Epidemiology, Morbidity, and Treatment of Overweight and Obesity

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Although still considered more of a cosmetic problem by both the general public and some areas of the medical community, overweight and obesity have reached epidemic proportions worldwide. Overweight and obesity have not only a significant psychological impact but also result in an increased risk for development of numerous chronic and sometimes fatal diseases. The morbidity from obesity-associated disorders increases with higher body mass index and begins within the normal weight range. The costs (direct and indirect) associated with treating obesity and its comorbid conditions are notable and increasing. Obesity rates in patients with schizophrenia are at least as high, if not higher, than in the general population. This article reviews the epidemiology and burden of obesity and its associated comorbid disorders. The guidelines from the National Heart, Lung, and Blood Institute of the National Institutes of Health for diagnosing and treating obesity are also discussed.

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Overweight and obesity have reached epidemic levels in the United States and almost all developing and developed countries.[1–3] In the United States alone, an estimated 97 million adults (1 in 2 adults) are overweight or obese.[1] Excess body weight substantially increases the risk of morbidity from a number of other conditions, including hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and endometrial, breast, prostate, and colon cancers. Increases in all-cause mortality are also associated with higher body weights, as are social stigmatization and discrimination.[1] Despite the clinical and psychological burden, treatment of obesity presents significant challenges to all health care providers, partly because there is not yet agreement on the best treatment approach. Obesity and overweight are complex, multifactorial conditions linked to environmental, hereditary, psychological, and physiologic factors, all of which must be addressed for successful treatment.[4] This article reviews the epidemiology and burden of obesity and its associated comorbid disorders. The guidelines from the National Heart, Lung, and Blood Institute of the National Institutes of Health for diagnosing and treating obesity are also discussed.

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The accepted method of defining overweight and obesity has been outlined in evidence-based clinical guidelines from the National Heart, Lung, and Blood Institute of the National Institutes of Health.[1] Overweight is defined as having a body mass index (BMI) of ≥ 25 kg/m^2 and obesity as having a BMI of ≥ 30 kg/m^2; these classifications are used by both the National Heart, Lung, and Blood Institute/National Institutes of Health and the World Health Organization.[5]

Waist circumference is also useful in defining overweight and obesity because it is an indicator of the amount of abdominal fat; excess abdominal fat is associated with dyslipidemia, hypertension, and glucose intolerance.[6] Waist circumference is the preferred measure of abdominal fat content because of its ease and low cost. Other, more specific measures include magnetic resonance imaging and computed tomography, but the cost for either outweighs the increased accuracy. The waist-to-hip ratio is not as accurate a measure of overweight.[1]

Historically, overweight and obesity were defined by weight-height scales, and many of the randomized, controlled studies of different therapies used those scales to measure outcomes. Weight-height scales are currently not used because they do not measure the amount of body fat. However, critics of BMI suggest that it can misrepresent the amount of fat in certain situations such as short stature, presence of edema, and high muscularity. The relationship between BMI and body fat content can also vary by age, gender, and possibly ethnicity because of differences in lean tissue composition, sitting height, and hydration state. Nonetheless, the risk of comorbidities has been shown to increase with BMI and waist circumference, so BMI and waist circumference are the currently accepted standards

Table 1. Relationship Between Body Mass Index, Waist Circumference, and Disease Risk[a]

Category	Body Mass Index	Disease Risk Relative to Normal Weight and Waist Circumference: Men ≤ 40 in, Women ≤ 35 in	Disease Risk Relative to Normal Weight and Waist Circumference: Men > 40 in, Women > 35 in
Underweight	< 18.5	...	...
Normal[b]	18.5–24.9	...	...
Overweight	25.0–29.9	Increased	High
Obesity I	30.0–34.9	High	Very high
Obesity II	35.0–39.9	Very high	Very high
Obesity III	≥ 40	Extremely high	Extremely high

[a]Reprinted with permission from the National Heart, Lung, and Blood Institute.[1]
[b]An increased waist circumference can indicate increased disease risk even in persons of normal weight.

by which healthy weight and the effectiveness of weight-management strategies are measured.[7–9]

In adults with a BMI of 25 to 34.9 kg/m^2, waist circumference should not exceed 35 inches in women or 40 inches in men because of the increased relative risk for the development of obesity-associated risk factors.[1] Table 1 shows the relationship between BMI, waist circumference, and disease risk.

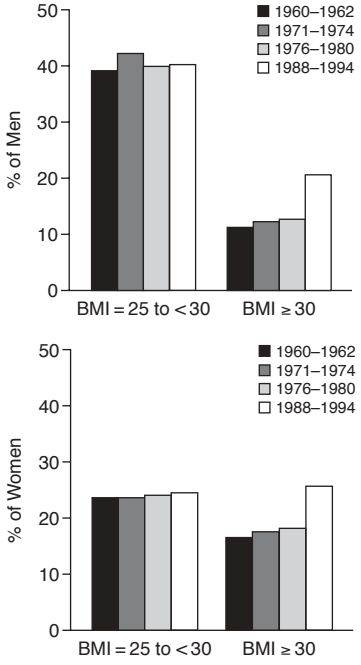
EPIDEMIOLOGY

The high prevalence of overweight and obesity in the United States is the result of a more than 50% increase in obesity during the past 3 decades (from 14.5% to 22.5%; Figure 1).[10] During this time, the prevalence of overweight has been almost unchanged. However, the increase in obesity varied by region in the United States. Mokdad et al.[11] reported the change in prevalence of obesity in each U.S. state from 1991 to 1998. In 1991, 4 of the 45 participating states had an obesity rate of at least 15%. In the subsequent 7 years, the number of states with an obesity rate ≥ 15% had increased to 37; most of the changes were seen in the eastern half of the country and on the West Coast. The increase in obesity was observed in both sexes and across all age groups, races, educational levels, and smoking statuses.

Allison et al.[12] have studied obesity rates in patients with schizophrenia and found the rates to be at least as high, if not higher, than in the general population (Figure 2). In particular, women with schizophrenia were more likely, on average, to be overweight than women without schizophrenia. An important caveat to their observations is that patients in the schizophrenia cohort were not institutionalized and were able to respond to an interview, so the data probably did not include a large proportion, if any, of acutely ill patients with schizophrenia.

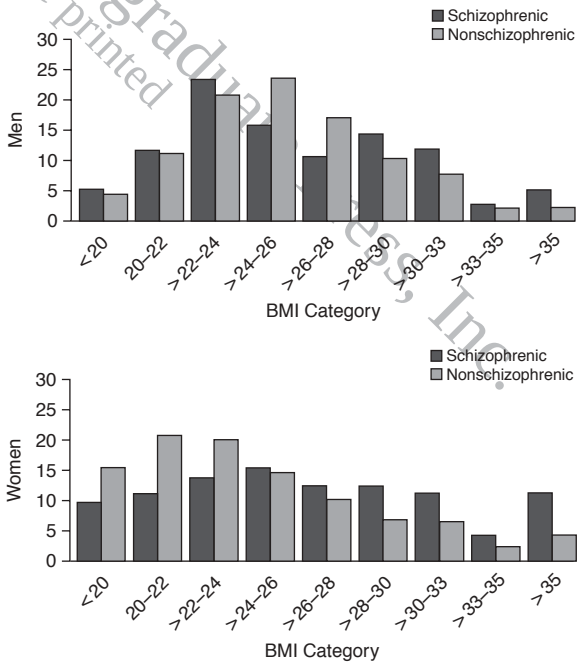
Several reasons, both illness and medication related, have been proposed for the causes of overweight and obesity in patients with schizophrenia. For example, inactivity and apathy are characteristic of schizophrenia and are supported by the confinement of institutionalization and lim-

Figure 1. Change in the Age-Adjusted Prevalence of Overweight and Obesity in Men and Women Aged 20 to 74 Years From 1960 to 1994[a]



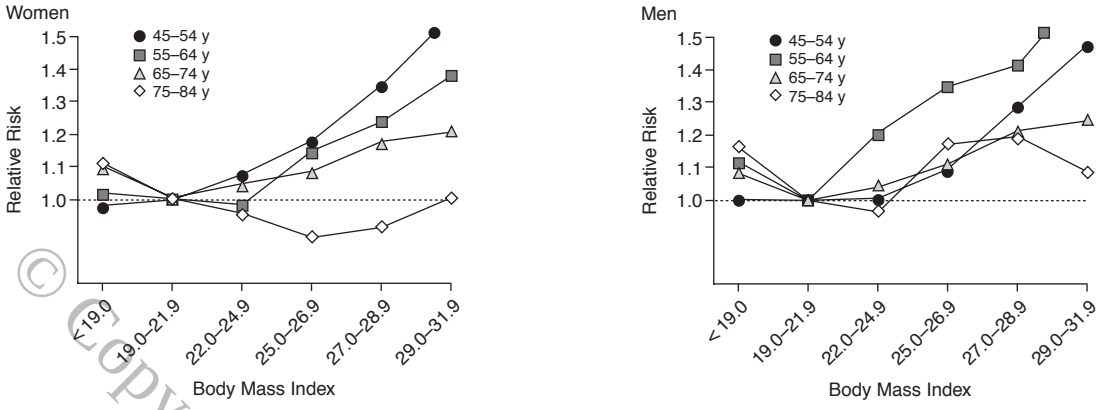
[a]Reprinted with permission from the National Task Force on the Prevention and Treatment of Obesity.[10] Abbreviation: BMI = body mass index.

Figure 2. Age-Adjusted Body Mass Index (BMI) Distributions Among Schizophrenic and Nonschizophrenic Individuals in the 1989 National Health Interview Survey Sample[a]



[a]Reprinted with permission from Allison et al.[12]

Figure 3. Age-Specific Relation Between Body Mass Index and Risk of Death Among Women and Men 45 to 75 Years of Age[a]



[a]Reprinted with permission from Willett et al.[15]

ited exercise. Also, poverty and poor access to good nutrition may lead to higher body weight. Medications used to treat schizophrenia can contribute to the problem, particularly clozapine and olanzapine. These issues will be discussed in different articles in this supplement.

CONSEQUENCES OF OBESITY

Mortality

Poor dietary patterns and physical inactivity rank second to smoking as preventable causes of death and account for 300,000 deaths annually.[13] The risk of death increases with higher BMI so that more than 80% of estimated obesity-attributable deaths (i.e., deaths due to the increased risk of comorbid conditions with obesity) occur in individuals with a BMI > 30 kg/m^2 (Figure 3).[14,15] However, the risk of death increases even at a BMI of 23 kg/m^2 when compared with the lowest risk group.

Stevens et al.[16] examined mortality over a 12-year period among 62,116 white men and 262,019 white women who were participating in the American Cancer Society's Prevention Study I. These patients had never smoked cigarettes and had no history of heart disease, stroke, or cancer other than skin cancer at baseline (1959–1960). The results showed that an increment of 1.0 in BMI was associated with higher mortality from all causes and from cardiovascular disease in men and women. The relative risk was highest for ages 30 to 44 years and decreased with age.

Comorbidities

The spectrum of disorders comorbid with obesity range from diabetes and coronary heart disease to osteoarthritis and cancer. Table 2 shows the proportion of disease prevalence attributable to obesity for many of the major comorbidities.[17] The relationship between BMI and the relative risk of a variety of comorbidities is shown in Figure 4.[15] Again, the relative risk for some conditions such as diabetes starts to increase at the relatively low BMI value of 21 kg/m^2.

Table 2. Proportion of Disease Prevalence Attributable to Obesity[a]

Disease	Prevalence (%)
Type 2 diabetes mellitus	61
Uterine cancer	34
Gallbladder disease	30
Osteoarthritis	24
Hypertension	17
Coronary heart disease	17
Breast cancer	11
Colon cancer	11

[a]Reprinted with permission from Wolf and Colditz.[17]

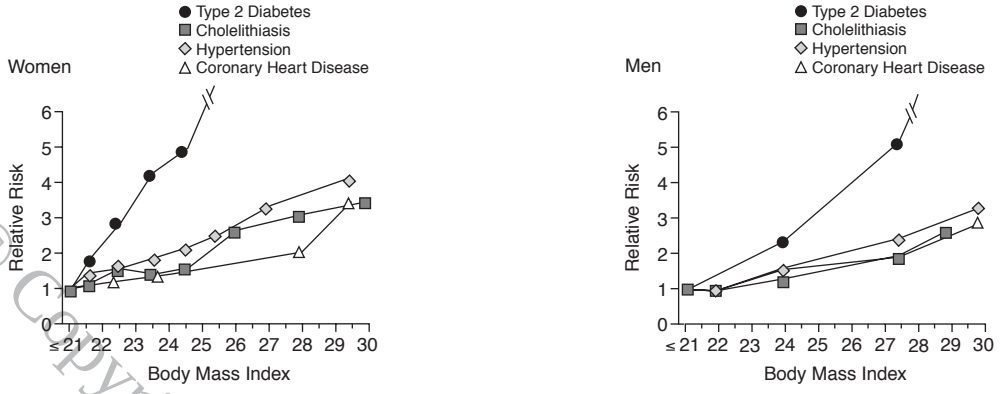
Small weight gains during adulthood are associated with significantly increased risks of many chronic diseases (Figure 5). At the same time, weight losses during adulthood can decrease the relative risks of some chronic diseases such as diabetes.

Hypertension. Two well-known studies show that weight gain is clearly associated with increases in blood pressure. In the Framingham Heart Study, obesity was shown to be one of the major determinants of hypertension in the general population.[18] The Nurses' Health Study showed that even fairly modest degrees of weight gain produce measurable increases in the risk for hypertension.[19] For example, women who gained approximately 5 to 10 lb (2.2–4.5 kg) over 2 or more years had a relative risk of developing hypertension of 1.38 (95% confidence interval [CI] = 1.28 to 1.48).

The age-adjusted prevalence of hypertension by BMI and sex is shown in Figure 6. The increase in prevalence of hypertension begins at relatively low levels of overweight.

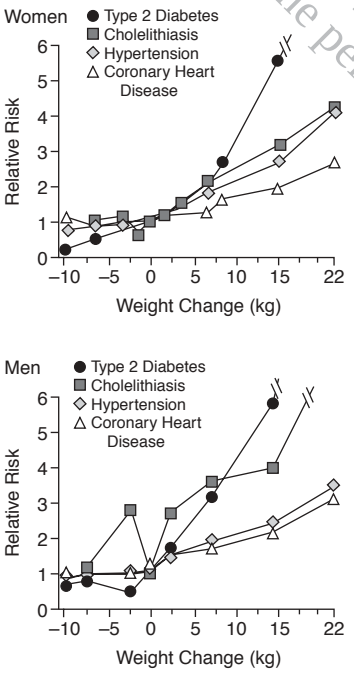
Dyslipidemia. The relationship between obesity and overweight and dyslipidemia is well established. Overweight and obesity are associated with elevated blood cholesterol levels (especially in women). Triglyceride and

Figure 4. Relation Between Body Mass Index Up to 30 kg/m^2 and the Relative Risk of Type 2 Diabetes, Hypertension, Coronary Heart Disease, and Cholelithiasis[a]



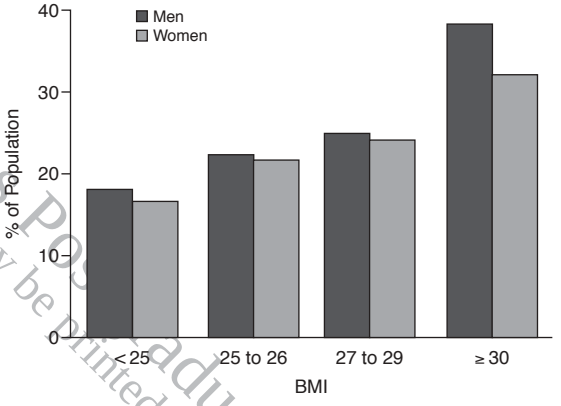
[a]Reprinted with permission from Willett et al.[15]

Figure 5. Relation Between the Change in Weight and the Relative Risk of Type 2 Diabetes, Hypertension, Coronary Heart Disease, and Cholelithiasis[a]



[a]Reprinted with permission from Willett et al.[15]

Figure 6. Age-Adjusted Prevalence of Hypertension (mean systolic blood pressure > 140 mm Hg, mean diastolic blood pressure > 90 mm Hg, or currently using antihypertensive medication) by Body Mass Index (BMI) and Sex[a]



[a]Reprinted with permission from the National Task Force on the Prevention and Treatment of Obesity.[10]

total cholesterol levels are usually higher in those with abdominal obesity (i.e., a waist-to-hip ratio of at least 0.8 in women and at least 1.0 in men).[20–24] Increasing BMI correlates negatively with high-density lipoprotein cholesterol levels and positively with low-density lipoprotein cholesterol levels.[20,21,24–27] The link between coronary heart disease and serum cholesterol is largely due to low-density lipoproteins.[1]

Coronary heart disease. Coronary heart disease and associated types of atherosclerotic disease (i.e., stroke, peripheral vascular disease) are the most significant problem associated with obesity and result from the impact of obesity on dyslipidemia, hypertension, increased insulin levels, and increased risk for type 2 diabetes mellitus. In fact, the American Heart Association has reclassified obesity as a major, modifiable risk factor for coronary heart disease.[28]

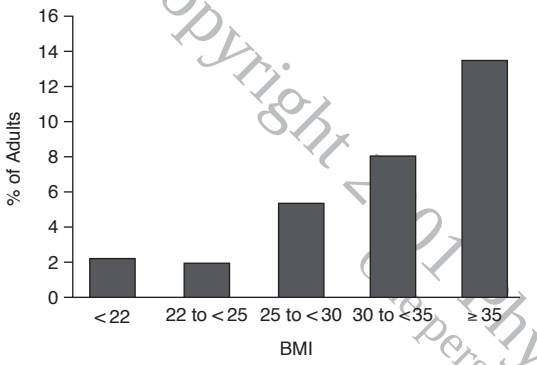
Overweight is a predictor of cardiovascular atherosclerosis independent of its effects on traditional risk factors. In fact, the increase in relative risk occurs at levels of overweight that are frequently considered clinically insignificant. For example, the risk is increased by 72% for fatal and nonfatal coronary heart disease in middle-aged

Table 3. Increased Risk of Stroke With Increasing Body Mass Index From the Nurses' Health Study[a]

Body Mass Index (kg/m^2)	Relative Risk of Stroke[b]	95% Confidence Interval
27–28.9	1.75	1.17 to 2.59
29–31.9	1.90	1.28 to 2.82
≥ 32	2.37	1.60 to 3.50

[a]Data from Rexrode et al.[30]
[b]Compared with those with a body mass index of < 21 kg/m^2.

Figure 7. Weighted Prevalence of Type 2 Diabetes Mellitus According to Body Mass Index (BMI) in Adults Aged 20 Years or Older[a]



[a]Reprinted with permission from the National Task Force on the Prevention and Treatment of Obesity.[10]

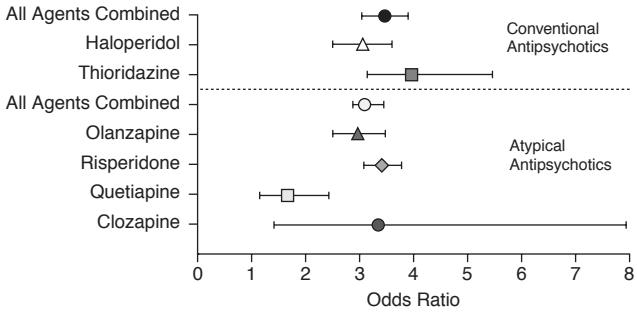
men with a BMI of 25 to 29 kg/m^2 compared with men having a BMI of < 23 kg/m^2.[29]

Stroke. The Nurses' Health Study showed that overweight may increase the risk of ischemic stroke but not hemorrhagic stroke.[30] Table 3 shows the increased risk of stroke with increasing BMI during 16 years of follow-up in 116,759 women.

Type 2 diabetes mellitus. As shown in Table 2, 61% of cases of type 2 diabetes mellitus may be attributed to obesity.[17] Using data from the Third National Health and Nutrition Examination Survey (NHANES-III), Must et al.[31] found a strong weight-dependent correlation between overweight and the development of type 2 diabetes mellitus. In fact, the increase in obesity in the past decade has been accompanied by a 25% increase in the prevalence of type 2 diabetes mellitus.[32] The prevalence of diabetes according to BMI is shown in Figure 7 and increases dramatically for BMI > 25 kg/m^2.

The association of some antipsychotic drugs with the development of diabetes mellitus is discussed in more detail in other articles in this supplement. However, all antipsychotics do not exhibit the same risk for the development of diabetes. For example, the relative risk of developing diabetes was examined in the Advance PCS prescription claim database of more than 300 million prescription claims per year for more than 50 million members.[33] The incidence of diabetes was determined using prescription claims for antidiabetic agents in the general population cohort and in those who also received a prescription for antipsychotic medication. When patients receiving conventional and atypical antipsychotics were compared, there was no significant difference in the risk of developing diabetes (relative risk = 0.966, 95% CI = 0.8 to 1.1, p = .6; Figure 8). At the same time, the relative risk of 1.7 for quetiapine was the lowest for all of the antipsychotics studied.

Figure 8. Odds of Diabetes Mellitus in Patient Cohorts Receiving Antipsychotic Drugs (N = 58,751) Relative to the General Patient Population (N = 50 million)[a]



[a]Data from Cavazzoni et al.[33]

Cancer. Increasing body weight is associated with an increased risk for various cancers such as colon and endometrial cancer.[34] A recent meta-analysis of the epidemiologic literature has shown that excess body mass accounts for 5% of all cancers in the European Union (or 72,000 cases of cancer annually).[35] The highest attributable proportions were for cancers of the endometrium (39%), kidney (25% in both sexes), and gallbladder (25% in men and 24% in women). The largest number of attributable cases was for colon cancer (21,500 annual cases), followed by endometrial (14,000 cases) and breast cancer (12,800 cases). The authors estimated that approximately 36,000 cases of cancer could be eliminated by reducing the prevalence of overweight and obesity in Europe by 50%.

Osteoarthritis. There is an increased risk of osteoarthritis in obese individuals due to both mechanical and inflammatory dysfunction. The increased risk has historically been considered a purely mechanical factor (i.e., the increase in weight exerts more pressure on the weight-bearing joints, causing more rapid deterioration).[36] However, an increase in osteoarthritis of the hands has also been observed in overweight and obese patients, possibly due to cytokines released from adipose tissue.[37] Overweight patients have a more inflammatory environment that may lead to osteoarthritis.[38,39]

Low back pain. In a study by Lean et al.[40] measuring the risk of various health outcomes associated with obesity, one third of men and women reported hindrance of

Table 4. Percentage of Patients in Different Categories of Body Mass Index (BMI) and Unadjusted Prevalence of Patients Whose Daily Life Was Affected Due to Low Back Pain in the Past 12 Months in Different Categories of BMI[a]

	BMI (kg/m^2)					
	Men (N = 2467)			Women (N = 3448)		
Variable	< 25	25–30	> 30	< 25	25–30	> 30
Percentage[b]	42.1	46.2	11.7	56.0	31.9	12.2
Daily business hindered	28.2	27.4	34.9[c]	25.3	30.2[d]	32.2[d]
Absence from work	25.4	23.0	27.6	18.8	23.2[c]	28.4[d]
Medical consultation	39.3	40.9	40.5	39.6	44.7[d]	45.7[d]
Job redundancy[e]	11.2	12.2	12.2	8.2	9.2	10.9
Job modification	8.7	8.3	8.3	7.0	7.7	3.2[c]

[a]Data from Lean et al.[40]
[b]Proportions of subjects in each category of BMI.
[c]Difference from a BMI lower than 25 kg/m^2, $p < .05$.
[d]Difference from a BMI lower than 25 kg/m^2, $p < .01$.
[e]Job redundancy equals retirement because of health reasons with disability pension.

daily business/absence from work due to low back pain, and more than 40% sought medical attention for their back pain. Again, the proportion of low back pain was significantly higher in those with higher BMI (Table 4).

Sleep apnea and respiratory disorders. Upper-body obesity is a risk factor for obstructive sleep apnea; those with a BMI of at least 30 kg/m^2 are at greatest risk.[41] Furthermore, it is well documented that the symptoms of sleep apnea improve with weight loss.[42]

Gallbladder disease. The risk for gallstones increases with higher body weight. For example, Stampfer et al.[43] observed a monotonic increase in gallstone disease risk with obesity so that there was a 7.4-fold increase in incidence in severely obese women (i.e., BMI ≥ 45 kg/m^2) compared with women who had normal weight (i.e., BMI < 24 kg/m^2).

Gynecologic abnormalities. Gynecologic abnormalities such as menstrual irregularities and infertility have been associated with increased body weight. A case-control study as part of the Nurses' Health Study showed that even mild increases in BMI at age 18 years resulted in an increased risk of ovulatory infertility.[44] Furthermore, maternal obesity is a significant risk factor for the development of gestational diabetes mellitus.[45,46]

Quality of life. Obesity and overweight significantly affect quality of life, especially in our modern physique-conscious society in which obesity is stigmatized and the obese are subject to discrimination. Despite the wealth of literature on associated morbidity with overweight disorders, few studies have looked at the functional impact of higher weight. However, 2 recent large-scale studies have addressed this issue. Coakley et al.[47] found that women (N = 56,510) aged 45 to 71 years with a BMI between 30.0 and 34.9 kg/m^2 experienced 10% lower function compared with women with a BMI between 22.0 and 23.9 kg/m^2. In fact, BMI was the single most important predictor of physical function, bodily pain, and impaired ability to work and was the second most important predictor of vitality after physical activity.

Fine et al.[48] studied more than 40,000 women aged 46 to 71 years by measuring health-related quality of life using the Medical Outcomes Study Short Form-36 (SF-36) health status survey (a self-administered, 36-item questionnaire). This was a longitudinal study over a 4-year period (1992–1996) that grouped women into the following categories: women whose weight remained within 5 lb (2.2 kg) of their baseline weight, women who lost 5 lb or more, and women who gained 5 lb or more. The results showed that weight gain more significantly impacted physical than mental health, based on the 7 health-related dimensions in the scale: physical functioning, vitality, bodily pain, limitations in role functioning due to emotional or physical problems, social functioning, and mental health. The impact of weight change was just as strong in women younger than 65 years as in those 65 years and older.

A small study of 38 mildly to moderately overweight women examined the efficacy of a lifestyle modification treatment program by measuring the effects on the Beck Depression Inventory, the SF-36, and clinical evaluations.[49] After a 13-week program of lifestyle physical activity or traditional aerobic activity, weight loss averaged 8.6 ± 2.8 kg (18.9 ± 6.2 lb). Patients reported significantly higher scores in 5 of the 8 domains of functioning on the SF-36. Again, the largest increases were seen in the areas of vitality, general health perception, and role-physical.

Economic Cost

Obesity and overweight have a high price in direct and indirect costs for both the patient and society. When considering the associated comorbidities as well, the economic and personal consequences increase exponentially. The direct costs associated with obesity are significant and growing—they now account for almost 6% of the national health expenditure in the United States.[17] Recent estimates indicate that the total cost attributable to obesity was $99.2 billion in 1995, and more than half was due to direct medical costs. Also, the number of physician visits related to obesity increased by 88% from 1988 to 1994. These estimates factor in the costs of treating other diseases attributable to obesity, such as type 2 diabetes mellitus; coronary heart disease; hypertension; gallbladder disease; breast, endometrial, and colon cancer; and osteoarthritis.

Indirect costs should not be overlooked, either. The same study of cost estimates in 1995 U.S. dollars showed that 39.2 million work days were lost, costing an additional $3 billion in lost productivity, all associated with obesity.[17]

Similarly, the pharmacotherapy costs for obesity-attributable diseases constitute a much higher percentage of total treatment costs than for other disease states. In

Table 5. A Guide to Selecting Appropriate Antiobesity Treatment[a]

	BMI (kg/m^2)				
Treatment	25–26.9	27–29.9	30–34.9	35–39.9	≥ 40
Diet, physical activity, and behavioral therapy	WC	WC	+	+	+
Pharmacotherapy	…	WC	+	+	+
Surgery	…	…	…	WC	+

[a]Reprinted with permission from the National Heart, Lung, and Blood Institute.[9] Abbreviation: WC = with comorbidities. Symbol: + = use of indicated treatment regardless of comorbidities. Prevention of weight gain with lifestyle therapy is indicated in any patient with a BMI ≥ 25 kg/m^2, even without comorbidities, while weight loss is not necessarily recommended for those with a BMI of 25–29.9 kg/m^2 or a high waist circumference, unless they have 2 or more comorbidities. Combined therapy with a low-calorie diet, increased physical activity, and behavior therapy provide the most successful intervention for weight loss and maintenance. Consider pharmacotherapy only if a patient has not lost 1 lb per week after 6 months of combined lifestyle therapy.

Table 6. Weight Loss Drugs[a]

Drug	Dose	Action	Adverse Effects
Sibutramine	5, 10, 15 mg; 10 mg po qd to start, may be increased to 15 mg or decreased to 5 mg	Norepinephrine, dopamine, and serotonin reuptake inhibitor	Increase in heart rate and blood pressure
Orlistat	120 mg; 120 mg po tid before meals	Inhibits pancreatic lipase, decreases fat absorption	Decrease in absorption of fat-soluble vitamins; soft stools and anal leakage

[a]Reprinted with permission from the National Heart, Lung, and Blood Institute.[9] Ephedrine plus caffeine, and fluoxetine have also been tested for weight loss but are not approved for use in the treatment of obesity. Mazindol, diethylpropion, phentermine, benzphetamine, and phendimetrazine are approved for only short-term use for the treatment of obesity. Herbal preparations are not recommended as part of a weight loss program. These preparations have unpredictable amounts of active ingredients and unpredictable, and potentially harmful, effects.

a study of a managed care organization patient cohort (N = 17,118), the total drug costs for severely obese patients (i.e., BMI ≥ 35) were twice the costs for those with a BMI of 20 to 25.[50] The greatest costs were for drugs to treat hypertension, diabetes, and cardiovascular diseases as well as antidepressants and respiratory and ulcer medications. These results indicate that the drug costs for treating obese patients are significantly higher than for nonobese patients.

TREATMENT OF OBESITY

Given the billions of dollars spent on weight-loss programs and products, it is clear that the therapeutic choices for treating obesity and overweight are many and can be effective in the short term. Ironically, one of the rate-limiting steps in treating obesity aggressively is the underreporting and undertreating of obesity by physicians. Stafford et al.[51] performed serial cross-sectional surveys of 55,858 adult physician office visits from the National Ambulatory Care Surveys and NHANES-III. Their results show that physicians reported obesity in only 38% of their obese patients, but those with comorbidities were treated more aggressively. Still, weight-loss counseling occurred at only 52% of visits. As noted by the investigators, barriers may include lack of skills needed to help patients lose weight, failure to prioritize obesity as a medical issue, lack of reimbursement for obesity-related activities, and failure to involve other ancillary providers (dietitians, physical therapists, mental health professionals). Psychiatrists may be even more susceptible to these obstacles.

Table 5 summarizes the recommended treatments for various BMI categories. In short, diet, exercise, and pharmacotherapy are appropriate for obese individuals. Diet, exercise, and behavioral therapy may be considered in those with a BMI up to 29.9 kg/m^2 if comorbidities are present. Pharmacotherapy may also be considered in those with a BMI of 27 to 29.9 kg/m^2 if comorbidities are present. Surgery is appropriate only in individuals with the highest BMI values.

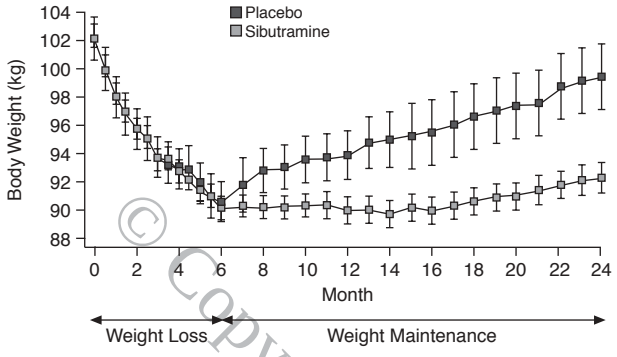
On a long-term basis, however, the results of dietary therapy are more discouraging. No commercial, clinical, or research program or model has been shown to be uniformly effective in long-term weight loss for obese patients. In fact, exercise has been shown to be critical to weight management, although the longest follow-up period in a study was only 5 years. Miller[52] proposes a new weight paradigm for obese patients in which the focus would shift from a particular weight or BMI endpoint to rethinking body image and implementing a healthy lifestyle. This new approach was also supported by the American Dietetic Association. Long-term treatment is clearly important because obesity is a lifelong, relapsing disorder.[53]

Pharmacotherapy

Two drugs approved for long-term treatment of obesity are orlistat and sibutramine. Table 6 lists the mechanism of action for drugs prescribed for the treatment of obesity and some of the more common side effects.[1] These drugs, however, have not been shown to be safe or effective in patients who are currently taking conventional or atypical antipsychotics.

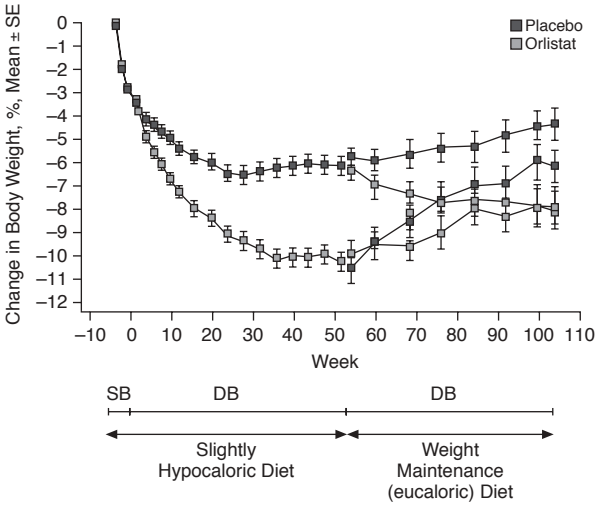
Sibutramine produces its therapeutic effects by inhibition of norepinephrine, serotonin, and dopamine reuptake. In 11 double-blind, placebo-controlled obesity trials with durations of 12 to 52 weeks, a dose-dependent significant weight loss was observed in sibutramine-treated patients compared with placebo-treated patients over the dose range of 5 to 20 mg once daily.[54] In a long-term, placebo-controlled study, 43% of those taking sibutramine for 18 months were able to maintain up to 80% of their original weight loss compared with 16% in the placebo group (Figure 9).[55] Beneficial changes in lipids, insulin, and uric

Figure 9. Mean Body Weight Changes During Weight-Loss and Weight-Maintenance Phases of Treatment With Sibutramine[a]



[a]Reprinted with permission from James et al.[55]

Figure 10. Mean Percentage Change in Body Weight From Start of Single-Blind Lead-In Until 2-Year Examination in Orlistat and Placebo Groups[a]



[a]Reprinted with permission from Sjostrom et al.[57] Abbreviations: DB = double-blind, placebo-controlled treatment during years 1 and 2; SB = single-blind lead-in period of 4 weeks. Initial body weight was close to a mean of 100 kg (222 lb) in both groups—percentage change therefore approximately matches kilograms lost.

acid levels achieved during the first 6 months were maintained with sibutramine but not with placebo.[54]

The adverse events were considered to be predictable based on the mechanism of action of the drug. The most common adverse events reported in placebo-controlled studies were headache (30.3%), dry mouth (17.2%), anorexia (13.0%), constipation (11.5%), and insomnia (10.7%).[54] Of note, potentially clinically significant increases in blood pressure were seen, but were infrequent, and would be detectable with routine monitoring of blood pressure. Sibutramine is contraindicated in patients with uncontrolled hypertension, coronary heart disease, or other vascular disease.[54] Also, caution is advised if sibutramine is administered concurrently with other psychotropic drugs.[54]

Orlistat is a nonsystemically acting drug that works locally to inhibit gastrointestinal lipases and thereby blocks or prevents the absorption of about 30% of dietary fat. A multicenter trial[56,57] demonstrated that after 1 year of treatment with orlistat, 120 mg 3 times a day, patients lost 10.2% of their starting weight compared with 6.1% in the placebo group. During year 2, patients continued on orlistat treatment regained half as much weight as those taking placebo. Positive effects on lipid levels and glucose and insulin concentrations were observed, and fewer orlistat-treated patients regained weight during the second year of treatment compared with placebo-treated patients (Figure 10).[56,57]

The most commonly observed treatment-emergent adverse events associated with the use of orlistat in clinical trials were gastrointestinal symptoms primarily due to the mechanism of action. These adverse reactions were generally mild and transient and decreased in frequency during the second year of treatment. The incidences of the most commonly observed adverse events during the first year of treatment (N = 1913 patients) were oily spotting (26.6%), flatus with discharge (23.9%), fecal urgency (22.1%), fatty/oily stool (20%), oily evacuation (11.9%), increased defecation (10.8%), and fecal incontinence (7.7%).[58] Fiber supplementation may mitigate the gastrointestinal side effects.

Surgery

Obesity surgery should be considered in patients with a BMI greater than 40 or between 35 and 40 who fail other methods of treatment if serious obesity-related complications are present.[59] Careful screening of candidates is required if the patient is to benefit from the procedure. Surgical candidates must be motivated and well informed about the risks of the procedure as well as the changes in their lives that will occur as a result of the procedure and its long term effects. These changes may be relatively minor, such as the need for long-term treatment with vitamin and mineral supplements, or could include chronic vomiting or diarrhea after meals.

In general, weight loss of 60% to 80% of the excess is achieved, reaches its maximum at 18 months to 2 years, with some weight regain up to the fifth year postoperatively and weight stability thereafter. Unfortunately, in some surgical series up to 20% of patients ultimately regain all lost weight.

Obesity surgery is best performed in specialty centers accustomed to performing procedures on high-risk obese patients. Long-term follow-up is required to ensure the best results and proper nutrition in the postsurgical patient.

The surgical approaches used to treat obesity include the vertical banded gastroplasty, also known as gastric stapling or banding, in which a 30-cm^3 pouch with a re-

stricted outlet is constructed along the lesser curvature of the stomach reducing the capacity of the stomach 100-fold, and the gastric bypass, which involves constructing a small proximal gastric pouch as with the gastroplasty whose outlet is a limb of small bowel of varying lengths, as in a Roux-en-Y gastrojejunostomy. More weight is lost with this procedure than with gastroplasty, but the risk of complications is greater. Calcium, iron, and vitamin B_{12} supplementation is recommended long-term. Of note, although technically challenging, laparoscopic gastric bypass surgery is now being performed on a regular basis. Gastric bypass produces weight losses of approximately one third of the initial body weight.[60]

CONCLUSIONS

Obesity and overweight are now global epidemics, with the most pronounced prevalence in the United States. No longer viewed as simply cosmetic problems, the serious and sometimes life-threatening ramifications of the associated comorbidities have been shown in the literature. Despite the limitations of some of the epidemiologic and pharmacoeconomic studies, the literature also shows that weight loss reduces the risk for those comorbidities, at least in the short term. Any treatment plan for weight reduction will need to be multifaceted for either short-term or long-term success and must take the patient's personal circumstances into account.

Overweight and obesity are just as prevalent or perhaps more prevalent in patients with schizophrenia, and the standard treatment practices for these patients are complicated because of their unhealthy lifestyle habits and propensity for significant weight gain associated with antipsychotic drugs. Type 2 diabetes mellitus is also a particular problem for this patient population. However, some antipsychotics may be associated with a lower relative risk for the development of obesity and diabetes than other antipsychotics.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), orlistat (Xenical), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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