercise intervention increased weight loss by -4.9 kg (mean differences weight loss from baseline; 95% CI -7.3 to -2.4) compared with diet/exercise alone (see also Table 6.18.2). However, no data on mortality, morbidity or quality of life were found in this review.
Table 6.18.2: Summary of results from a Cochrane Review of behavioural intervention for overweight and obesity in adults

<table>
<thead>
<tr>
<th>Interventions studied</th>
<th>Intervention (No. of participants)</th>
<th>Control (No. of participants)</th>
<th>Effect size (mean change in weight loss in kg)</th>
<th>Upper 95% CI</th>
<th>Lower 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour therapy versus control, Outcome: Mean change in weight – studies 12 months or less duration.</td>
<td>686</td>
<td>619</td>
<td>-4.46</td>
<td>-4.57</td>
<td>-4.34</td>
</tr>
<tr>
<td>Behaviour therapy versus control, Outcome: Mean change in weight - studies &gt;12 months duration.</td>
<td>673</td>
<td>581</td>
<td>-2.00</td>
<td>-2.03</td>
<td>-1.97</td>
</tr>
<tr>
<td>Behaviour therapy plus diet / exercise versus diet / exercise, Outcome: Mean change in weight - studies 12 months or less duration.</td>
<td>235</td>
<td>232</td>
<td>-4.71</td>
<td>-4.97</td>
<td>-4.45</td>
</tr>
<tr>
<td>More intensive versus less intensive behaviour therapy, Outcome: Mean change in weight - studies with a duration of 12 months or less</td>
<td>155</td>
<td>151</td>
<td>-2.34</td>
<td>-3.27</td>
<td>-1.41</td>
</tr>
</tbody>
</table>

Source: Author’s own elaboration from Shaw et al

In a review of the evidence on cost-effectiveness of non-pharmacological interventions in obese adults the National Institute for Clinical Excellence concluded in 2007 that these interventions are cost-effective but points out that there are several limitations in the quality of evidence. Preventive programmes are cost-effective in the long run but not necessarily in the short run. A study published in 2011 on the cost-effectiveness of diet and exercise on overweight and obesity in Australia concluded that these interventions could be considered cost-effective if time and travel of the participants are ignored.

2.2.2 Non-pharmacological treatment of childhood obesity

As in adults, non-pharmacological and non-surgical interventions are the first-line treatment for childhood obesity. Currently the step care approach is the recommended model to treat overweight and obesity in children and adolescents in the United States. With this approach, intensity (and associated treatment risks) is increased according to the degree of excess weight, age/maturation, health risks and motivation: starting with simple preventive messages to those who are not overweight, to weight-management interventions with increasing intensity for those who have become overweight and have weight-related health problems.

Treatment is recommended in children with a BMI of equal or above 95th percentile of their age and gender or equal or above the 85th percentile with co-existing co-morbidities. The goal of treatment of childhood obesity is to reduce childhood morbidity, increase childhood functioning and reduce risk of morbidity and mortality in adulthood.

Non-pharmacological interventions include dietary changes and increasing activity levels and often involve the family or the care takers of children or adolescents. Changing behaviour such as diet can be extremely difficult. To support behaviour changes several techniques have been proposed which are based on the assumption that successful

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1 NICE has not published newer evidence on the cost-effectiveness of non-pharmacological treatment.
behaviour change can be achieved through self-monitoring, problem-solving, goal setting, rewarding of successful change and minimizing exposure to unhealthy food.\textsuperscript{14}

In childhood obesity, evidence suggests that increasing physical activity alone is effective to achieve changes in adiposity.\textsuperscript{47, 49} There is no general agreement between professional associations and institutions about the exact recommended energy intake relative to body weight to achieve medium/long-term weight loss.\textsuperscript{16} One of the challenges in children and adolescents is the potential harm of a diet that is too restrictive in energy intake as it can affect growth and social and biological development.\textsuperscript{16} Some authors have calculated that the reduction in energy intake needs to be significant (around 250kcal per day) to achieve a least no weight gain in children with more than 90\% of overweight children;\textsuperscript{50} 250 kcal represent nearly one fifth of the total daily energy intake and children would need to walk one to two hours at a speed of 2 km/hour to burn this amount of energy.

A meta-analysis of interventions to treat overweight or obesity in children or adolescence showed larger effects for moderate- to high-intensity behavioural interventions (standardized mean difference in weight loss (SMD): -1.01 [95\% confidence interval (CI): -1.24 to -0.78]) compared to very low-intensity interventions (SMD: -0.39 [95\% CI: -0.66 to -0.11]).\textsuperscript{14} Only half of the studies report on secondary outcomes and those that do report only minimal impact with respect to lipid levels, blood pressure, diet, physical activity level, and psychosocial measures.\textsuperscript{14} Another meta-analysis done by a Cochrane Review concluded similarly that combined behaviour lifestyle interventions are recommended over self-help or standard clinical care, and they have proven to result in clinically meaningful reduction in overweight children.\textsuperscript{49}

### 2.3 Pharmacotherapeutic options

The development of current pharmacotherapeutic options for the treatment of obesity is derived from the knowledge of the biological pathway of the anabolic and catabolic effects (for more detailed information see also Appendix 6.18.2). It has been found that both insulin and leptin are secreted in proportion to body fat and serve as adiposity signals.\textsuperscript{16} Ghrelin, which is secreted by the stomach and duodenum, serves as a hunger signal at the hypothalamus and brainstem, whereas other peptides secreted by the gastrointestinal tract, including peptide YY and GLP-1, act as satiation signals.\textsuperscript{16} The main mechanism of action of existing pharmacotherapeutic agents are to: (1) block the absorption of macronutrients; (2) decrease energy intake; (3) increase energy expenditure.

The FDA\textsuperscript{51} and EMA\textsuperscript{52} coincide that a key requirement of a medicine to be granted market authorization is weight reduction plus clinically meaningful improvements in cardiovascular risk factors. Weight reduction alone is insufficient. Table 6.18.3 shows the different criteria that the FDA and EMA have defined in order to consider market authorization of an anti-obesity product.
Table 6.18.3: Criteria defined by the Food and Drug Authority (FDA) and the European Medicines and Health Product Authority (EMA)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between intervention and control group</td>
<td>The difference in mean weight loss between drug candidate and placebo at one year should be equal or more than 5% and this difference must be statistically significant</td>
<td>Clinically significant weight loss is equal or lower than 10% of baseline body weight at one year, which is also equal or more than 5% greater than achieved on placebo, and this difference should be statistically significant</td>
</tr>
<tr>
<td>Effect size in weight loss</td>
<td>The proportion of subjects who lose 5% or less of their baseline body weight in the drug-candidate group should be at most 35%, and be approximately twice the proportion in the placebo-treated group with the difference again being statistically significant</td>
<td>The clinical response is equal or lower 10% weight loss at the end of one year, the proportions of responders in various treatment arms could be considered as an alternative primary efficacy criterion.</td>
</tr>
</tbody>
</table>

Source: Author’s own elaboration with information from FDA\(^5\) and EMA\(^6\)

Since obesity has been described as a chronic condition which requires treatment over a long period of time, short-term trials of these interventions are of limited value to assess the effects of pharmacotherapy among other interventions.\(^4\) Short term trials (less than one year) are indeed overly optimistic for long term prognosis as patients often regain weight after treatment is discontinued. With respect to the duration of the clinical trials, Han et al\(^16\) writes that with reference to child obesity: “long-term clinical trials are needed to show safety and efficacy of treatments, not only for a few months, but also during the crucial period of active growth and maturation.”

2.3.1 Orlistat in adults

The only marketed pharmaceutical product licensed for the long-treatment of obesity in the Europe is orlistat.\(^5\) Orlistat blocks a fat digesting gastric and pancreatic enzyme lipase. It has to be taken three times per day and patients have to supplement diet with vitamins to avoid nutritional deficits.\(^4\) In its reduced strength it is available over the counter in Europe, the USA and some other countries.

A Cochrane Review found 16 clinical studies with a length of at least 12 months on orlistat. Average weight loss compared to placebo was 2.9 kg (95% confidence interval (CI) 2.5 to 3.2 kg) (see also Appendix 6.18.3).\(^4\) Since the weight loss is moderate, the majority of patients remain significantly obese. Regarding secondary outcomes, orlistat has been shown to reduce the incidence of diabetes. It also improves total cholesterol, LDL-cholesterol and blood pressure (systolic and diastolic) and slightly lowers HDL levels. In diabetic patients it improved glycaemic control. No RCT has mortality as a primary outcome.

In contrast to some other systemic acting anti-obesity agents orlistat has minimal systemic side-effect but a series of undesired effects, most importantly some very unpleasant gastrointestinal side effects including the production and occasionally leaking of a fatty
Even though the discontinuation rate was relatively low with about 5% of patients, data from clinical practices have reported that only 10% of patients continue treatment after one year.

Cost-effectiveness varies by health care setting. A recently published systematic review of cost-effectiveness of orlistat in primary care in the United Kingdom, including 10 trials comparing orlistat with some kind of life-style invention, found that the mean incremental cost-effectiveness ratio was £1 665.4 The authors concluded that using a threshold of 20 000 GBP per QALY “In clinical practice orlistat should be considered [in the United Kingdom] to aid weight reduction with lifestyle interventions in those individuals who have not been successful in reducing their weight with lifestyle alone”.4 For the Australian health care setting, it was found not to be cost-effective when defining an Incremental Cost-Effectiveness Ratio (ICERs) below 50 000 Australian dollars per disability adjusted life year (DALY) averted as good value for money.5 The authors argued that in contrast to previous studies that found orlistat cost-effective, their model was more pessimistic in assuming weight regain to baseline within two years; in addition, only a (substantial) ‘utility’ gain to reductions in disease-related quality and length of life and not only weight gain itself attributable to the treatment was taken into account.5. Adherence can be relevant to consider: in a study published in 2011 using data from 1.8 million HMO members in Israel found that only 25% of patients continue therapy for four months and less than 2% of patients completed 12 months of therapy.6 In general, there are not many studies analysing adherence to orlistat in routine clinical practice.

Clinical guidelines recommend the criteria that patients should fulfil before considering to start orlistat. NICE in the United Kingdom recommends pharmacotherapy for patients with a BMI of 28.0 kg/m² or more with associated risk factors (such as diabetes or hypertension) or a BMI of 30.0 kg/m² or more. In terms of continuation beyond three months this should only be done if the person has lost at least 5% of their initial body weight since starting drug treatment (unless the patient has diabetes which might slow down loss of body weight). The decision to use drug treatment for longer than 12 months (usually for weight maintenance) should be made on an individual basis.26

### 2.3.2 Orlistat in children and adolescents

Orlistat has also been used in adolescents (12 years and above) resulting in small BMI reduction (0.85 kg/m² for orlistat). In combination with lifestyle changes the additional BMI loss found between placebo and orlistat at six months after initiation was −0.76 kg/m² (95% CI −1.07 to −0.44).5,6 No effect on secondary outcomes was found. Only one randomized controlled trial was for over 12 months, which showed a statistically significant change between the intervention group (orlistat) and placebo, −0.55 kg/m² versus 0.31 kg/m² respectively.6 With respect to secondary outcomes, there was a small reduction in the diastolic but not in the systolic blood pressure when compared to the control group (−0.51 mmHg in the intervention group compared to an increase the patients on placebo (1.30 mmHg) (p=0.04).6

In comparison with life-style interventions orlistat has shown side-effects similar to those in adults: oily stool (42%), abdominal pain (11%), faecal incontinence (9%), and new cholelithiasis (2%).6 The placebo controlled trial reported 11 adverse events with the intervention group of 352 adolescents which included seizure, depression, asthma attack,
appendicitis, gallbladder disorder followed by cholecystectomy, pilonidal abscess, adenoidal hypertrophy, cholelithiasis and aseptic meningitis.  

Due to a lack of data on long-term effects of drug treatment and poor effectiveness, pharmacological treatment is only recommended in children with a BMI higher than the 95th percentile who have substantial medical complications of obesity.  

In 2006, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom reported that there was not sufficient evidence to conclude that the use of orlistat in children and adolescents is cost-effective.  

2.3.3 Metformin  
Metformin is a first-line drug for type II diabetes, particularly in overweight and obese patients as it has shown a favourable effect on body weight. It is usually well tolerated, with gastrointestinal side effects being the most common. There is increasing body of evidence demonstrating benefits of metformin in non-diabetic patients both as diabetes prevention and also for weight loss: in a long-term follow-up study with adults who had impaired glucose tolerance or elevated fasting glucose, the mean weight loss was ~2.7 kg in the metformin group and ~0.4 kg in the placebo group at the one year follow-up. Only about 4% of participants were unable to continue metformin due to adverse effects.  

Metformin might also be beneficial in overweight adolescents with impaired fasting glucose or impaired glucose tolerance when combined with life-style modifications. Interestingly, even in the absence of weight loss, metformin was reported to have the ability to improve insulin sensitivity in obese adolescents.  

2.3.4 Lorcaserin and phentermine plus topiramate  
Two new pharmaceutical products have been granted market authorization in the USA in 2012: lorcaserin, a centrally acting selective agonist of the serotonin (5-hydroxytryptamine) 2C (5-HT2c) receptor, and phentermine plus extended-release topiramate. Phentermine is a non-selective releaser of noradrenaline, dopamine and 5-HT, acting as an anorectic agent and topiramate an antiepileptic drug.  

They are indicated in adults who are obese (defined as having a BMI of ≥30) or overweight (BMI ≥27) at least with one weight-related coexisting condition and only recommended in combination with a reduced-calorie diet and increased physical activity.  

Both medicines have been studied in placebo-controlled trials in combination with life-style modifications indicating meaningful weight loss (over 5% of body weight) in more than half of the study participants in the intervention group. For lorcaserin, the placebo subtracted mean percentage body weight loss from baseline was 3.0 to 3.3%. The placebo subtracted mean percentage body weight loss from baseline was substantially higher for phentermine plus topiramate (from 3.5 to 6.6% weight loss with the lower dose of the combination and 8.6 to 9.4% with the full dose of it weight). Even though the higher weight loss with phentermine plus topiramate is regarded as sufficient to achieve market authorization in Europe, it received a negative opinion by EMA in October 2012 due to cardiovascular and psychiatric side effects, but also because of a high probability of extensive off-label use.
In addition to weight loss, lorcaserin and phentermine plus topiramate demonstrated favourable effects in cardio-metabolic and anthropometric parameters (e.g., blood pressure, high-density lipoprotein cholesterol levels and waist circumference). Both medicines also improved glycated hemoglobin levels in overweight and obese participants with type 2 diabetes. However, both products have potentially serious side-effects and the FDA is concerned about off-label use particularly in patients who would like to lose some pounds for cosmetic reasons but could do so using interventions which do not pose such potentially serious side-effects.

In 2010, the FDA denied market authorization to lorcaserin arguing that according to the study information it achieved only marginal weight loss (a placebo adjusted average weight loss of only 3.6%). Preclinical studies indicated a potential increase in the risk of breast cancer and astrocytoma at relatively low doses. Also in 2012, the FDA pointed out two potentially life-threatening side-effects of lorcaserin; multiple tumours and valvulopathy. With respect to the latter, the FDA later concluded that it is unlikely that lorcaserin increases the risk of valvulopathy in humans. Other side-effects reported with lorcaserin are increased incidences of blurred vision, dizziness, somnolence, headache, gastrointestinal disturbance and nausea.

For phentermine plus topiramate teratogenicity and elevations in resting heart rate are safety concerns. For women taking topiramate during their pregnancy there is an elevated risk for infants born with an orofacial cleft. The FDA decided that this product requires a Risk Evaluation and Mitigation Strategy (REMS) consisting among other measures of a medication guide, a patient brochure and prescriber training; the prescriber has to inform the patient about the teratogenic risk and the need for contraception for women of the reproductive age. The FDA has requested that both manufacturers monitor the long-term cardiovascular risks in patients taking the products.

### 2.4 Surgical interventions

#### 2.4.1 Surgical interventions in adults

Bariatric surgery is an intervention in which the stomach size is reduced and/or the absorption of nutrients decreased and has proven to provide consistent and long-term weight loss for the morbidly obese. Procedures include gastric banding (a band is put around the stomach to reduce it size) and gastric bypass (the surgeon creates a bypass which reroutes food to a small stomach pouch). Other procedures include removing a portion of the stomach (sleeve gastrectomy) and bilo-pancreatic diversion (see also more detailed explanation in Appendix 4). Laparoscopic interventions instead of open surgeries are most commonly done. The mechanism by which bariatric surgery works is not fully understood yet.

As invasive interventions, they are associated with surgical risks but also with long-term digestive problems and nutritional deficiencies. Hence, life-long care is needed for patients undergoing this type of intervention. Financial savings are achieved three to four years after the surgery for the health care systems but whether these savings are maintained after ten years is unclear.
The rate of surgery varies between countries and within countries: in the USA around 220,000 individuals underwent bariatric surgery in 2008, making this the second most frequent elective surgery.\textsuperscript{70} In comparison to the USA, the number of people undergoing bariatric surgery in the United Kingdom is much smaller but has risen ten-fold between 2000 and 2010.\textsuperscript{71} Reports indicate that in 2008 most bariatric surgeries were carried out in France (over 13,000) followed by Belgium (8,700), Spain (6,000), Italy (4,842), the Netherlands (3,500), Greece (2,875), Germany (2,117), Denmark (2,004) and Austria (1,741).\textsuperscript{69} Considering the millions of patients in Europe for whom the need for surgery would be indicated, these numbers can be considered low.

There is evidence that more women and girls undergo surgical treatment than men.\textsuperscript{72} Barriers to accessing surgery for those in need have been identified in a number of settings.\textsuperscript{73}

A Cochrane Review on the efficacy of bariatric surgery did a meta-analysis using a total of 26 studies out of which six studies compared surgery with non-surgical treatments and the rest compared different bariatric surgery procedures.\textsuperscript{73} From the six studies comparing surgical with non-surgical intervention it is clear that surgical interventions resulted in larger weight-losses over time; but comparison in the effect size was difficult as the studies used different measures (excessive weight loss, percentage weight loss from baseline, difference in BMI between intervention and control group).\textsuperscript{73} Secondary outcomes such as diabetes and hypertension also improved; one important secondary outcome measure was quality of life, which improved after the first two years after surgery. However, there was conflicting evidence with respect to long-term quality of life (more than 10 years after surgery).\textsuperscript{73} Even though there was a difference in the percentage of patients dying between different surgical interventions (2.1\% died who underwent open Roux-en-Y gastric bypass, but no death occurred in patients undergoing laparoscopic adjustable gastric banding) this difference was not found when adjusting for risk factors (patients undergoing open Roux-en-Y were more ill than patients receiving other types of surgeries).\textsuperscript{73}

A long-term study (20 years of follow-up) found that patients with surgery had on average a 17\% weight loss at 10 years and 18\% at 20 years compared to a weight gain of 1\% at 10 years and a loss of 1\% at 20 years among those in the control group.\textsuperscript{74} Another long-term cohort study\textsuperscript{75} and two RCT\textsuperscript{76,77} were consistent in reporting improvement in diabetes: those enrolling individuals with no diabetes found a reduced incidence of diabetes at ten years.\textsuperscript{75} The number of individuals with diabetes before surgery recovering from diabetes was higher in the intervention than the control group.\textsuperscript{77} Therefore, some proposed diabetes as an independent indication for patients whose BMI is less than 35 kg/m\textsuperscript{2} (metabolic surgery).\textsuperscript{69}

Long-term studies found a reduced mortality of 29\% when compared to standard weight loss measurements.\textsuperscript{79} A study enrolling 4,776 patients undergoing bariatric surgery in the USA found that 4.1\% of the patients had at least one major adverse outcome (death, development of blood clots, repeat surgeries, or failure to be discharged from the hospital within 30 days of surgery).\textsuperscript{70} Another systematic review reported a two-year mortality which ranged from 0\% after sleeve gastrectomy to 1.7\% after bilo-pancreatic diversion.\textsuperscript{79} An estimated mortality of 1 in 200 for bariatric surgery has been described.\textsuperscript{79} For surgical compared with non-surgical interventions, an increased incidence of cholelithiasis and cholecystectomies was reported for men but not for women. Comparing different surgical interventions showed that there is only limited evidence to recommend one surgical procedure over the other.\textsuperscript{73} However, there is limited evidence that biliopancreatic
diversion/duodenal switch surgery had the greatest weight loss and diabetes resolution compared with other types of surgery. One out of ten patients required further surgery at some point due to inadequate weight loss, regained weight, or early or late complications.

In terms of costs, a recent 20-year observational study showed that compared to patients without a surgical intervention, patients who underwent bariatric surgery had a higher utilization of in-hospital and specialists’ care in the first six years after surgery; after that period no difference was found. However, a reduction in medication costs, particularly antihypertensive and antidiabetic medicines was found seven years after surgery.

What seems clear is that the benefit of bariatric surgery outweighs the risk for those with a BMI of 30 and over. However, patients need to be committed to change their life-style profoundly and to receive long-term follow-up care. The reduction of 30 to 35% of overweight has often been much lower than the expected or desired weight loss by patients undergoing surgery. Many patients wish for a weight loss of around 70% of excessive weight as their target but only very few are able to achieve this target.

**Which patients will benefit most from surgical interventions?**

Clinical recommendations vary from country to country in Europe. As an example the National Institute of Health and Clinical Excellence in the United Kingdom recommends in their guidelines for the prevention and management of obesity in adults and children which was published 2006 the following criteria that patients should fulfil:

- a BMI of 40 kg/m² or more, or between 35 kg/m² and 40 kg/m² and other significant disease (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight;
- all appropriate non-surgical measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least six months;
- the person has been receiving or will receive intensive management in a specialist obesity service;
- the person is generally fit for anaesthesia and surgery and is committed to the need for long-term follow-up.

Also, surgery is recommended as a first-line option (instead of lifestyle interventions or drug treatment) for adults with a BMI of more than 50 kg/m² in whom surgical intervention is considered appropriate.

**2.4.2 Surgical interventions in children and adolescents**

A systematic review on surgical interventions in children and adolescents from 19 observational studies reported for gastric banding a 95% CI of −13·7 to −10·6 kg/m² for change in BMI from baseline, and for gastric bypass, at one to three years a 95% CI of −17·8 to −22·3 kg/m². Life-threatening adverse outcome was pulmonary embolism; other adverse outcomes reported were shock, intestinal obstruction, postoperative bleeding, staple-line leak and severe malnutrition. Currently, surgical interventions in children and adolescents are only recommended to patients with a BMI ≥50 kg/m², or ≥40 kg/m² with important comorbidities. Without evidence from long-term follow-up studies it is difficult to say whether the potentially life-threatening risks of the surgical interventions and life-long nutritional deficiencies outweigh the benefit of a reduction in morbidity and mortality.
2.4.3 Other interventions

Other invasive interventions such as a more recent endoscopically delivered duodeno-jejunal bypass device (EndoBarrier) has been developed that reduces the absorption of food from the small intestine; as it has been insufficiently evaluated yet, it will not be further discussed.\(^8\)

3. Why does the disease burden persist?

It has been argued that a series of measures are necessary to halt the obesity epidemic and that it will be much more complicated to succeed than for instance, in tobacco control.\(^4\) As with many other medical conditions, obesity is caused by genetic and environmental factors. Whereas genetic factors can explain in part the development of overweight and obesity it has been argued that environmental factors should be given priority in addressing obesity globally.\(^9\) A major factor in the rise of the obesity epidemic has been the increased energy intake which has to do with a change in the food supply which provides affordable, well marketed and energy dense food; another has been reduced physical activity.\(^9\)

As it is so difficult to reverse obesity through interventions, many argue that prevention is the only way to tackle it. Reversing obesogenic environments seems one of the most important objectives.\(^4\) Even though international institutions have recommended a series of population measures over the last 10 years, national governments have made only very slow progress in implementing these.\(^9\) The disease burden persists due to at least two other factors: (1) current individual treatment options are not effective while there is still an increase of the epidemic in many countries and (2) very few examples exists in which interventions at population level have had an effect on the disease burden.\(^43\) Another important aspect determining interventions is patient adherence, especially to achieve long-term weight loss maintenance.\(^72\)

Evidence of how to most effectively prevent childhood obesity is lacking.\(^16\) A Cochrane Review on interventions to prevent or treat childhood and adolescent obesity undertook a meta-analysis by age-subgroups.\(^15\) A meta-analysis of eight interventions (non-pharmacological) of less than 12 months in young largely non-overweight children (0-5 years old) have only shown moderate effect size (-0.26 loss in BMI in the intervention group when compared to the control group) which was not statistically significant, although it indicated a tendency towards a positive impact of the interventions. These studies only measured the effect on the adiposity and not on other related risk factors such as cardiovascular disease risk factors, e.g. blood pressure, heart rate, blood lipids, or cardiovascular fitness. Except for a single study, none of the eight studies targeting 0-5 year olds explicitly reported unintended outcomes or measures of harm.\(^15\)

Another meta-analysis of interventions targeting mostly non-overweight 6 to 12 year old children taking place in educational institutions (32 out of 39 studies) report a mean effect size of -0.15 BMI (on average the BMI of the intervention group decreased statistically significant by 0.15 more than the control group). While these effect sizes may appear small, they represent important reductions at a population level if sustained over several years.\(^15\) As most of the studies in children and young people are of less than 12 month duration, long-
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term follow-up of study participants is most likely to provide valuable insight into the effect size over time.

4. What can be learnt from past/current research into pharmaceutical interventions for this condition?

So far it has been very challenging to develop a treatment that has an acceptable benefit/risk profile but with a clinically meaningful reduction in the risks of development of diabetes and cardiovascular diseases.\(^4\) Most pharmacotherapies achieve a weight loss of 2 to 7.9 kg more than that usually achieved with placebo treatment.\(^4\) (Whether this is sufficient to result in a clinically meaningful reduction of cardiovascular diseases or diabetes; a reduction of 5 to 10% body weight has found to be sufficient to result in changes in glycemic control, blood pressure, HDL cholesterol, and triglycerides at one year in adults with type II diabetes, depends on the individual goal of weight loss).\(^5\) The overall picture of available treatment for overweight and obesity has changed significantly over the last few years as requirements for tolerability and safety have become more stringent.\(^6\) In the past, many pharmacotherapeutic options were anorectics only for short-term use of less than 12 weeks.\(^8\) There is widespread fear of abuse due to the addictive potential of amphetamine and its derivates;\(^9\) which have been withdrawn in many countries. When proven to be effective it is expected that those medicinal products would be used in a very large and diverse population group, often off-label, which makes assessment of benefit-risk balance and subsequent market authorization very complex.\(^6\)

A series of pharmaceutical products have been taken off the market in recent years (see Table 6.18.4) due to an unfavourable benefit-risk balance.\(^4\)

Table 6.18.4: Pharmaceutical products that have been taken from the market in recent years

<table>
<thead>
<tr>
<th>Product names</th>
<th>Active substance</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menocil®</td>
<td>Aminorex</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Redux® Pondimin®</td>
<td>Fenfluramine and dexfenfluramine</td>
<td>Valvulopathy</td>
</tr>
<tr>
<td>Acutrim® Dex-A-Diet®</td>
<td>Phenylpropanolamine</td>
<td>Stroke</td>
</tr>
<tr>
<td>Acomplia®</td>
<td>Rimonabant</td>
<td>Suicidal ideation and behavior</td>
</tr>
<tr>
<td>Reductil®</td>
<td>Sibutramine</td>
<td>Myocardial infarction and stroke</td>
</tr>
</tbody>
</table>


FDA and EMA have taken the position that pharmacotherapies are not acceptable if there are severe side-effects.\(^5\) However, it has been argued that expecting that a pharmacotherapy has a safety and efficacy profile similar to a change in diet and exercise is unrealistic, and that different risk benefit profiles should be recognised within the population with obesity.\(^6\) Managing risks after market approval have shown to be very important but also very
challenging. Even though the requirements in terms of safety and efficacy are very high, there is a window of opportunity in which new agents in the development pipeline could offer important clinical advantages over existing therapies.

5. **What is the current "pipeline" of products?**

There is a wide variety of targets and pharmacotherapeutic options being tested at present, out of which only the most advanced in their development will be described in the following sections.

5.1 **Fixed-dose combinations of central nervous system (CNS) agents**

Some of the options for weight loss are fixed-dose combinations of CNS agents which have previously been used for weight loss but were taken from the market due to safety concerns and products which are currently used off-label for weight loss. Fixed-dose combinations offer the advantage of multi-target therapy with sometimes higher efficacy, but may also reduce side effects and risks.

Two of the fixed dose combinations include bupropion, a norepinephrine and dopamine reuptake inhibitor which is combined with the opioid receptor antagonist naltrexone or with the sulfonamide anticonvulsant, zonisamide. For the combination of bupropion and naltrexone; four pivotal, 56-week, multicentre, randomized, double-blind placebo controlled studies have been conducted which show that 23 to 37% of patients achieved a weight reduction from baseline of over 5% of their body weight and 13 to 22% achieved a reduction of at least 10%. Lipid profile and glycaemic control also improved: an increase in high-density lipoprotein cholesterol and triglycerides were reported as well as a reduction in fasting plasma insulin and glucose concentrations. The most frequent side-effects were gastrointestinal but also headache, dizziness, insomnia and dry mouth. Due to concerns over increasing blood pressure in patients taking the combination, in 2011 the FDA denied market authorization and requested data from long-term cardiovascular outcome trials. However, the manufacturer is planning to resubmit its market authorization application in early 2013.

Quite substantial weight losses have been reported in phase II studies for the combination of bupropion with zonisamide: a reduction of body weight of 15% in obese people with no other co-morbidity in the absence of diet and exercise. Since the clinical studies involved zonisamide are short-term evaluations it needs to be seen if the clinical studies of more than three months duration and more subjects will not result in the identification of serious adverse side effects which would change the risk-benefit profile of the medicine. Studies for up to three months reported headache, insomnia, nausea and urticaria.

5.2 **Antidiabetic agents (GLP-1 and amylin analogs)**

Some authors believe that since metabolic syndrome is not a discrete disease entity that is accepted by the FDA and EMA, diabetes is viewed as the most appropriate alternative indication. Emerging type II anti-diabetic agents have been discussed as potential
candidates for effective weight loss. Table 6.18.5 presents a series of new anti-diabetic agents with weight loss properties.\textsuperscript{90}

**Table 6.18.5: New antidiabetic agents with weight loss properties**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Reported serious adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>Glucagon-like peptide-1 (GLP-1) analogs</td>
<td>Pancreatitis, thyroid cancer\textsuperscript{*}.</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Glucagon-like peptide-1 agonist</td>
<td>Hemorrhagic and necrotizing pancreatitis, renal impairment and failure, thyroid cancer\textsuperscript{*}.</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Amylinomimetic (amylin analog)</td>
<td>No serious adverse effects reported so far but needs to be injected three times daily it has not been tested in large clinical trials</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>SGLT-2 inhibitor</td>
<td>So far no serious side effects reported as not tested in large clinical trials</td>
</tr>
</tbody>
</table>

Source: Author’s own elaboration from Ioannides-Demos\textsuperscript{90} and Thomson Reuters\textsuperscript{86}; thyroid cancer has only been reported in rodents not in humans.

Liraglutide, a glucagon-like peptide-1 (GLP1) analogue, and exenatide, a GLP-1 receptor agonist (GLPs), were developed and are approved for the treatment of type 2 diabetes. Both increase the secretion of leptin which suppresses appetite, energy intake and delays gastric emptying and they have both demonstrated a reduction in blood pressure and HbA1c levels.\textsuperscript{90} In a trial comparing liraglutide with orlistat\textsuperscript{91} for nondiabetic patients, greater weight losses were found in patients taking liraglutide which was dose-dependent from 4.8 kg and 7.2 kg for liraglutide compared with 2.8 kg with placebo and 4.1 kg with orlistat (\(P < .0001\)). The most common adverse events with liraglutide were nausea and vomiting.

Pramlintide, a synthetic analog of the pancreatic hormone amylin, has been associated with reduced appetite and food intake.\textsuperscript{90} In a RCT with subcutaneous administration of pramlintide over 16 weeks, an average of 3.7% weight loss was achieved with 31% of patients achieving a ≥5% weight loss (\(P < .001\)). Pramlintide has also been tested in a variety of fixed-dose combinations such as metraleptin.\textsuperscript{84}

For canagliflozin the information available is very limited. One published trial published in 2012 reports that canagliflozin reduced HbA1C levels more than placebo and for higher dosing (200 and 300 mg) the reduction was larger than for sitagliptin.\textsuperscript{92}

Other agents that regulate appetite include gut hormones such as ghrelin, cholecystokinin, peptide YY and oxyntomodulin.\textsuperscript{53} However, when given as infusion PYY3–36 to lean and obese individuals it was associated with nausea and increased postprandial glucose\textsuperscript{84} although there might be advantages when used in combination with oxyntomodulin, which has a glucose level-reducing effect.\textsuperscript{93}

Ghrelin, an amino acid peptide which stimulates food intake and inhibits insulin secretion, has been tested in studies but they were inconclusive.\textsuperscript{93} It is not clear whether it can be used
in the future for weight reduction. Similarly, cholecystokinin (CCK), a gastrointestinal hormone secreted from the I-cells, has been studied but has not shown success.

A recently developed co-agonist comprising of a single molecule with the combined property of activating both glucagon and GLP-1 receptors such as glucagon analogues with additional GLP-1 receptor agonistic activity has been tested in animals. When they were PEGylated and administered over a month long period in mice they showed body weight reduction and improved glucose tolerance.93

Several analogues of oxyntomodulin, a peptide and an agonist both for GLP-1 and glucagon receptors, are in preclinical development.93 Overall, apart from the agents mentioned above, peptide agents mimicking satiety hormones have not demonstrated efficacy. It is hoped that better delivery formulations will provide more promising candidates for the treatment of obesity.

Another avenue to develop new therapies for obesity is the combination of gut hormones analogues in an attempt to mimic the physiological fed state using combination of gut hormone analogues. It has been found that after gastric bypass surgery the gut hormones including PYY and GLP-1, are elevated.94 A study administering analogues of PYY and GLP-1 after infusion reported that the individuals had a 27% reduction in energy intake which was not observed with administration of these agents individually.94

### 5.3 Other agents currently tested

Most ahead in the development is cetilistat which has a very similar acting mechanism to orlistat. Table 6.18.6 provides an overview of newer agents currently being tested in addition to cetilistat. Not much is known about them as some of them are still in the pre-clinical development phase.86

<table>
<thead>
<tr>
<th>Candidates</th>
<th>Type of class</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetilistat</td>
<td>Non-systemic lipase inhibitor</td>
<td>Potentially improved tolerability</td>
<td>Dry mouth, GI disturbances and insomnia, potential for heart rate and blood pressure increases</td>
</tr>
<tr>
<td>Tesofensine</td>
<td>NeuroSearch’s monoamine reuptake inhibitor, modulates appetite and increases metabolic energy expenditure and fat metabolism</td>
<td>Potentially least twice the level of weight loss of currently available drugs</td>
<td></td>
</tr>
<tr>
<td>Velneperit</td>
<td>Oral neuropeptide y5 antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obinepitide</td>
<td>7TM Pharma’s synthetic analog of Pyy3-36 and pancreatic polypeptide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. **What are the opportunities for research into new pharmaceutical interventions?**

6.1 **Non-pharmacological interventions**

With respect to non-pharmacological intervention, comprehensive prevention strategies are needed to improve diet and increase physical activity. Many country-wide programmes have been launched, including programmes in schools. There is an increasing sense that changing behaviour needs to be integrated with strategies to modify the environment.

There is continuing discussion on whether price policies including taxation and subsidies are an effective mechanism to promote healthier food choices. Some argue that consumers, instead of choosing healthier foods, would prefer to buy other unhealthier food as a result of pricing policies. Another argument is that taxes on food are regressive in that they have a greater effect on the poor. However, it has been pointed out that the revenue generated will disproportionally benefit the poor. Some believe that a better way to change consumer behaviour is to make unhealthy food less easily available (for instance, not offering them right next to the check-out in a supermarket). More social marketing of healthier food choices by linking them to fictional characters or making them more attractive might be more effective at reaching children and parents than prohibitive measures. Using the example of Denmark, the tax on food rich in fat, was abolished in 2013 for a variety of reasons including that some consumers bypassed the intended reduction in butter consumption by crossing the country border to neighbouring countries to do their shopping. There were also commentaries that it was to appease business in an already weak economy. The evidence base seems not yet sufficient to evaluate the chances of success of a well-designed, well-marketed food tax.

There are a series of aspects which are unresolved. With respect to life-style interventions, very little is known about who is most likely to respond to them. In the USA, around 40% of adults state that they want to lose weight but only very few are successful in losing significant weight on a long-term basis. In general, addressing inequality related to obesity remains difficult. Inequality does not only play a role in non-pharmacological inventions but also in accessing pharmaceutical and surgical interventions.

With regard to child obesity, raising public awareness through the media and more informative labelling of food might have a positive effect on energy balance. There is likely to be more leverage that can be used to promote healthier food choices in the media.

6.2 **Pharmacological interventions**

At present there are very large unmet medical needs for safe and effective pharmacotherapeutic interventions for the treatment of overweight and obese patients. Despite the fact that the centrally acting agents have a much higher risk of side effects, several of these are still considered good candidates, as they are expected to show larger effect size (e.g. the combination of zonisamide plus bupropion).
In 2012, the FDA deliberated on the assessment of cardiovascular safety of anti-obesity medication, since this has shown to be of major concern in many medicines marketed or applying for market authorization over the last decade. This will potentially result in an updating of the current guidance on the appraisal of weight-loss products and subsequently to different criteria for the benefit-risk assessment of those products.

6.3 Surgical interventions

So far, it has been argued that it is not feasible to treat all patients requiring surgery due to costs and risks of complications. For instance, in 2010 out of one million severely and morbidly obese people in the United Kingdom there were an estimated 230,000 people eligible for surgery; however, fewer than 2% of these patients actually received this treatment, one reason being the current limited capacity to perform the surgery. In the USA, 15% of the adult population would be eligible for bariatric surgery given current guidelines.

However, it is important to develop robust pricings for bariatric surgery procedures to more accurately estimate the direct and indirect costs of the interventions including pre-operative and post-operative management.

Finally, biomarkers and genetic profiling might be useful to identify those who will be most successful in benefitting from life-style interventions, even in the short-term. More research is needed in this field.

In summary, while about 33% of individuals with BMI of 30 or more obtain some benefit from lifestyle interventions, the challenge remains to identify the profile of those who will be successful, even in the short-term. The development of biomarkers may prove useful in this regard. It is not clear who will benefit from what type of surgery; better tailoring is needed and this requires more intervention research. At the same time there is need for health care management, which is more integrated between primary and tertiary care, surgical and medical care where obese patients can be managed by a multidisciplinary care team including rehabilitation, nutrition and mental health.

7. Feasibility of closing the gap in the next 5 to 10 years worldwide and in Europe?

Given the current level of the epidemic, there are many millions of patients that are eligible for treatment resulting in an enormous level of unmet clinical need.

Dealing with the causes at the same time as the consequences is relevant. The key will be to make our environment less obesogenic. As mentioned before, at a population level there is no exemplar which leads the way to reverse the epidemic of obesity at country level. There are political and ethical questions around the governmental mandate to steer individual choices.

There are many avenues that are currently being explored in developing new pharmacotherapy for the treatment of obesity. It seems that it is not only the research and
development part that needs to be taken into account when promoting investment into developing new pharmacotherapeutic options but also the way in which regulatory decisions are made. Some authors have argued that regulatory decision-makers are perhaps too restrictive when it comes to evaluating medicinal products for obesity given the large unmet need for treatment.\footnote{98}

With respect to pharmacotherapy in children and adolescents it has been argued that as long as there is a lack of efficacious medicines for clinically substantial weight loss, priority should be given to a model that is targeting those with the greatest metabolic risk. Long-term studies of pharmacotherapeutic interventions are needed to determine their benefit-risk profile; at present there is a lack of high quality evidence from long-term studies, both in terms of efficacy and of safety of pharmacological agents.\footnote{82} There are safety concerns in terms of severe liver disease related to orlistat.\footnote{99} Currently there is a lack of options with proven efficacy in practice for child obesity.\footnote{100}

Key problems with bariatric surgery are the low number of procedures done in comparison to the scale of the problem and the perception of the public (reluctance to finance the intervention and labelling obesity as an individual problem and choice).\footnote{68}

8. **Conclusions**

As a chronic and multi-factorial condition, obesity will be near the top of the public health agenda globally for many years to come as quick solutions are not within sight. The complexities of factors that are at play influence the epidemic (national wealth, government policy, cultural norms, the built environment, genetic and epigenetic mechanisms, and biological bases for food preferences and biological mechanisms that regulate motivation for physical activity) and require a very comprehensive package of strategies, a large stakeholder involvement and a long-term perspective. Scaling up effective interventions at national level and evaluation of their effects on sustainability and equity will be a priority. There is a need to develop and better target intervention strategies.

Pharmacotherapy has not yet played a large part in reducing the burden of the disease, as effect size is small or benefit-risk profiles of different products have not been regarded as acceptable assuming that the products will be used by a large and diverse group of the population. Even though surgery for obese adults has been regarded as cost-effective in a variety of settings, only a small proportion of those in need have received surgery, one major factor being the capacity of health services to carry out the intervention as well as to provide pre- and post-operative care.

Since existing non-invasive therapeutic options have only a moderate effect on reducing obesity-related illness and deaths, there may be an opportunity to develop effective and affordable treatment for those affected by obesity in Europe and worldwide.

More research is needed on adherence and the regaining of body weight after discontinuation of pharmacotherapy in order to better evaluate its cost-effectiveness.\footnote{8} Research is also needed into the long-term savings of surgical interventions.
Even though the current emphasis on prevention at population level should be the focus to combat the epidemic, there is a large unmet need for effective treatment for those affected when lifestyle changes are insufficient.

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Appendix

Appendix 6.18.1: Cost-effectiveness for selected interventions evaluated in Australia

<table>
<thead>
<tr>
<th>Target population</th>
<th>Strength of evidence</th>
<th>DALYs saved</th>
<th>Gross cost ($ million)</th>
<th>Net cost per DALY saved ($ million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unhealthy food and beverage tax (10%)</td>
<td>Adults</td>
<td>4</td>
<td>$59,000</td>
<td>18.00</td>
</tr>
<tr>
<td>Seatbelt legislation</td>
<td>Adults</td>
<td>5</td>
<td>41,100</td>
<td>81.00</td>
</tr>
<tr>
<td>Reduction of advertising of junk food and beverages</td>
<td>Children (6-14 years)</td>
<td>2</td>
<td>37,000</td>
<td>0.13</td>
</tr>
<tr>
<td>School-based education programme to reduce television viewing</td>
<td>Primary schoolchildren (5-10 years)</td>
<td>3</td>
<td>85,000</td>
<td>27.70</td>
</tr>
<tr>
<td>Multi-faceted school-based programme including nutrition and physical activity</td>
<td>Primary schoolchildren (5 years)</td>
<td>1</td>
<td>8,000</td>
<td>40.00</td>
</tr>
<tr>
<td>School-based education programme to reduce sugar-sweetened drink consumption</td>
<td>Primary schoolchildren (7-11 years)</td>
<td>3</td>
<td>5,000</td>
<td>3.30</td>
</tr>
<tr>
<td>Family-based targeted programme for obese children</td>
<td>Obese children (10-11 years)</td>
<td>1</td>
<td>7,000</td>
<td>11.00</td>
</tr>
<tr>
<td>Multi-faceted targeted school-based programme</td>
<td>Overweight/obese primary schoolchildren (5-10 years)</td>
<td>3</td>
<td>270</td>
<td>0.65</td>
</tr>
<tr>
<td>Gastric banding—adolescents</td>
<td>Severely obese adolescents (14-18 years)</td>
<td>1</td>
<td>12,000</td>
<td>130.00</td>
</tr>
<tr>
<td>Gastric banding—adults</td>
<td>Adults BMI &gt;35 kg/m²</td>
<td>1</td>
<td>140,000</td>
<td>120.00</td>
</tr>
<tr>
<td>Diet and exercise</td>
<td>Adults BMI &gt;25 kg/m²</td>
<td>1</td>
<td>100,000</td>
<td>140.00</td>
</tr>
<tr>
<td>Active after Schools Communities Program</td>
<td>Primary schoolchildren (5-11 years)</td>
<td>5</td>
<td>450</td>
<td>40.30</td>
</tr>
<tr>
<td>Weight Watchers</td>
<td>Adults</td>
<td>1</td>
<td>140</td>
<td>5.00</td>
</tr>
<tr>
<td>Lighten up—a healthy lifestyle weight-loss programme</td>
<td>Adults</td>
<td>4</td>
<td>38</td>
<td>4.00</td>
</tr>
<tr>
<td>TravelSMART schools</td>
<td>Primary schoolchildren (10-11 years)</td>
<td>4</td>
<td>90</td>
<td>13.10</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Adults BMI &gt;30 kg/m²</td>
<td>1</td>
<td>2,400</td>
<td>150,000</td>
</tr>
<tr>
<td>Walking School Ruts</td>
<td>Primary schoolchildren (5-7 years)</td>
<td>3</td>
<td>450</td>
<td>40.30</td>
</tr>
</tbody>
</table>

BMI = body mass index. *This classification (1=strongest; 5=weakest) is based on criteria adopted in AACE Preventions.† Limited evidence of effectiveness. Effectiveness is shown by sufficient evidence from well-designed randomized controlled trials. ‡ Limited evidence of effectiveness is demonstrated by limited evidence from studies of varying quality (i.e., level 4-5 evidence); or from a Level II study design; or from a high-quality level III-IV study. § Limited evidence of effectiveness is similar to evidence of effectiveness 2 but potentially not significant and bias cannot be excluded as a possible explanation. ¶ Limited evidence or inadequate evidence (i.e., 6 in original studies). ‖ Cost per DALY saved: gross costs minus cost offsets divided by number of DALYs saved (costs only for reductions in obesity-related disease and not including unrelated health care costs). Interventions drawn from ACE. Prevention study 2010. **Interventions drawn from ACE. Obesity study.

Source: Gortmaker et al, Lancet 2011
Appendix 6.18.2: Simplified model of the leptin signaling pathway

Source: Han et al, 2010
### Appendix 6.18.3: Comparison 1 Orlistat: Anthropometric Outcomes, Outcome 1 Orlistat: Change in Weight (%)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 1 Orlistat: Anthropometric Outcomes

Outcome: 1 Orlistat: Change in Weight (%)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Control</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Mean Difference N(Random/95% CI)</th>
<th>Weight</th>
<th>Mean Difference N(Random/95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davidson 1999</td>
<td>Orlistat</td>
<td>657</td>
<td>-8.8 (10.25)</td>
<td>Control</td>
<td>223</td>
<td>-5.8 (10.45)</td>
<td>5.5 % [-3.00 [-4.58, -4.42]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollander 1998</td>
<td>Orlistat</td>
<td>163</td>
<td>-6.2 (6.39)</td>
<td>Control</td>
<td>159</td>
<td>-4.3 (6.3)</td>
<td>6.7 % [-1.39 [-3.28, -0.52]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hauptman 2000</td>
<td>Orlistat</td>
<td>210</td>
<td>-7.9 (11.45)</td>
<td>Control</td>
<td>212</td>
<td>-4.2 (8.74)</td>
<td>4.0 % [-3.47 [-5.64, -1.76]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berne 2004</td>
<td>Orlistat</td>
<td>111</td>
<td>-5.9 (5.97)</td>
<td>Control</td>
<td>109</td>
<td>-1.8 (5.97)</td>
<td>5.5 % [-3.20 [-4.76, -1.62]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broom 2002</td>
<td>Orlistat</td>
<td>259</td>
<td>-5.8 (7.8)</td>
<td>Control</td>
<td>263</td>
<td>-2.3 (6.2)</td>
<td>8.8 % [-3.65 [-4.71, -2.29]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finer 2000</td>
<td>Orlistat</td>
<td>110</td>
<td>-8.5 (10.3)</td>
<td>Control</td>
<td>108</td>
<td>-5.4 (9.35)</td>
<td>2.3 % [-3.10 [-5.74, -0.46]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelley 2002</td>
<td>Orlistat</td>
<td>266</td>
<td>-3.76 (4.24)</td>
<td>Control</td>
<td>269</td>
<td>-1.22 (4.92)</td>
<td>12.9 % [-2.54 [-3.32, -1.76]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kromp 2003</td>
<td>Orlistat</td>
<td>346</td>
<td>-5.4 (11.16)</td>
<td>Control</td>
<td>350</td>
<td>-2.6 (9.35)</td>
<td>5.8 % [-3.80 [-4.33, -1.27]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindgarde 2000</td>
<td>Orlistat</td>
<td>190</td>
<td>-5.9 (5.5)</td>
<td>Control</td>
<td>186</td>
<td>-4.6 (5.4)</td>
<td>9.0 % [-1.30 [-2.40, -0.20]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miles 2002</td>
<td>Orlistat</td>
<td>250</td>
<td>-4.6 (4.74)</td>
<td>Control</td>
<td>254</td>
<td>-1.7 (3.19)</td>
<td>13.9 % [-2.90 [-3.61, -2.19]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rossner 2000</td>
<td>Orlistat</td>
<td>242</td>
<td>-9.7 (6.3)</td>
<td>Control</td>
<td>237</td>
<td>-6.6 (6.8)</td>
<td>8.3 % [-3.10 [-4.27, -1.93]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sjostrom 1998</td>
<td>Orlistat</td>
<td>343</td>
<td>-10.2 (7.4)</td>
<td>Control</td>
<td>340</td>
<td>-6.1 (6.45)</td>
<td>9.6 % [-4.10 [-5.14, -3.06]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swinburn 2005</td>
<td>Orlistat</td>
<td>170</td>
<td>-4.4 (6.6)</td>
<td>Control</td>
<td>169</td>
<td>-0.9 (3.9)</td>
<td>8.5 % [-3.50 [-4.68, -2.35]]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>3317</strong></td>
<td><strong>2879</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>-2.93 [-3.35, -2.50]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.21; Chi² = 1897.97, df = 12 (P = 0.000); I² = 37%
Test for overall effect: Z = 13.45 (P < 0.0001)

Source: Padwal et al, 2009 4
Appendix 6.18.4: Different forms of bariatric surgery

**Figure 1**
Gastric banding: An adjustable gastric band is used to divide the stomach into a small proximal compartment (pouch) and a larger distal compartment (residual stomach).

**Figure 2**
Roux-en-Y gastric bypass: The stomach is taken down a few centimeters distal to the gastric inlet. The jejunum is divided 50 cm beyond the ligament of Treitz, and its aboral end is connected to the small gastric pouch. Some 150 cm distal to this point, ...

**Figure 3**
Sleeve gastrectomy: More than 80% of the stomach is resected, and the gastric remnant is tubularized, with an initial filling volume of less than 100 ml. Mechanism of effect: restriction and hormonal mechanisms.

**Figure 4**
Biliopancreatic diversion (BPD) with duodenal switch (DS): First, the stomach is reduced in size as in sleeve gastrectomy. Next, the duodenum is divided distal to the pylorus, and the jejunum is divided 250 cm proximal to the ileocecal valve and anastomosed ...

Source: Runkel et al, 2011

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