XENICAL®

Module One

INTRODUCTION

Designed and Developed by:
XXXXXXX

Table of Contents

PREFACE

Welcome to the Sales Desk Reference (SDR) for XENICAL® **(orlistat)**, the antiobesity drug from Roche Laboratories. XENICAL®, the first and only gastrointestinal **lipase** inhibitor, was approved by the U.S. Food and Drug Administration (FDA) in April, 1999 for the long-term treatment of obesity. XENICAL's® unique mechanism of action selectively inhibits the breakdown and absorption of fat in the gastrointestinal tract. XENICAL® provides a safe, effective, pharmacologic means to combat obesity and its comorbid diseases.

XENICAL® (orlistat) Roche Laboratories' antiobesity drug – the first gastrointestinal lipase inhibitor

lipase: an enzyme that breaks down fat

orlistat: generic name for XENICAL®

This SDR presents the essential information you will need to introduce XENICAL® to a wide range of healthcare professionals. The material has been arranged in easy-to-follow sections, organized as five training modules.

At strategic locations within each module you will find "Progress Checks" followed by questions to help you assess your understanding of the material. Move on to the next section only when you are sure that you have correctly answered the questions from the previous one. The correct answers to all questions are found at the end of each module.

As you work through these modules you will notice boldfaced words throughout the text. Definitions for these words are found in the glossary at the end of the module as well as in the margin of the pages on which the terms appear.

Some of the information presented throughout the SDR are referenced to journal articles, websites, and other primary sources. You are encouraged to look up and read articles that interest you to gain a deeper understanding of XENICAL® and its role in weight loss and weight management.

What to Expect

This Sales Desk Reference is organized into five modules:

Module I – Introduction

Module I presents an overview of the SDR, including an introduction to obesity, its causes, and its treatment, diseases associated with obesity, the medical benefits of weight loss, and differences between XENICAL® and its competitors . Module I also outlines XENI*Care*, the patient support program available to every patient taking XENICAL®.

Module II – Scientific Background

Module II outlines material that will enable you to discuss obesity confidently with healthcare professionals. Topics include the biochemistry of fat and fat accumulation, as well as physiologic and metabolic factors that contribute to obesity.

Module III – Treatment Options

Module III discusses the relative contributions of diet, exercise, lifestyle, and medical interventions (pharmaceuticals, surgery) towards achieving long-term weight loss and weight management. After completing this module, you will understand the environment and competitive marketplace into which XENICAL® has been introduced.

Module IV – Prescribers and Influencers

Module IV describes medical specialties critical to the success of XENICAL®, plus a brief discussion of the role of managed care in obesity treatment.

Module V – Comorbidities

Module V outlines comorbidities – medical conditions that occur with, and in some cases are worsened by, obesity.

MODULE I: INTRODUCTION

Overview

Obesity is a growing health problem that has reached epidemic proportions in the United States. According to a report from the U.S. Surgeon General, 61% of adult Americans were classified as overweight or obese in 1999, compared with 47% in the late 1970s.[1] In 2000, the total societal costs of obesity reached $117 billion, a figure believed to be higher than the health costs of smoking.[2] Slightly more than half these costs were incurred for treating obesity and overweight; the remainder result from indirect costs such as lost days of work.[3]

Overweight individuals are at significant risk for developing serious diseases such as heart and circulatory problems, diabetes, and osteoarthritis. In addition, obese people suffer unnecessary psychological problems and social stigmas resulting from their own and others' perceptions of their weight.

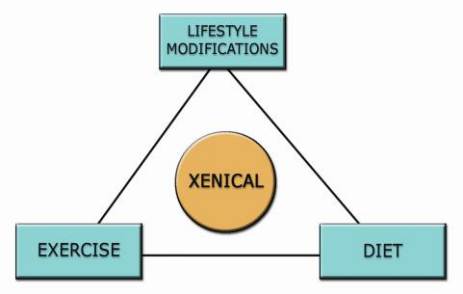
In short, overweight and obesity are not just "problems" – they are medical conditions that can and should be treated.

No single approach can promote and sustain long-term weight loss. In fact, numerous studies suggest that weight loss may only be achieved and maintained through a combination of a healthy diet, exercise, and behavioral changes. For many obese and overweight people XENICAL® is a sensible, safe, effective way to help achieve significant weight loss within the context of a healthy diet and lifestyle modification.

Unlike appetite suppressants, which affect the central nervous system, XENICAL® acts primarily in the intestines to block the absorption and digestion of fats. XENICAL® use is associated with essentially no systemic side effects since less than 2% of the dose is absorbed by the body.

In this module you will learn the basics about obesity and how XENICAL® can help seriously overweight people lose weight.

Figure 1-1. A Healthy Weight-loss Program



"Xenical Supports Traditional Diet, Exercise, and Lifestyle Modification in a Healthy Weight Loss Program"

LEARNING OBJECTIVES OF MODULE I

After completing Module I, the representative will be able to:

1. Define and measure obesity.
2. Describe the medical, social, psychological, and economic impact of obesity.
3. Understand the causes of obesity.
4. Compare available obesity treatments.
5. Explain what XENICAL® is, how it works, and why it's different.

COMMON PERCEPTIONS OF OBESITY

Americans are obsessed with weight, but too often social attitudes and perceptions can limit our ability to see obesity for what it is – a treatable disease.

Look over the following common statements about obesity and circle the answer that most closely matches *your* perception of obesity.

1. Obese people are gluttons – that's how they became obese in the first place

____True ____Some truth to it ____False

2. Obesity can kill you

____True ____Some truth to it ____False

3. The only sure way to lose weight is to eat less

____True ____Some truth to it ____False

4. It's not my fault. Being heavy runs in my family

____True ____Some truth to it ____False

5. If you exercise, you don't have to worry about putting on weight

____True ____Some truth to it ____False

6. If you think you look fat, then you probably are fat

____True ____Some truth to it ____False

7. It's harder to lose weight as you get older

____True ____Some truth to it ____False

8. Fasting is the best way to flush fat from your body

____True ____Some truth to it ____False

Now check the answers on the following page and give yourself one point for each correct response.

1. ***Obese people are gluttons – that's how they became obese in the first place***. **False**. Although obesity results from eating more in calories than you use in energy, the role of over-eating is not so clear-cut. Genetic, environmental, and learned behavioral factors all play a part in developing obesity.

2. ***Obesity can kill you***. **True**. Dietary factors and sedentary lifestyle account for at least 300,000 deaths per year.[4] Obesity ranks second only to smoking as a preventable cause of life-threatening illness.[5]

3. ***The only sure way to lose weight is to eat less*. False**. Eating more of certain foods may actually be the best way to lose weight. For example, which seems like "more": a small bag of potato chips or 7 cups of popcorn? They both have about 150 calories, but the popcorn has less fat and will satisfy the appetite better than chips.

4. ***It's not my fault. Being heavy runs in my family.*** **Some truth to it**. You can inherit a predisposition to obesity. A genetic tendency towards obesity affects how you absorb and metabolize food.[6] Keep in mind, however, that to gain weight you still have to take in more calories than you use – whatever your genetic makeup.

5. ***If you exercise, you don't have to worry about putting on weight.*** **Some truth to it**. However, while exercising does use calories and therefore helps in weight loss, exercising does not make as dramatic a contribution to weight loss as is commonly believed, perhaps because it may result in increased hunger and therefore higher food intake.[7] Exercise is beneficial in *maintaining* weight loss, which is why it should be included in any weight loss program.[8]

6. ***If you think you look fat, then you probably are fat***. **False**. Body image can often be skewed. Patients with certain eating disorders may view their bodies as grossly overweight when in reality they may be normal or even thin.

7. ***It's harder to lose weight as you get older***. **True**. Many people get heavier as they age, often by adding body fat. This may be due to age-related changes in how we expend energy.[9] Often, people become less active as they age. Also, lifestyle changes needed to lose weight are more difficult to make when habits have been ingrained for many years.

8. ***Fasting is the best way to lose weight*. False**. Fasting is dangerous and is not an acceptable or healthy method of losing weight. Fasting may also be self-defeating, because it causes excessive loss of lean body mass (muscle) and causes the body to expend less energy.[10]

How did you do?

6-8 points: Your attitude towards obesity and its causes are realistic.

3-5 points: You are somewhat influenced by popular stereotypes of obesity

0-2 points: You have preconceived notions about obesity and should approach material in this SDR with an open mind.

Key Points

- Obesity is a treatable disease caused by multiple factors.
- Over-eating, genetic makeup, and learned behavior all play roles in the development of obesity.
- At least 300,000 deaths per year in the United States are attributable to obesity.
- Societal costs of obesity have reached $117 billion in the United States.
- Exercise alone rarely helps obese people lose significant amounts of weight.
- Fasting, although popular as a "fad diet," is neither effective nor safe for obese individuals.

REVIEW 1

A. True or false. Over-eating is the only cause of obesity.

_____ 1. true

_____ 2. false

B. Approximately how many deaths per year are attributable to obesity?

C. Which statement is true:

_____ 1. Fasting is an excellent way to lose weight

_____ 2. Exercise alone can help obese people take off weight and keep it off

_____ 3. Losing weight becomes more difficult as we get older

D. Societal costs of obesity have reached _____ .

Please check your answers with those given on page 1-38.

THE FACTS ABOUT OBESITY

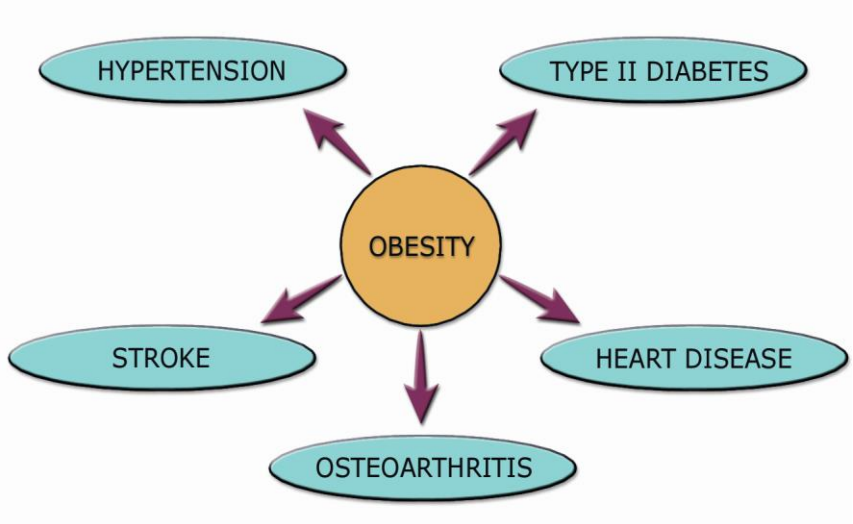
What is Obesity?

Obesity is a chronic disease resulting from a complex set of genetic, environmental, and behavioral factors.

The terms *obesity* and *overweight* are often used interchangeably, but they do not mean the same thing. *Overweight* is a more general term meaning an excess of body weight which may include weight from bone, muscle, water, and/or fat. *Obesity* refers specifically to excess body fat. For example, a bodybuilder may be overweight without being obese.[11]

Usually, individuals want to lose weight because of their appearance. However, not looking one's best is just a small part of being overweight. Obesity is associated with health problems that can lead to illness and premature death. These conditions include hypertension, Type II diabetes, cardiovascular disease, cancer, infertility, gallbladder disease, osteoarthritis, and stroke. In addition, obesity has significant impact on quality of life.[12]

Figure 1-2. Obesity is Associated with Serious Comorbidities



How Obesity Develops

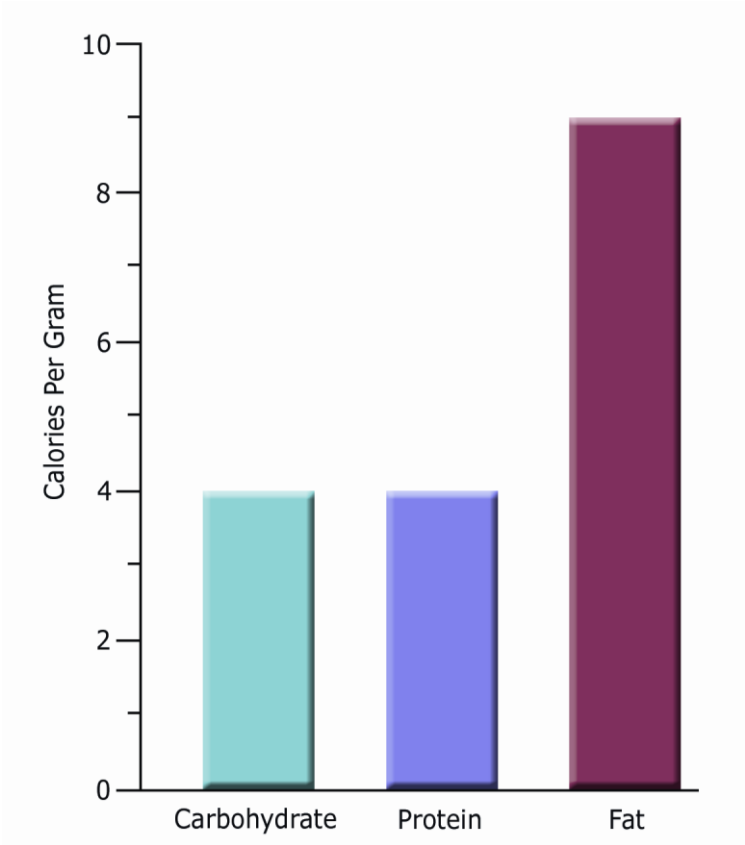
Obesity results from taking in more calories through food and drink than are expended through activity. Calories that are not expended are stored as fat.

If you took a chemistry or physics course you may have learned about *calories*, which are a measure of heat or energy. The calories we refer to when discussing food and obesity are also a measure of energy – the energy content of food or of fat stored in the body.

Technically speaking, food calories are actually *kilocalories* (one thousand calories). However, in everyday usage they are almost always referred to simply as *calories*.

Different foods supply different calorie amounts by weight. Carbohydrates and protein provide about 4 calories per gram; fats provide about nine calories per gram.[13] Research has shown that the diets of overweight people are usually higher in fat than diets of normal-weight individuals.[14]

Figure 1-3. Calories Per Gram for Carbohydrate, Protein, and Fat



Where is Fat Stored?

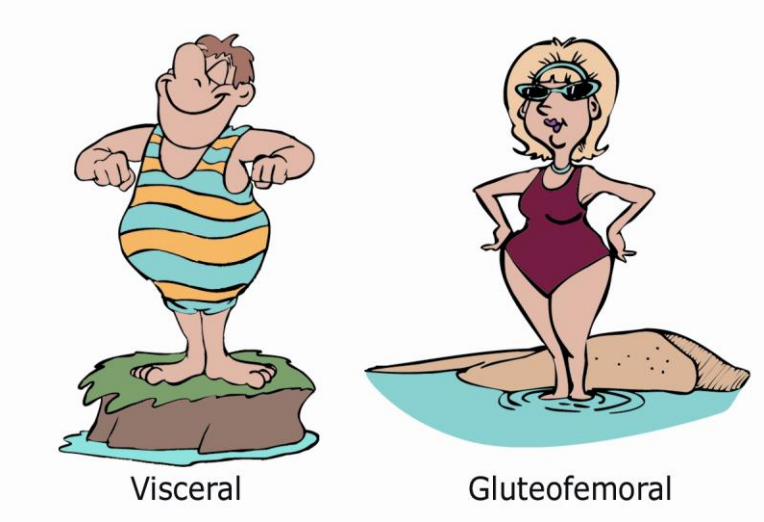
Fat is stored in globules in **adipose tissue,** also called fat cells, which is located under the skin and around the organs. The most important fat storage types are known as **visceral** and **gluteofemoral**. Visceral fat, also called abdominal fat, is located in or near internal organs in the abdominal region. Gluteofemoral fat is found in and around the thighs and hips.

adipose tissue: a type of connective tissue that stores fat

visceral: pertaining to the abdominal area

gluteofemoral: pertaining to the thighs or hips

Figure 1-4. Visceral (left) vs. Gluteofemoral (right) Fat Deposits Have Widely Different Effects on Overall Health



Men tend to accumulate visceral fat around their gut, giving them an "apple" shape; women tend to have gluteofemoral deposits that impart a "pear" shape. Postmenopausal women also tend to develop the "apple" shape.

The distinction between two types of fat accumulation is important because visceral fat is associated with higher mortality and higher prevalence of **comorbid conditions**.[15, 16] We will discuss comorbid conditions in greater detail in Module V of this SDR.

comorbid condition: a medical condition that exists at the same time as, or along with, another condition

Measuring Obesity

According to guidelines issued by the National Heart, Lung, and Blood Institute, a branch of the National Institutes of Health, obesity is measured in two ways:

- Body mass index
- Waist circumference[17]

body mass index (BMI): weight (in kilograms) divided by height squared (in meters)

Body mass index (BMI) is an indirect measure of body fat that also correlates with relative health risk. BMI is calculated by dividing body weight (in kilograms) by height squared (in meters). Since Americans (including physicians) are more comfortable using feet, inches, and pounds than meters and kilograms, BMI values in Table 1.1 are expressed in these units.

How to Read the BMI Table

To read the BMI table, pick a height in inches in the left-most column (Ht), then move across the page until you reach the person's weight. Now go to the number at the top (under "Body Mass Index") that corresponds to the height and weight you've chosen.

A BMI below 25 is normal. Individuals with values between 25 and 29.9 are considered overweight and at moderate health risk. A BMI of 30 or more puts an individual into the obese category and at high health risk. For individuals with a BMI above 30, mortality rates from all causes, especially cardiovascular disease, are increased by 50 to 100% above that of persons with BMIs in the normal range.[18] Remember, BMI does not take into account visceral vs. gluteofemoral fat, comorbid conditions, or lifestyle patterns that may put individuals at even higher risk.

Table 1-1. Body Mass Index Table

Body Weight (in Pounds) According to Height (in Inches) and Body Mass Index																
	Body Mass Index															
	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Ht.	Body Weight															
58	91	95	100	105	110	114	119	124	129	133	138	143	148	152	157	162
59	94	99	104	109	114	119	124	129	134	139	144	149	154	159	164	169
60	97	102	107	112	117	122	127	132	138	143	148	153	158	163	168	173
61	101	106	111	117	122	127	132	138	143	148	154	159	164	169	175	180
62	103	109	114	120	125	130	136	141	147	152	158	163	168	174	179	185
63	107	113	119	124	130	135	141	147	152	158	164	169	175	181	186	192
64	111	117	123	129	135	141	146	152	158	164	170	176	182	187	193	199
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204
66	118	124	131	137	143	149	156	162	168	174	180	187	193	199	205	212
67	121	127	134	140	147	153	159	166	172	178	185	191	198	204	210	217
68	125	132	13	145	152	158	165	172	178	185	191	198	205	211	218	224
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230
70	133	143	147	154	161	168	175	182	189	196	203	210	217	224	231	237
71	136	140	150	157	164	171	179	186	193	200	207	214	221	229	236	243
72	140	148	155	162	170	177	185	192	199	207	214	221	229	236	244	251
73	143	151	158	166	174	181	189	196	204	211	219	226	234	241	249	257
74	148	156	164	171	179	187	195	203	210	218	226	234	242	249	257	265
75	151	159	167	175	183	191	199	207	215	223	231	239	247	255	263	271
76	156	164	172	181	189	197	205	214	222	230	238	246	255	263	271	279

Waist Circumference

Physicians often rely on waist circumference – belt size – as a rough measure of visceral fat accumulation. Although it is not a perfect measure of overweight, waist circumference is helpful as a "before-after" measure for patients who are on a weight loss regimen. As a rule of thumb, waist measurements above 40 inches for males, and above 35 inches for females, are associated with increased health risks.[19]

Key Points

- Individuals with BMIs 25 or above are overweight; those with BMIs 30 or above are considered obese.
- Obesity's relationship to comorbid diseases such as heart, circulatory, and metabolic disorders makes treating obesity an important priority.
- Excess weight in the abdominal region is considered more dangerous than fat deposits on the hips and thighs.
- Measures of obesity used by physicians include BMI and waist circumference.

REVIEW 2

A. Obesity is a condition caused by:

_____ 1. genetics

_____ 2. environmental factors

_____ 3. behavior

_____ 4. all of the above

B. Which type of fat is associated with a higher incidence of comorbid conditions?

_____ 1. visceral fat

_____ 2. gluteofemoral fat

C. A husband and wife sit down to dinner. The husband's meal contains 20 grams of carbohydrates, 20 grams of protein, and 10 grams of fat. The wife's meal contains 10 grams of carbohydrates, 10 grams of protein, and 30 grams of fat. Who has the higher-calorie meal?

_____ 1. husband

_____ 2. wife

_____ 3. both the same

D. Which two measures of obesity are used most often by physicians?

_____

_____

Please check your answers with those given on page 1-38.

THE MEDICAL RISKS OF OBESITY

Obesity creates an increased risk of disabling and sometimes life-threatening comorbid conditions. Obesity-related comorbidities usually worsen as weight increases and improve when individuals lose weight. Some of these comorbid conditions include:

- Heart and blood vessel disease,[20] including high blood pressure[21] and stroke
- Impaired glucose tolerance, **hyperinsulinemia**, and type II diabetes[22]
- **Hyperlipidemia**[23]
- Osteoarthritis[24]
- Cancer[25]
- **Sleep apnea**
- Gallbladder disease
- Infertility

hyperinsulinemia: high levels of insulin in the blood

hyperlipidemia: high levels of fat, especially cholesterol, in the blood

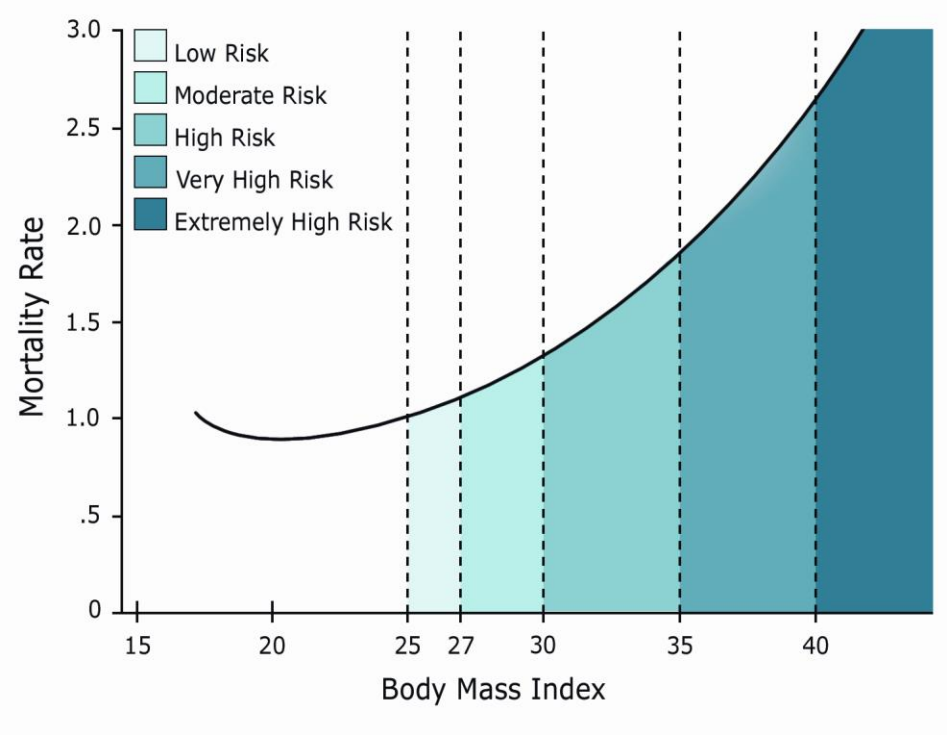
sleep apnea: difficulty breathing during sleep

Epidemiologic studies have correlated a high BMI with one or more comorbid diseases. For example:

- Patients with a BMI of 35 or higher almost always have at least one comorbidity.[26]
- Death from cardiovascular disease in nonsmoking women is directly related to an increase in BMI[27]
- An extremely strong correlation has been found between BMI and the risk of type II diabetes[28, 29]

As weight increases in obese patients, risks for developing comorbid diseases also increases. Conversely, modest weight loss improves existing comorbidities,[30, 31] reduces mortality,[32] and reduces the risk of developing new comorbidities.[33] Figure 1-5 illustrates the relationship between body mass index and mortality risk.

Figure 1-5. Body Mass and Mortality Risk



PSYCHOSOCIAL IMPACT OF OBESITY

In addition to its serious physical consequences, obesity may affect a person's psychological or social well-being, which can affect quality of life. Obese individuals often suffer low self-esteem, job discrimination, social stigmatization, and may even experience clinical depression. Even physicians may view obese patients as weak-willed and responsible for their condition.

Even physicians may view obese patients as weak-willed and responsible for their disease

TREATING THE OBESE PATIENT

Although many obese individuals strive to achieve a so-called "ideal body weight," even modest weight loss can result in significant health benefits. For example, a weight loss as modest as 5% can improve control of diabetes and reduce cardiovascular risk factors.[34, 35] Increased understanding of the relationship between obesity and health risks provides a strong rationale for treating obesity as the underlying disease.

XENICAL® is an important advance in obesity management because it can help patients achieve and maintain clinically meaningful weight loss.

Creating an Energy Deficit

To lose weight, an individual must ingest fewer calories as food or drink than he or she uses up in activity. That discrepancy is known as an "energy deficit." Since one pound of fat is equal to about 3,500 calories, in theory a deficit of 500 calories per day should result in the loss of one pound of fat in about a week.

Increasing physical activity is an important part of any weight-loss program

However, that simple equation doesn't always work because as we eat less, our bodies adjust to the reduction in calories. After a few weeks of dieting, the body is able to function on fewer calories. What this means in practice is that it's possible to lose weight initially on a low-calorie diet, but eventually weight loss slows dramatically as the body gets used to the lower caloric intake. When individuals go back to their original diet, all the weight (and more) returns because their **metabolism** is still operating in low-calorie mode. Exercising can help counteract this energy-conserving mechanism.[36]

metabolism: process by which food is digested and converted to energy

Weight Loss Regimens

All weight loss programs are based on taking in less energy than is expended, thus forcing the body to utilize fat stores for energy

All weight-loss regimens use some combination of diet, physical activity, lifestyle modification, surgery, or pharmacotherapy.

Diet

At any given time tens of millions of Americans are dieting.[37] Although diet is an essential part of losing weight, the long-term results of dieting alone are disappointing. One review of obesity treatments found that almost all people who lost weight only by dieting regained most of the weight within two years. The addition of lifestyle modification to dieting increased weight loss for the first year or two, but this effect disappeared over three to five years. When exercise was added to diet and lifestyle modification, patients regained less weight up to six years later – provided they continued exercising.[38]

The main types of weight-loss diets are:

hypocaloric: low in calories

- Mildly **hypocaloric** diets based on 1,200 to 1,800 calories per day, usually without the use of formulated foods.[39]
- "Low-calorie" diets of 800 to 1,200 calories per day, which may incorporate formulated foods. Individuals with comorbid conditions should attempt such a diet only under medical supervision
- "Very low calorie diets," which provide fewer than 800 calories per day, must always be medically supervised. Individuals on these diets typically use formulas that provide nutrients with a minimum of fat and calories

Although many individuals believe they can lose weight by going on a "starvation diet" or by fasting, medical experts believe these extreme diets are unhealthy and completely inappropriate for dealing with obesity.40

Physical Activity

Although increasing physical activity can help in weight loss, exercise alone does not make a dramatic contribution to weight loss because it simply does not use up many calories. However, even a modest increase in exercise provides health benefits aside from weight loss. People who exercise regularly tend to preserve lean body mass during weight loss. Exercise as a part of a weight loss program may prevent re-gain of weight.[41] Finally, physically active overweight people have a lower risk of illness and death than those who are equally overweight but sedentary.[42]

Figure 1-6. Physical Activity

Lifestyle Modification

Since obesity results from the complex interplay of genetics, environment, and behavioral factors, it makes sense that successful weight loss requires a change in behavior. Lifestyle modification can help individuals identify their behavioral barriers to weight loss and find ways to change that behavior. Some examples of lifestyle changes include:

- Self-monitoring; keeping a food diary
- Identifying situations associated with overeating
- Rewarding good eating habits
- Managing stress
- Social reinforcement from family, friends, or support groups

Figure 1-7. Lifestyle Modification

Surgery

Surgery is a weight-loss option reserved for extremely obese patients who are at very high risk for comorbid disease and who have failed to lose weight by other means. Surgical procedures for weight loss are of two major types:

- Gastric procedures, which decrease food intake
- Shunting and bypass techniques, which cause less food to be absorbed by the intestinal tract

Pharmacotherapy

Pharmacologic management of obesity has suffered a bad reputation because many of the early weight loss medications were amphetamines, which are addictive and have serious side effects.[43] Between 1972 and 1996, no new pharmacologic agents for weight loss appeared on the U.S. market.[44]

The two main categories of "diet drug" are appetite suppressants and lipase inhibitors – medicines that block the digestion and absorption of fats.

For many years physicians prescribed appetite suppressants, also called **anorectics,** for overweight patients. In 1997 the U.S. Food and Drug Administration ordered the withdrawal of two widely prescribed anorectics, dexfenfluramine (Redux, Wyeth), and fenfluramine (Pondimin, Wyeth) after reports linked these drugs to serious heart conditions. The popular combination therapy "Phen-Fen," consisting of fenfluramine plus phentermine, has also become unavailable due to the withdrawal of dexfenfluramine. Phentermine, a central nervous system agent used in weight loss, is still sold as an appetite suppressant.

anorectic: appetite suppressant medication

Despite the recalls of fenfluramine and dexfenfluramine and evidence linking these drugs to fatal heart conditions, the FDA approved a similar agent, Meridia™ (Abbott), in 1998. Meridia is considered a competitor to XENICAL® and will be discussed in detail in Module III.

Key Points

- Obesity increases the risk of comorbid conditions such as cardiovascular disease, diabetes, osteoarthritis, sleep apnea, and cancer.
- Obese individuals often suffer low self-esteem, job discrimination, social stigmatization, and may even experience clinical depression.
- Weight loss as modest as 5% of body weight may improve overall health.
- The goal of any healthy, sensible weight loss regimen is to create an "energy deficit."
- Diet, exercise, and lifestyle changes are the cornerstone of any weight loss program. For some individuals, pharmacologic approaches and even surgery may be indicated.

REVIEW 3

A. In the context of overweight and obese individuals, what is the best definition of "comorbid disease"?

_____ 1. a disease that causes obesity

_____ 2. a disease that occurs with obesity

_____ 3. a disease that occurs with rheumatoid arthritis

B. True or false. Achieving an ideal body weight is an important medical goal.

_____ 1. true

_____ 2. false

C. Circle the correct answer: It is [always] [sometimes] [never] a good idea to check with your physician before beginning a low-calorie or very low calorie diet.

D. Appetite suppressants are known as _____ drugs.

E. A hypocaloric diet is a diet relatively:

_____ 1. high in calories

_____ 2. low in calories

Please check your answers with those given on page 1-38.

Gastrointestinal Lipase Inhibition

Since diet, exercise, and lifestyle modification alone are not always effective for long-term weight loss, the potential benefits of a safe, effective weight-loss agent are enormous. The skepticism with which physicians view appetite suppressant drugs, plus the recall of fenfluramine and dexfenfluramine, have created a void in the marketplace for obesity drugs. That void represents an exciting opportunity for XENICAL®, the only lipase inhibitor approved by the FDA.

XENICAL® works by limiting the absorption of ingested fat by one-third, creating an energy deficit that leads to weight loss. XENICAL's® unique mode of action involves the inhibition of a family of **enzymes** known as lipases. Enzymes are proteins that carry out work in the body by facilitating important chemical reactions. Lipase enzymes, for example, break down dietary fat so it can be absorbed in the intestines. Since XENICAL® inhibits, or *interferes with* lipases, fats that would normally be digested as food are eliminated undigested.

enzyme: a protein that performs work in living systems

XENICAL's® mode of action differs radically from those of appetite suppressants, which act on the central nervous system. Since XENICAL® works locally in the gastrointestinal tract, with less than 2% absorbed by the body, it has no clinically meaningful systemic effects.

Key Points

- XENICAL® blocks fat absorption, a unique mechanism of action for a diet drug.
- XENICAL® belongs to a class of medication known as lipase inhibitors.
- Appetite suppressants affect the central nervous system, whereas XENICAL® works only in the intestines. Less than 2% of XENICAL® is absorbed systemically, therefore the drug has an extremely favorable systemic side effect profile.
- In seven multicenter, double-blind, placebo-controlled clinical studies (four of which lasted for two years), XENICAL® promoted weight loss, prevented weight regain, and appeared to reduce the risk of obesity-related comorbidities.

REVIEW 4

A. Appetite suppressants work on the _____ _____ _____ whereas XENICAL® acts primarily in the _____.

B. What is the function of lipase enzymes?

_____

C. XENICAL® reduces fat absorption by about _____ %.

D. In addition to receiving XENICAL® medication, for no additional cost patients will be able to take advantage of a support program known as _____ to help them in their weight loss regimen.

Please check your answers with those given on page 1-38.

Efficacy: XENICAL® Clinical Studies

Long-term clinical trials for XENICAL® were the largest ever undertaken for an obesity drug. XENICAL® was tested in seven double-blind, placebo-controlled, multicenter clinical studies – four in the United States, three in Europe. Four of the seven trials lasted two years. XENICAL® clinical studies were designed on the premise that XENICAL® could have positive benefits for both weight loss and comorbidities. Figure 1-8 lists the XENICAL® studies and numbers of patients in each.

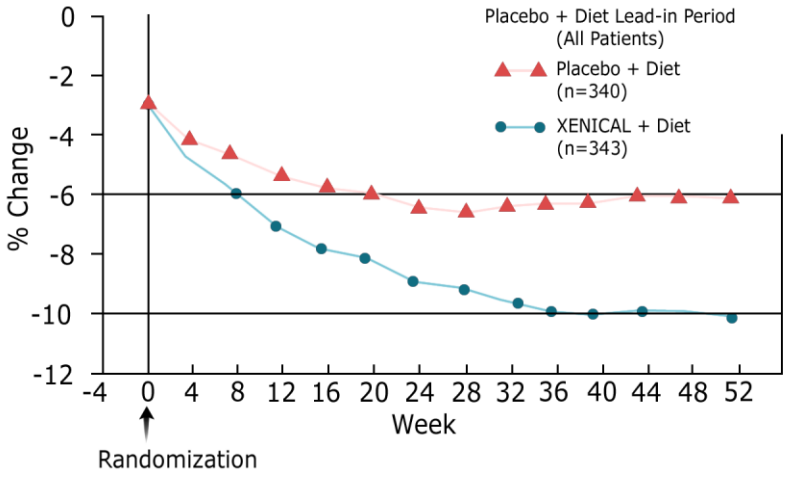
Figure 1-8. XENICAL® Long-Term Clinical Trials

Study	Number of Patients*
2-Year Trials	
European multicenter weight loss/maintenance	683
European multicenter weight loss/maintenance	716
US multicenter weight loss/maintenance	880
US primary care weight loss/maintenance	635
1-Year Trials	
UK multicenter weight loss	218
US multicenter prevention of weight gain	720
US multicenter weight loss in type 2 diabetes	321
Total of 7 long-term studies with 4173 patients	

* ITT population. Data on file (Refs. 038-001: 038-020).
Please see complete product information

Figure 1-9 illustrates the effectiveness of sustained, significant weight loss in patients treated with XENICAL® plus diet in clinical trials. Of patients treated with XENICAL®, 69.1% lost >3% of initial body weight by week 12. Mean weight loss at week 12 was 13 lbs and at week 52 was 19 lbs (pooled data from five clinical trials). And at week 52, of patients who lost >3% by week 12, 27.5% had lost less than 5%, 35.2% had lost between 5% and 10%, 21.6% lost between 10% and 15%, and 15.7% lost 15% or more. These numbers suggest that early success with XENICAL® plus diet may lead to significant long-term weight loss.

Figure 1-9



P< 0.001 based on ITT population, last observation carried forward
* Multicenter trial 1411C (Sjostrom L, et al. Lancet. 1998; 352; 167-172)
Please see complete product information

Figure 1-10. Categorical Weight Loss at Week 52 in Patients Who Lost ≥ 3% of Body Weight at Week 12 (n=735)

Weight Loss Category at Week 52	Percent (n) of Patients in Category	Mean weight Change (lb)
<5%	27.5 (202)	-4.3
≥5%-<10%	35.2 (259)	-15.9
≥10%-<15%	21.6 (159)	-25.5
≥15%	15.7(115)	-41.7

Pooled data. Completers population from randomization
Data on file (Ref. 038-041)

Side Effects

Gastrointestinal side effects were the most commongroup of adverse events observed during XENICAL® clinical studies (see table 1.2). These side effects are believed to have resulted from XENICAL's® mechanism of action – blocking fat absorption in the intestines.

Most of the observed side effects began during the first three months of treatment, were mild, and lasted for between one and four weeks, with about half of all gastrointestinal side effects lasting for less than a week. Side effects generally decreased by the second year of treatment.

Since side effects associated with Xenical® treatment result from Xenical's® fat-blocking activity, reducing fat consumption in the diet is one strategy for lessening side effects. A recent study has shown that adding a common fiber product to the diet reduces gastrointestinal side effects associated with Xenical® treatment by more than three-fourths.[1]

Other systemic side effects did not occur at significantly higher frequency in XENICAL® than in placebo groups. For example, CNS side effects (headache, dizziness) occurred at approximately the same frequency in XENICAL®- and placebo-treated groups.

Table 1-2. Adverse Events Commonly Observed During XENICAL® Clinical Trials

Adverse Event	Year 1		Year 2	
	XENICAL % of Patients (N=1913)	Placebo % of Patients (N=1466)	XENICAL % of Patients (N=613)	Placebo % of Patients (N=524)
Oily spotting	26.6	1.3	4.4	0.2
Flatus with discharge	23.9	1.4	2.1	0.2
Fecal urgency	22.1	6.7	2.8	1.7
Fatty/oily stool	20.0	2.9	5.5	0.6
Oily evacuation	11.9	0.8	2.3	0.2
Increased defecation	10.8	4.1	2.6	0.8
Fecal incontinence	7.7	0.9	1.8	0.2

[1] Cavaliere H, Floriano I, Medeiros-Neto G. Gastrointestinal side effects of orlistat may be prevented by concomitant prescription of natural fibers (psyllium mucilloid). *Int J Obes Relat Metab Disord* 2001;25:1095-1099,

Key Points

- FDA approval of XENICAL® was supported by seven clinical trials.
- In all studies, XENICAL®-treated patients lost more weight and experienced a reduction in risk factors for serious disease compared with placebo-treated patients.
- Treatment with XENICAL® was associated with lower systolic and diastolic BP.
- Diabetic patients taking XENICAL® experienced added benefits such as better glycemic control, lower requirements for diabetes medications, and healthier lipid profiles.

REVIEW 5

A. True or false. XENICAL® clinical studies were designed to assess the drug's affect on both obesity and comorbid conditions.

_____ 1. true

_____ 2. false

B. Compared with patients taking placebo, XENICAL®-treated study subjects experienced:

_____ 1. about the same weight loss

_____ 2. about twice the weight loss

_____ 3. about three times the weight loss

_____ 4. about seven times the weight loss

C. Compared with patients taking placebo, XENICAL®-treated study subjects experienced:

_____ 1. Slightly higher systolic blood pressure

_____ 2. About the same systolic blood pressure changes

_____ 3. About twice the amount of systolic blood pressure lowering

_____ 4. About three times the amount of systolic blood pressure lowering

D. Metformin is a drug used to treat _____ .

E. Treatment with XENICAL® is associated with (better/the same/worse) glycemic control than treatment with placebo.

F. Side effects of XENICAL® treatment are primarily limited to the _____ _____ _____ .

Please check your answers with those given on page 1-39.

XENI*Care* – THE XENICAL® LIFESTYLE MODIFICATION PROGRAM

Healthcare professionals you encounter will be eager to learn about XENICAL's® efficacy and long-term safety. They may also be surprised to hear that Roche Laboratories offers everyone with a XENICAL® prescription a no-cost patient support program called XENI*Care*. Patients may enroll in XENI*Care* through the XENI*Care* website (www.xenicare.com), by calling 1-800-XENI*Care*, or by mailing in their registration information.

Through XENI*Care*, patients receive personalized nutritional and lifestyle counseling from a registered dietitian by phone and/or email, plus periodic information kits. The first kit includes:

- XENI*Care* guidebook
- Q&A on XENICAL®
- Map to Success
- *The Road to Healthy Eating*
- Daily Achievement Journal
- Fat counter booklet

At various times XENI*Care* patients will also receive incentives for free or discounted XENICAL®.

As an added resource, the XENI*Care* website (www.xenicare.com) offers a wealth of information on diet, exercise, healthy cooking, and other health topics to support weight loss with XENICAL®. The website even features directories for locating gyms and "healthy" restaurants.

While selling XENICAL®, do not underestimate the value of XENI*Care* to overweight individuals and the healthcare professionals who treat them.

Key Points

- Through XENI*Care*, Roche offers everyone with a prescription for XENICAL® a comprehensive, personalized support program at no extra charge.
- The XENI*Care* website, www.xenicare.com, is an excellent resource for overweight individuals.
- Do not underestimate the value of XENI*Care* to healthcare professionals you encounter.

REVIEW 6

A. What is the web address for the XENI*Care* program?

_____

B. Which of the following are true about the XENI*Care* program?

_____ 1. It is available to all XENICAL® patients

_____ 2. XENI*Care* is available at modest cost to most XENICAL® patients

_____ 3. Patients may enroll in XENI*Care* through a registered dietitian

_____ 4. XENI*Care* was designed to help diabetics control their blood sugar levels

Please check your answers with those given on page 1-39.

Individual Differences in the Development of Obesity

We have learned that obesity is the result of taking in more calories than are expended as energy through physical activity. However, the "big picture" is somewhat more complex. For example, why are some individuals prone to becoming overweight or obese, while others never have a problem with their weight?

The answer may lie in the interplay of complex factors, some of which may be unique to individuals. These factors include genetic makeup, environment, behavior, and psychological factors.

Genetic Factors

Genetic factors are inherited characteristics that include hair and eye color, height, and predisposition to disease. Our current genetic makeup developed when food was not always plentiful. The desire to eat calorie-rich foods, and the ability to store fat to be used as energy in times of scarce food supply, were once powerful advantages for survival. Today, Americans have a surplus of food, but possess the same mechanisms for dealing with famine as our ancient ancestors. That includes a propensity to store fat.

Research has demonstrated a link between specific genes and obesity. In 1994, researchers isolated the "Ob" gene, which apparently interacts with the central nervous system to regulate food intake and the size of fat stores. Mice with mutations in this gene, for example, ate more and gained more weight than did normal mice.[45]

Family Heritage

Strong evidence for the genetic basis of obesity may be found in studies of families, especially identical twins. In one study of twelve pairs of identical twins of average weight all were fed 1,000 excess calories per day for 100 days. Twins in each pair gained about the same amount of weight in the same places, but the results for different *sets* of twins varied dramatically. For example, one set of twins gained 10 pounds while another gained 29 pounds. Some pairs added muscle, others added fat, etc. This study suggests that the rate at which people put on weight and the distribution of that weight is genetically determined.[46]

A study of more than 500 adopted children in Denmark found that children's weight patterns more closely followed that of their biological parents rather than their adoptive parents.[47] This finding further supports the notion that genetic factors determine obesity patterns. Another adoption study, however, showed weight-pattern correlations between children and both biological and adoptive parents. This finding suggests that environment, as well as genes, may play a role in the development of obesity.[48]

Set Point

set point: hypothetical internal control mechanism for regulating weight gain and fat accumulation

One way genetics may play a role in weight regulation may be through establishment of a **set point** – a genetically programmed "ideal" weight or weight range for an individual. The idea of a set point is similar to that of a thermostat regulating temperature. When a person deviates from his or her set point, mechanisms come into play which tend to return the person to their preset or "set point" weight range.[49]

Environmental and Behavioral Factors

Environmental and behavioral factors are closely related in the development of obesity. At a very basic level, our comfort-filled environments create a sedentary lifestyle that is conducive to gaining weight. More complex is the relationship between how people, places, and things around us affect our behavior with regards to eating and overeating.

Despite evidence of the role genes play in obesity, diet and physical activity are nevertheless important behaviors in weight gain. Poor dietary habits are learned behaviors that may be associated with "trigger foods" and "trigger behaviors" which, without one's knowledge, may affect how and how much one eats.

Other triggers include social situations such as parties or special events, or times of day when unhealthy eating is more likely.

Psychological Factors

The relationship between overeating and psychological conditions is controversial. Early theories attempted to correlate anxiety and depression as factors in overeating.[50] Other studies have linked overeating with childhood sexual abuse. However, the best research available has failed to uncover a connection between underlying psychological or personality problems and obesity.[51] The problem with most studies supporting the "psychological theory" of obesity is a failure to demonstrate that obesity results from psychological problems rather than causing those problems.

Key Points

- Genes, behavior, and environment are the principal factors in development of obesity.
- Some individuals are susceptible to environmental “triggers” for unhealthy eating behavior.
- Psychological factors do not appear to be significant in developing obesity.

REVIEW 7

A. Twin studies have shown that weight patterns correlate between:

_____ 1. children and their adoptive parents.

_____ 2. children and their biological parents.

_____ 3. all of the above.

B. True or false. Genetic traits that developed thousands of years ago may still be evident in humans today.

_____ 1. true

_____ 2. false

C. Set point is best described as:

_____ 1. weight before exercise.

_____ 2. weight after dieting.

_____ 3. weight which the body attempts to maintain.

D. True or false. Research has shown conclusively that underlying psychological problems cause obesity.

_____ 1. true

_____ 2. false

Please check your answers with those given on page 1-39.

GLOSSARY

adipose tissue (ad'i•poce): a type of connective tissue that stores tat

anorectic (an"o•reck'tick): an agent that decreases appetite and/or increases satiety

body mass index: weight (in kilograms) divided by height squared (in meters)

comorbid (co•more'bid) condition: a condition associated with another, in this case, a condition associated with obesity

enzyme (en'zime): a protein that performs chemical reactions in living systems

gluteofemoral (gloo'ee•o•fem'o'rul): pertaining to the area around the hips and thighs

hyperinsulinemia (high"pur'in'sue•lin•nee'mee•uh): high levels of insulin in the blood

hyperlipidemia (high'ur•lip'i•dee'mee•uh): high levels of fat, especially cholesterol, in the blood

hypocaloric: low in calories

lipase (lye'pace): an enzyme involved in the breakdown of fat

metabolism (me•tab'o'liz•um): the sum total of the chemical changes or reactions occurring in the body. Energy metabolism is the process by which energy from food is released and used

orlistat: generic name for XENICAL®

set point: hypothetical internal control mechanism for regulating weight gain and fat accumulation

sleep apnea (ap'nee•uh): difficulty breathing during sleep

visceral (vis'ur•ul): pertaining to the abdominal area

REVIEW ANSWERS

Review 1

A. 2

B. 300,000

C. 3

D. $117 billion

Review 2

A. 4

B. 1

C. 2

D. Body mass index (BMI) and waist circumference

Review 3

A. 2

B. 2

C. always

D. anorectic

E. 2

Review 4

A. central nervous system; intestines

B. to break down dietary fats

C. 33%

D. XENI*Care*

REVIEW ANSWERS (Contd.)

Review 5

A. 1

B. 2

C. 3

D. type 2 diabetes

E. better

F. lower gastrointestinal (GI) tract

Review 6

A. www.xenicare.com

B. 1

Review 7

A. 3

B. 1

C. 3

D. 2

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