Continuing Education

Obesity and Weight Loss

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Universal Activity #: 0178-0000-17-106-H04-P | 1.25 contact hours (.125 CEUs)

Initial Release Date: December 4, 2017 | Expires: June 30, 2020

Objectives

- Identify the classification of obesity based on body mass index
- Identify at least two medications and two environmental factors that are risk factors for obesity
- List at least three health consequences of obesity
- Discuss the Alabama State Laws regarding BMI, body fat content, and waist circumference in regard to prescribing prescription weight loss medications

Introduction

Today, most people are busy with their daily lives, and have difficulty finding enough time to eat and live a healthy lifestyle. Unhealthy foods high in fat and low in fiber and vitamins such as fast food and junk food, along with lack of exercise, contribute to the high risk of becoming overweight and obese. These individuals may experience decreased productivity at work, low self-esteem, and increased risk for many serious diseases and health conditions such as heart disease, stroke, type 2 diabetes and certain types of cancer.[1] As a consequence, these issues can result in poorer health, quality of life and financial status.

The prevalence of obesity has more than doubled since 1980 around the globe, and more than one-third of adults are reported to be obese in America.[1,2] In 2015 Alabama, Louisiana, Mississippi, and West Virginia showed the highest rates of obesity (≥35%) compared to other states in the U.S.[3] Middle aged adults 40 – 59 years old (40.2%) have the highest prevalence of obesity followed by elderly ≥ 60 years old (37%), and younger aged adults 20 – 39 years old (32.3%).[1] The highest rate of obesity is in Non-Hispanic African Americans (48.1%) followed by Hispanic Americans (42.5%), non-Hispanic White Americans (34.5%), and non-Hispanic Asian Americans (11.7%). [1]

The terms "overweight" and "obese" are defined as "abnormal or excessive fat accumulation that may impair health".[2] Body Mass Index (BMI) has long been considered an indicator of excess body fat; however, many physicians are calling its preciseness and usefulness into question because BMI measures excess weight rather than excess fat.[4]

BMI is defined as weight in kilograms divided by height in meters squared (kg/m2).[2] BMI between 25 and <30 is considered "overweight". A BMI between 30 and 35 is considered "class 1 obese", and a BMI between 35 and <40 indicates "class 2 obese".[5] BMI >40 indicates "class 3- extreme or severe obesity".[5]

Waist Circumference (WC) is another clinical indicator to assess obesity that measures the circumference between the last rib and the top of the iliac crest and is recorded in inches or centimeters.[6] Men with a WC >40 inches (>102 cm) and women with a WC >35 inches (>89 cm) are considered "high-risk WC".[6]

Waist-to-hip ratio (WHR) is an additional clinical indicator that measures body fat distribution. The ratio can be calculated when the waist circumference is divided by the hip circumference. By doing so, it provides an index of both subcutaneous and intra-abdominal adipose tissue, known as "abdominal fat."[7]

In recent years, there has been increased skepticism about using BMI, suggesting that it is not the best clinical indicator to measure body fat. The 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults used BMI as the current cut-off point to identify obesity indicating that being overweight (BMI ≥25.0 kg/m^2) and obese (BMI ≥30 kg/m^2) are linked to an increased risk of combined fatal and nonfatal coronary heart disease.[8]

Some researchers have found that weight-hip-ratio (WHR) is a more precise indicator to predict the risk of cardiovascular disease and

premature death compared to BMI.[9] Sahakyan KR et al. found that adults with a normal BMI but a large WHR have the lowest long-term survival and an increased risk for CV mortality compared to adults with normal fat distribution regardless of BMI level.[10] Increased fat around the waist can increase the risk of inflammation, diabetes, and CV disease.[11] In another study, Cerhan JR et al. found that higher waist circumference (WC) has a positive association with higher mortality at all levels of BMI from 20 – 50 kg/m^2 for men and 15 – 50 kg/m^2 for women. [12] The results of these two recent trials support the opinion that obesity-induced morbidity and mortality is more associated with visceral fat, the fat inside the abdomen, rather than total body fat which is reflected by the BMI.

According to the World Health Organization (WHO), experts recommend that BMI, waist circumference (WC) and waist-hip ratio (WHR) are all predictive of the risk of chronic disease. For this reason, any WC and WHR cut-off points could be used alone or in conjunction with BMI. [7] Based on the recommendations from the WHO, abdominal obesity is defined as WHR ≥0.90 for males and ≥0.85 for females, and these cut-off points indicate a substantial increased risk of metabolic syndrome. Metabolic syndrome is a condition characterized by "glucose intolerance, IGT [impaired glucose tolerance] or diabetes mellitus, and/or insulin resistance together with two or more of the following: abdominal obesity, raised arterial pressure, raised plasma triglycerides (TG), and microalbuminura." [7] The recommended sex-specific cut-off points of WC includes > 37 inches (94 cm) for men and > 31.5 inches (80 cm) for women for increased risk of metabolic complications, and > 40 inches (102 cm) for men and > 34.6 inches (88 cm) for women for substantially increased risk of metabolic complications. [7] The WHO cut-off points and risk of metabolic complications are outlined in Table 1.

Table 1. **World Health Organization (WHO) Cut-off points and risk of metabolic complications**[7]

Indicator	**Cut-off points**	**Risk of metabolic complications**
Waist Circumference (WC)	>37 inches (94 cm) (M); >31.5 inches (80 cm) (W)	Increased
	>40 inches (102 cm) (M); >34.6 inches (88 cm) (W)	Substantially increased
Waist-Hip-Ratio (WHR)	≥0.90 (M); ≥0.85 (W)	Substantially increased

*M, men; W, women

Risk factors

There are various factors that can cause one to become overweight: one is associated with family history and genetics; others include acquired factors such as environment, medical conditions, and medications.

Although many single-gene mutations that cause extreme obesity have been found, it is reported that these mutations cause obesity in a very small percentage of cases. [6] For instance, changes in the melanocortin 4 receptor (MC4R) is most common, but their impaired functions contribute to only a small fraction (≤5%) of obese people in diverse ethnic groups.[13] It is known that the brain controls food intake by coordinating signals transmitted by hormones (e.g., leptin, insulin, and ghrelin) and responding to those signals in the body: either by increasing consumption of food and decreasing energy use, or vice versa. [13] Obesity-causing gene mutations can change the level of the brain's response to those signals from adipose tissue, the pancreas, and the digestive tract. [13] By doing so, genetic factors may change the level of hunger, the amount of food converted into

energy and the amount of calories burned during exercise. [13]

As technology and the economy have developed over the past decades, the rate of obesity has greatly increased which is mostly attributed to increased accessibility and the food supply. [6] Sedentary working styles and busy daily lives have led to a reduction in daily exercise and an increase in consumption of foods high in fat. Family lifestyle is one of the major environmental factors that can increase the risk of being obese since family members share similar diet patterns and activity habits.[14] A person's socioeconomic status can also have a strong influence on the risk of being obese.[14] If one does not have enough money to buy healthy foods or lives in a dangerous area, he or she is more likely to gain weight which can lead to obesity. [14] Lack of sleep is another factor that can contribute to becoming obese. [14] Sleep deprivation can give rise to changes in hormones that stimulate one's appetite, which can result in weight gain. [14] Other than the environmental factors mentioned above, cultural factors and religious beliefs may contribute to the increase in the prevalence of obesity in society. [6] For instance, many traditional Japanese foods, such as raw fish, steamed brown rice, seaweed, sea vegetables, and miso soup, are high in complex carbohydrates and vitamins and low in fat and calories. Meanwhile, many American foods have been replaced with foods high in fat and low in fiber and vitamins attributed to increased food consumption in restaurants, increased snacking time between meals, and increased availability of fast foods.[15]

Obese people often have medical conditions associated with weight gain such as growth hormone deficiency, insulinoma, and leptin deficiency.[6] Patients with insulinoma suffer from hypoglycemia resulting from endogenous hyperinsulinism.[16] Hypoglycemia can cause hunger and weight gain, which accounts for 20 – 40 % of reported weight gain among these patients.[17] It is noted that physical activity and low caloric diet can actually worsen symptoms of insulinoma. [17] A sufficient amount of growth hormone and leptin sends signals to the brain inhibiting hunger when enough energy is stored in the adipose cells.[18] The insufficient growth hormone and leptin production or a resistance to the effects of these hormones in the body that is seen in growth hormone or leptin deficiency also increases the risk of obesity.[18,19] Despite the fact that hypothyroidism is often considered a medical condition associated with weight gain, it rarely causes significant weight gain but causes fluid retention instead.[6] The clinician should recognize that there are medical conditions that can potentially cause weight gain when they assess patients for obesity, and obese patients are recommended to have physical examinations, including an assessment for secondary causes of weight gain such as genetic syndromes.[6]

In some cases of obesity, the side effects of prescription medications are the cause of weight gain. Examples of these medicines include anticonvulsants (eg, carbamazepine, gabapentin, pregabalin, and valproic acid), antidepressants (eg, mirtazapine and tricyclic antidepressants), atypical antipsychotics (eg, clozapine, olanzapine, quetiapine, and risperidone), conventional antipsychotics (eg, haloperidol), and hormones (eg, corticosteroids, insulin, and medroxyprogesterone).[6] Individuals with Cushing syndrome or mental illness are prone to gaining weight not because of the medical condition itself but because of adverse reactions from taking corticosteroids and anti-psychotics [6] Although weight gain is a side effect of many medications, the exact mechanisms associated with weight gain are unknown in most cases.[6] If patients seem to experience drug-induced weight gain, their medications should be re-evaluated and modified, or discontinued if possible.

Other factors that can induce weight gain are quitting smoking and age. With advancing age people are more likely to gain weight due to a loss of muscle mass which requires fewer

calories and reduced physical activity. Quitting smoking is also correlated with weight gain. [14] Although people may become obese after tobacco cessation, due to increased food consumption that usually replaces the smoking habit, they may benefit from quitting smoking in terms of health in the long run. [14] The risk factors for being overweight and obese are summarized in Table 2.

Table 2. **Risk Factors for Obesity**		
Congenital factors	Genetic influences	• Gene mutations
Acquired factors	Environmental factors	• Abundant and easily accessible food supply • Sedentary lifestyle • Family lifestyle • Socioeconomic status • Cultural factors • Religious beliefs • Lack of sleep
	Medical conditions	• Growth hormone deficiency • Insulinoma • Leptin deficiency • Genetic syndromes
	Medications	• Anticonvulsants (eg, carbamazepine, gabapentin, pregabalin, and valproic acid) • Antidepressants (eg, mirtazapine and tricyclic antidepressants) • Atypical antipsychotics (eg, clozapine, olanzapine, quetiapine, and risperidone) • Typical antipsychotics (eg, haloperidol) • Hormones (eg, corticosteroids, insulin, and medroxyprogesterone)
	Miscellaneous	• Quitting smoking • Age

Clinical Consequences of Obesity

High blood pressure

High blood pressure is correlated with obesity and being overweight.[20] Extra fat tissues necessitate more blood circulating to the whole body in order to supply enough oxygen and nutrients to those additional tissues.[21] People with a large body size are more likely to have increased blood pressure because their heart must pump harder to supply blood to all their body tissues, including extra fat cells. [20]

Heart disease

People who are obese or overweight often eat unhealthy foods high in fat which increase cholesterol levels, resulting in dyslipidemia. High blood cholesterol builds up the fatty acid deposits in blood vessels and narrow arteries. [21] These narrowed arteries increase the risk of coronary artery disease such as angina or a heart attack. Also, if an intracranial vessel is occluded by blood clot formation in the narrowed arteries, a stroke may occur. [21]

Diabetes

Obesity is one of the major etiologies of type 2 diabetes mellitus (T2DM). [21] The insulin hormone is produced by beta cells of the pancreas, but being overweight or obese causes the body cells lose their ability to respond to

this insulin hormone. Insulin insensitivity decreases the ability of the body's cells to take up glucose from the blood resulting in hyperglycemia. [20] Consequently, beta cells of the pancreas must work harder to reduce the increased blood sugar level, leading to a loss of their function to produce insulin. [6]

Cancer

Weight gain during adulthood may increase the risk of developing certain cancers.[20] Even though the mechanism is not exactly identified, it is reported that hormones which induce cell growth may be released by fat cells.[20] Women who are overweight or obese have a higher risk of having breast cancer and endometrial cancer while men who are overweight or obese have a higher risk of prostate cancer.[21] Both genders who are overweight or obese are prone to have a higher risk of colon cancer or gallbladder cancer.[21]

Sleep Apnea

Obesity is the most significant risk factor of developing sleep apnea.[20] Obese people with fat stored around their neck may have a smaller airway to breathe, which can cause difficulty in breathing, stertorousness (snoring), or discontinuation of breathing for short periods of time. These interrupt sleep throughout the night and cause sleepiness during the day. This sleep apnea is reported to result in difficulty concentrating and even heart failure. [20]

Osteoarthritis

Being overweight or obese can adversely affect the joints of the hands, knees, hips, and lower back.[20] Extra pressure exerted on these joints and cartilage can cause them to wear out more quickly, leading to pain and stiffness in the joints. Extra body fat may also cause inflammation in the joints, another risk factor for osteoarthritis. Obese people are not recommended to have joint replacement surgery since artificial joints are reported to increase the risk of the joint loosening and causing further joint damage.[21] In addition, patients with high BMI are more likely to have the increased risk of periprosthetic joint infection (PJI) after having total joint arthroplasty (TJA).[22] Some studies found that BMI >40 kg/m2 (obese) increases the risk of PJI by 3.3 times, and BMI >50 kg/m2 (morbidly obese) increases the risk of PJI by 21 times compared with a normal BMI.[23, 24] Currently, there is no absolute cut-off point with respect to BMI prior to joint replacement surgery; patients should still have a BMI <40 kg/m2 with optimal nutrition status before going through joint replacement surgery.[22]

Fatty liver disease

Fatty liver disease, also called nonalcoholic steatohepatitis (NASH), often occurs in people who are middle-aged, overweight or obese, and/or diabetic.[20] If the liver is severely damaged because of fat deposit in the liver, it can result in cirrhosis, or even liver failure. It is reported that weight loss may improve results in liver function tests and reverse the progression of liver disease to some degree.[20]

Pregnancy Issues

Weight gain may cause health problems in both mother and baby during pregnancy.[20] Obese mothers are at increased risk of developing gestational diabetes and pre-eclampsia, and/or requiring a C-section during childbirth. In addition, either obese babies or obese mothers have higher risk of experiencing a premature birth, stillbirth, and neural tube defects (defects of the brain and spinal cord) Mothers and babies who gain too much weight during pregnancy are prone to staying obese even after childbirth.[20]

Psychosocial effects

If obese people live in communities where the standard of beauty is to be thin, they often tend to have various disadvantages. [21] For example, they are considered to be lazy and/or weak regardless of the cause of being obese. Due to the social bias against obese people, they tend to have difficulty setting a high standard for jobs which leads to a lower income. [21] They also have difficulty starting or continuing romantic

relationships. These consequences can result in obese people having low self-esteem or mental concerns such as depression, binge-eating disorder, or delusion of persecution. A growing antipathy towards overweight people may promote bias, discrimination, and even torment. [21]

Respiratory complications

Excessive fat in the chest wall and abdomen may make obese people suffer from respiratory complications, which result from decreased lung volume, altered respiratory pattern and reduced compliance of the respiratory system.[25] As a result, these people can often experience a ventilation perfusion abnormality, marked by hypoxia with normal arterial pCO_2 (partial pressure of carbon dioxide). In addition, they may suffer from reduced vital capacity and total lung capacity. [25]

Nonpharmacologic Therapy – Lifestyle Modifications

General Approach to Treatment

In order to accomplish meaningful weight loss goals, treatment plans must incorporate a comprehensive lifestyle intervention that includes a healthy diet, adequate physical activity and behavioral modifications (which may or may not include pharmacotherapy).[8] Once BMI and/or WC has been measured and accompanying risk factors established, the readiness of the patient to engage in weight loss efforts and any barriers to success should be assessed. Proper counseling on the potential health consequences of continued excess body weight and the benefits that can be gained with appropriate weight management should be done. Weight loss requires a tremendous effort on the part of the patient to make these lifestyle changes and comply with the treatment plan. If any reluctance by the patient is noted, early counseling can decrease the likelihood of frustration for the patient, clinician, and possibly family members. This can lead to a significant change in motivation and desire to lose weight and also improve compliance. Once it is determined the patient is properly motivated, specific weight loss goals should be established. For most patients, a weight loss goal of 5-10% of initial weight is reasonable.[8]

Nonpharmacologic Treatment

According to the Endocrine Society Clinical Practice Guidelines for the Pharmacological Management of Obesity, the first-line therapy for all patients with a BMI ≥ 25 kg/m^2 is the combination of reduced caloric intake, increased physical activity, and behavioral modification.[26] It should be noted, however, that the AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults do not recommend weight loss treatment until the patient has a BMI ≥ 30 kg/m^2 unless that patient has BMI 25-29.9 kg/m^2 AND cardiovascular risk factors.[8]

Reduced Caloric Intake

The cornerstone of weight loss is reduced caloric intake through adherence to a low-calorie diet (LCD). This diet should provide a daily calorie deficit of 500-750 kcal/day. This will correlate to a total of 1200-1500 kcal/day for women and 1500-1800 kcal/day for men.[8] Adherence to a LCD has been shown to result in an average weight loss of 8% after 6 months.[27] Very-low-calorie diets that provide less than 800 kcal/day are rarely recommended and should only be done by trained practitioners in a medical care setting where medical monitoring and high-intensity lifestyle intervention can be provided. This is due to the rapid rate of weight loss and potential for health complications, such as gallstones and malnutrition.[8] Although very-low-calorie diets often result in significant early weight loss, these results are extremely difficult to maintain due to inability to maintain compliance.[28]

There are many diet and nutrition plans available to help patients maintain this reduced caloric intake, and the guidelines allow the patient to choose from many evidence-based diet plans. These include moderate energy-deficient diets (eg, Weight Watchers and Jenny

Craig), vegetarian-based (eg, Omish), and low carbohydrate plans (eg. Zone and Atkins).[8] Short-term results are significant for most diet plans, but long-term weight loss and management is difficult due mostly to lack of adherence. Therefore, the choice of diet plan should be patient-specific and based on patient preference, health status, and ability to comply with restrictions of the diet.[8] A meta-analysis of 48 clinical trials assessed the efficacy of various popular named diets (e.g., Atkins, Weight Watchers, and Zone). The conclusion showed that the difference in weight loss among the diets are not clinically significant. For example, the Atkins diet resulted in an estimated weight loss of only 1.71 kg more than the Zone diet at 6-month follow-up (95% CI, 0.35 to 3.09 kg).[29] This observation further shows that the exact composition of the diet may not be as important as the ability of the patient to consistently adhere to the reduced caloric consumption.

Increased Physical Activity

Increased physical activity is an integral component of any weight loss strategy. Increasing physical activity alone (not also reducing caloric intake) only results in modest weight loss - only 2.9 ± 0.4 kg (6.38 ± 0.9 lb) over 15 weeks.[30] Yet, when it is combined with a LCD, it can increase weight loss and improve obesity-related comorbidities and cardiovascular risk factors.[8, 27] The 2013 AHA/ACC/TOS Guidelines recommend 30 minutes of moderate physical activity per day, on most days of the week.[8] Greater levels (i.e. 200-300 min/week) may be needed for increased weight loss and to maintain weight loss. Advise patients to start slowly with any exercise program and increase intensity gradually. Also, all obese patients should undergo a complete medical evaluation before starting any physical activity program.

Comprehensive Lifestyle Intervention

Comprehensive lifestyle intervention is a compilation of reduced caloric intake, increased physical activity and behavioral modification. Current obesity guidelines recommend this type of program to help patients be more adherent to the chosen LCD and increased physical activity per week. It is recommended that a patient become involved in an on-site, high intensity behavioral counseling session with a trained clinician on at least 14 occasions in a 6-month time period. Those who have lost weight during the first 6 months are recommended to continue to participate in a comprehensive lifestyle program.[8] The purpose of these programs is to help patients choose lifestyles that promote a safe and sustained weight loss. Many use self-monitoring of diet and exercise to increase patient awareness of behavior and to improve upon compliance and motivation. Clinical studies assessing the efficacy of comprehensive lifestyle interventions that include a LCD, increased physical activity and in-person behavioral counseling sessions reported an average weight loss of 8kg (17.6 lbs) in 6 months.[8] These programs are offered through bariatric physicians, as well as commercially through popular diet programs such as Weight Watchers and Jenny Craig.

Weight Loss Programs

State-Wide Programs

Scale Back Alabama[31]
Cost: Free
A program geared toward adults to develop a healthier lifestyle that includes opportunities to compete as teams to win prizes. The program even has a free app to create your own profile to track progress toward goals. For more information, visit: scalebackalabama.com.

Health Insurance Programs

Individuals should check with their health insurance provider to see if they offer free programs to help with weight loss. Some programs offer incentives to meet fitness goals. One example is Blue Cross Blue Shield of Alabama (BCBC-AL) Walking Works program.[32] Walking Works is a free program in which BCBS-AL members can enroll to track and manage fitness goals. The program has an app that can

be synced to a fitbit device to track steps or a pedometer can be purchased from BCBS at a reduced cost. BCBS members can find out more at: bcbsal.org

National Programs

Real Appeal[33]
Cost: Free
A program that individuals or companies can enroll in for better health outcomes. United Healthcare uses this program for their members which includes resources and access to coaches for real outcomes.

Prescription Medications for Weight Loss

There are several classes of FDA approved prescription weight loss drugs which include: gastrointestinal lipase inhibitors, serotonin 2C receptor agonists, a combination of phentermine-topiramate, naltrexone-bupropion combination, glucagon-like peptide-1 antagonist, and noradrenergic agents.[6] These agents have various mechanisms of action with accompanying varying efficacies. Generally, over half of the patients on these agents, accompanied with diet and exercise, tend to lose at least 5% of their body weight within a year. Table 3 provides a literature summary of the average weight loss achieved as well as the percentage of patients who achieved a 5, 10, or 15% weight loss with the available prescription weight loss agents during clinical trials.

None of the prescription weight loss drugs are recommended in pregnancy. alli® is the only FDA-approved OTC weight loss agent.[34] Many of the agents have specialized dosing and administration instructions. Table 4 summarizes dosing and major patient counseling points for the FDA-approved weight loss drugs.

Phendimetrazine (Bontril), phentermine (Adipex-P, Lomaira), diethylpropion, and benzphetamine are noradrenergic agents that stimulate the CNS to act as an appetite suppressant.[35] These agents have specific administration regarding meals which can be found on Table 4. Benzphetamine should only be used short-term (8-12 weeks).[35]

Weight loss drugs should be used with caution in diabetic patients (hypoglycemia) as well as renal and hepatic impairment. These agents may worsen depression, cause kidney stone formation, increase blood pressure, cause dizziness and constipation, and many should be used on a regular schedule which may include skipped doses. [35] See Table 4 for additional agent-specific information and patient counseling.

Herbals and Supplements

Although there are no rigorous studies showing their efficacy, many herbals have been used for weight loss. As a health care provider, it is important to know that many herbal weight loss products contain many ingredients in both unidentified and varying amounts. The herbal agent, which may be identified on the label as the scientific name or common name, can be important to recognize drug interactions or ADRs which may lead to poor patient outcomes. [36] See Table 5 for a list of common herbal agents and their suggested mechanisms.

Risks of Herbals

Stimulants (bitter orange and caffeine products) can produce various side effects. Bitter orange has cardiovascular complications such as hypertension, and although there is no reported incidence, there is a possibility of MI, stroke and seizures. [36] Caffeine can also cause GI problems (nausea and distress) and should not be used in those with gastric ulcers. Caffeine can also cause headaches, insomnia, anxiety, and heart palpitations. Also use caution in patients with renal disease, hyperthyroidism, prone to muscle spasms, and those on anticoagulation medication. [36] For details on specific agents, see Table 5.

Table 3. **Efficacy of Prescription Weight Loss Drugs**

Study Design		Comparator Drugs	Results					Patient Characteristics	ADRs
					% of Participants Who Lost:				
			BW* Change	% Change in BW	≥5%	≥10%	≥15%		
Naltrexone/Bupropion (Contrave)	COR-I: Multicenter (34 sites), randomized, double-blind, phase 3 study; also with low-calorie diet and exercise for 56 weeks[37]	Sustained-release (SR) Naltrexone 32 mg/ SR Bupropion 360 mg (n=296)	ND**	-8.1% (BW)	62%	34%	17%	Mostly white females, average 99kg, BMI of 36, dyslipidemia (50%)	Nausea (~30% in each group), headache (~14% in naltrexone groups), constipation (~15% in both naltrexone groups). Slight decrease in BP and slight increase in pulse in both naltrexone groups.
		SR Naltrexone 16 mg/ SR Bupropion 360 mg (n=284)	ND	-6.7%	55%	30%	14%		
		Placebo (n=290)	ND	-1.8%	23%	11%			
	COR-II: Randomized, double-blind, phase 3 trial [38]	SR Naltrexone 32 mg/ Bupropion 360 mg (Completed 28 Weeks) (n=619)	-7.6 kg	-7.8% BW	68.8%	35.7%	13.4%	Mostly white females, average age 44 years, same characteristics as COR-I.	ND
		Placebo (28 Weeks) (n=319)	-2.5 kg	-2.4% BW	22.23%	9.4%	2.2%		
		SR Naltrexone 32 mg/ Bupropion 360 mg (56 Weeks) (n=434)	-7.9 kg	-8.2% BW	64.9%	39.4%	18.9%		
		Placebo (56 Weeks) (n=267)	-1.5 kg	-1.4% BW	21.7%	7.9%	3.4%		
	Sub-study of Phase 2 trial, with suggested low-calorie diet and 30 minute walks most days, for 24 weeks[39]	Naltrexone/Bupropion (n=57)	ND	-8.2% BW	Greater reduction in BF (visceral and abdominal) accompanied with large decrease in lean mass with combination therapy. Proportion of fat:lean mass losses in combo comparable to placebo. Half combination patients and 30% of placebo lost 4% BW (78% was BF).			Mostly white females, in their 40's, average BMI of ~35, weighing 95-101 kg.	ND
		Naltrexone Monotherapy (n=15)	ND	-1.3% BW					
		Bupropion Monotherapy (n=12)	ND	-1.3% BW					
		Placebo (n=23)	ND	-2.1% BW					

Orlistat (Xenical)	XENDOS: Double-Blind study of 3,305 patients with lifestyle changes (52% Orlistat and 34% of placebo patients completed 4 year study)[40]	After year 1	Orlistat (Xenical) (n=1487)	-11.4 kg	ND	73%	41%	ND	Male and female type 2 diabetes patients with average age of 43 years, BMI of 37.	Both agents produced GI events, but there was a higher incidence with Orlistat during year 1(91 vs. 65%) and similar rates (36 vs. 23% during year 4.
			Placebo (n=1295)	-7.5 kg	ND	45.1%	20.8%	ND		
		After Year 4	Orlistat (n=851)	-6.9 kg	ND	52.8%	26.2%	ND		
			Placebo (n=567)	-4.1 kg	ND	37.3%	15.6%	ND		
	Randomized, double-blind study[41]	Orlsitat 120 mg TID after year 1 (n=343)		10.3 kg	-10.2% BW	9.3% Orlistat and 2.1% placebo groups lost 20% of baseline BW. Year 2: Orlistat patients gained half as much as placebo. When placebo patients switched to Orlistat, patients lost 0.9 kg as opposed to gaining 2-5 kg on placebo.			Average BMI of 36, average weight of 99 kg, average age 44 years, 83% female.	ADRs of Orlistat include: fatty/oily stool, increased defecation, oily spotting, soft stool, and liquid stools.
		Placebo TID after year 1 (n=340)		6.1 kg	-6.1% BW					
Lorcaserin (Belviq)	BLOOM-DM: One year randomized trial of 604 patients (401 completed study) [42]	Lorcaserin 10 mg BID (n=169 patients)		-5.6 kg	-5.5% BW	44.6%	20.8%	ND	Type 2 diabetes, average age of 53 years, slightly more women than men. 52-68% of patients were white, and average BMI of 35.	Systolic BP and diastolic BP were reduced. Back pain occurred more frequently in this group
		Lorcaserin 10 mg QD (n=75 patients)		-5.9 kg	-5.8% BW	54.7%	22.7%	ND		Systolic and diastolic BP increased slightly. Nasopharyngitis, headache, and dizziness occurred more frequently in this group
		Placebo (n=157 patients)		-1.9 kg	-1.7% BW	17.9%	5.8%	ND		Systolic BP and diastolic BP were reduced
	Multicenter, double-blind trial for 52 weeks. 1553 continued to year 2 [43]	Lorcaserin 10 mg BID (55% of 1595 Lorcaserin patients completed 1 year) (n=583)		ND	-5.81% BW	66.4%	36%	At least 5% reduction in BW at 1 year: the loss was maintained in 67.9% of lorcaserin and 50.3% of placebo patients	Most of the original patient population was white (67%), female (83%), average age of 44 years, and average weight of 100 kg.	Most common ADRs: headache, upper respiratory infection, and nasophartngitis.
		Placebo (45.1% of 1587 placebo patients completed 1 year) (n=737)		ND	-2.16% BW	32.1%	13.6%			

(Qsymia)	CONQUER trial: multicenter, randomized trial for 56 weeks (LOCF) [44]	Controlled-release (CR) phentermine 15 mg/ topiramate 92 mg combination (n=981)	-10.2 kg	-9.8%	70%	48%	ND	Average age 51 years, 70% women, 86% white, average 103 kg, and average BMI of 36.	Dry mouth, paresthesia, constipation, upper respiratory tract infection, and nasopharyngitis for both combination groups. The 15/92 mg P/T group also experienced metallic taste, insomnia, headache, and dizziness.
		CR phentermine 7.5 mg/ topiramate 46 mg (n=488)	-8.1 kg	-7.8%	62%	37%	ND		
		Placebo (n=979)	-1.4 kg	-1.2%	21%	7%	ND		
Topiramate/Phentermine	SEQUEL (56 week extension of CONQUER): randomized, double-blind trial including a lifestyle modification program of 676 patients (ITT-LOCF) [34]	CR phentermine 15 mg/ topiramate 92 mg combination (n=295)	-10.9 kg	-10.5%	79%	54%	32% (15.3% with ≥ 20% loss)	Average age was 52 years, ~68% women, >80% were white, weighed an average of 102 kg, and average BMI of 36.	Fewer ADRs than the 56 week CONQUER trial with upper respiratory tract infection being the most common.
		CR phentermine 7.5 mg/ topiramate 46 mg (n=153)	-9.6 kg	-9.3% BW	75.2%	50.3%	24.2% (9.2% with ≥ 20% loss)		
		Placebo (n=227)	-2.1 kg	-1.8% BW	30%	11.5%	6.6% (2.2% with ≥ 20% loss)		
Phendimetrazine	Small, double-blind, 12-week study[45]	Phendimetrazine (Bontril) (n=36)	-0.62 lb/week	ND	ND	ND	ND	65 males and 25 females, ages 20-69 years of age were originally randomized.	Insomnia, dry mouth, lightheadedness, nervousness, thirst, urinary frequency, and GI symptoms were likely
		Placebo (n=35)	-0.09 lb/week	ND	ND	ND	ND		
Diethylpropion (Tenuate)	Randomized, double-blind 6 month, placebo controlled trial. Months 7-12 open label study with all participants receiving diethylpropion[46]	Month 6: Diethylpropion 50 mg BID (n=37)	-9.3 kg	-9.8% BW	67.6%	51.3%	ND	Mostly female, average age of 36 years, mean BMI of 36, and mean weight of 95 kg.	There was a higher incidence of ADRs during the first 3 months and dry mouth, insomnia, constipation, headache, and irritability were common in both groups during months 0-3. Dizziness was also common in the diethylpropion group.
		Month 6: Placebo (n=32)	-3.1 kg	-3.2%	25%	3.13%	ND		
		Month 12: Diethylpropion 50 mg BID Continued	-0.8 kg (Total: -10.1 kg)	-10.6% BW (months 1-12)	74%	52%	ND		
		Month 12: Placebo→Di-ethylpropion	-3.6 kg (-6.7 kg total)	-7% BW (months 1-12)	50%	26%	ND		

Liraglutide (Saxenda)	Randomized, double-blind trial of 3731 patients for 56 weeks[47]	Liraglutide (n=2437)	-8.4 kg	-8% BW	63%	33%	ND	Mostly female, ~45 years of age, mostly white, ~106 kg in weight, and mean BMI of 38.	Most common in both groups: nausea, nasopharyngitis, and headache. Liraglutide patients also commonly experienced diarrhea, constipation, vomiting, and decreased appetite.
		Placebo (n=1225)	-2.8 kg	-2.6% BW	27.1%	10.6%	ND		

* BW-body weight **ND-No Data

Table 4. **Characteristics of Prescription Weight Loss Drugs**

Generic Name (Brand)	Class	Mechanism	Dosing	Patient Counseling
Orlistat (Xenical) RX approved for ages 12+[36] **Orlistat (Alli)** OTC approved for ages 18+[36]	Gastro-intestinal Lipase Inhibitor	Reversibly inhibits intestinal lipases in order to prevent hydrolysis of dietary triglycerides to absorbable fats. Only approved long-term treatment of obesity.[34]	**RX:** 120 mg PO TID **during or within 1 hour of fat-containing meal** **OTC:** 60 mg PO TID within 1 hour of fat-containing meal	• Take with nutritional meals with 30% calories from fat (recommended) • Use with Multivitamin (A, D, E, K, and beta-carotene) 2 hours before or after drug[36] • Caution: history of oxalate kidney stones • Common ADRs include: defecation urgency, flatulence, oily soiling, and abdominal discomfort. • ADRs similar to prescription strength but less common and should improve within a few weeks[36]
Lorcaserin (Belviq, Belviq XR)	Serotonin 2C Receptor Agonist	Believed to activate 5-HT 2C receptors in hypothalamus which encourage satiety	IR: 10 mg PO BID; ER: 20 mg PO QD • D/C if < 5% Weight Loss By Week 12 • MAX 20 mg/Day	• Administer with or w/o food • Do not use hazardous machinery until effects realized
Phentermine and Topiramate (Qsymia)	Phenermine/Topiramate Combo	Phentermine: weight loss may be result of increased catecholamine release in hypothalamus which impairs appetite. Topiramate: appears to suppress appetite by encouraging satiety possibly by influencing GABA and inhibiting excitatory receptors or inhibiting carbonic anhydrase[35]	3.75 mg/23 mg (P/T) PO QD for 14 days then increase to 7.5 mg/46 mg (P/T) QD • After 12 Weeks MD: If <3% Loss D/C or Increase Dose • Escalation: 11.25/69 mg PO QD for 14 Days, Then Increase to 15/92 mg QD. If 5% Loss Not Met, Gradually D/C. • D/C: 15/92 mg: Take 1 Dose Every Other Day For At Least 1 Week (Seizure Prevention)	• Administer with or w/o food • Morning admin to avoid insomnia • Do not suddenly D/C (possible seizure) • Maintain hydration to avoid kidney stone formation • May cause constipation, dry mouth, dizziness, upper respiratory infection, and insomnia

Generic Name (Brand)	Class	Mechanism	Dosing	• Patient Counseling
Bupropion and Naltrexone (Contrave)	Naltrexone/ Bupropion Combo	Proposed mechanism: Increase neuronal firing in hypothalamus (appetite control) and mesolimbic dopamine system (reward)	Week 1:1 Tab QAM Week 2: 1 Tab BID Week 3: 2 Tabs QAM and 1 QHS Week 4 and Beyond: 2 Tabs BID • MAX 32 mg and 360 mg (N/B) • D/C is 5% Decrease in Weight Not Achieved After 12 Weeks of MD	• DO NOT ADMINISTER WITH A HIGH FAT MEAL • Report suicidal ideation, mood change (BBW) • A regular schedule should be maintained, including skipping a missed dose if necessary • May increase BP and HR. May also cause constipation, nausea, vomiting, dry mouth, headache, and insomnia.
Liraglutide (Saxenda)	Glucagon-Like Peptide-1 Agonist	Regulates appetite via receptors in brain	0.6 mg SubQ QD. Increase in Increments of 0.6 mg/day until 3 mg Subcutaneously QD	• Inject SubQ in abdomen, thigh, or upper arm • Administer without regard to meals • If miss more than 3 days, re-initiate at 0.6 mg/day and titrate • Stay hydrated • **BBW** for dose- and treatment-dependent tumors and carcinomas
Phendi-metrazine (Bontril extended release)	Nor-adrenergic Agent	Sympathomimetic amine which suppresses appetite, which can also elevate BP	ER 105 mg: Once Daily 30-60 Minutes Before Morning Meal IR 35mg: 2-3 Times Daily 1 Hour Before Meals • MAX: 70 mg TID	• See Dosing for meal considerations • Should not be taken within 14 days of MAOIs, taken with other stimulants, or alcohol • Avoid in patients with a history of drug abuse, glaucoma, or hypertension • Common side effects of this class include: dry mouth, increased BP, constipation, insomnia, dizziness, and headache
Phentermine (Adipex-P, Lomaira)		Stimulates CNS and increases BP. Exact weight loss mechanism is unknown but may be related to CNS action or metabolic effects. Approved for only short-term use as monotherapy. [34]	**Caps**: 15-30 mg PO QD 2 Hour After Breakfast **Lomaira**: 8 mg PO TID ½ Hour Before Meals **Tab**: 37.5 mg PO QD Before Breakfast or 1-2 Hour After Breakfast	
Diethylpropion (Tenuate)		Stimulates CNS, BP and acts as an appetite suppressant	**ER**: PO QD (Midmorning) **IR**: 25 mg PO TID, 1 Hour Before Meals, May Take 1 Dose Mid-evening for Nighttime Cravings	
Benzphet-amine (Didrex, Regimex)		Stimulates CNS, BP and acts as an appetite suppressant. Has a high potential for abuse and addiction and should only be used in the short term (8-12 weeks) [48]	25-50 mg PO QD, up to TID	• Take in mid-morning or mid-afternoon • Limit treatment to those who respond within the first 4 weeks; D/C if tolerant • Avoid sudden D/C (withdrawal) • Short-term (8-12 weeks) use only

Table contents adapted from Pharmacotherapy: A Pathophysiologic Approach, 10e.and DRUGDEX Database[6,36]

Table 5. **Herbals and Supplements Commonly Used for Weight Loss**			
Agent	**Common Name**	**Notes**	**Claim/ Mechanism**
Citrus aurantium	Bitter orange Seville orange Sour orange	Usually in combo with caffeine-containing products. Contains synephrine and likely acts as an adrenergic agent with potential appetite suppression and lipolysis properties. Same risks as ephedra. A study has found significant increases in HR and BP in healthy adults caused by bitter orange and other stimulants in the product studied. [36] No efficacy has been established with clinical trials.	Stimulant to Increase Metabolism and Energy
Cola acuminate *Cola nitida*	Cola Nut	Source of caffeine. Caffeine is also a diuretic that can promote weight loss through urination	
Paullinia cupana *Paullinia sorbilis*	Guarana		
Ilex paraguarienis	Maté		
Camellia sinensis	Green tea	Products: Exolise. Thermogenic activity and oxidation of fat of undetermined significance. [49] Also considered to be an energy booster (contains caffeine)	Alters Fat or Carbohydrate Metabolism therefore Promoting Reduced Body Fat and Increased Lean Muscle
Cyamopsis tetragonolobus	Chromium	Tolerated at low doses but can cause rhabdomyolysis and renal failure with large doses. Possible cognitive, mood, and sleep changes[36]	
Garcinia Cambogia	Garcinia Brindleberry	High dose produces GI distress and should not be used in patients with diabetes mellitus or dementia[36]	
Glycyrrhiza glabra	Licorice	Possible pseudoaldosteronism, hypertension, and hypokalemia[36]	
Cyamopsis tetragonolobus	Guar gum	ADRs: Flatulence, GI distress, N/V	Appetite Suppressant and Satiety Enhancer
Amorphophallus konjac	Glucomannan		
Plantago ovata [50], *Plantago lanceolate, Plantago major, Plantago psyllium, Plantago arenatia*	Psyllium or Plantain	ADRs: Flatulence, GI distress, N/V. Also a laxative. Interaction with lithium or carbamazepine.	
Hoodia goronii	Hoodia	No reported risks	
-	Chitosan	Possible GI upset, flatulence, N, constipation	Blocks Absorption of Dietary Fat in Gut
Panax	Ginseng	Excitation, nervousness, lack of concentration, estrogenic effects, Stevens-Johnson Syndrome, hypoglycemic effects (miller). May interact with warfarin, digoxin, alcohol, and phenelzine (miller)	Blocks Carbohydrate Absorption
Rhamnus Purshiana [50]	Cascara sagrada	Laxative. Will not prevent caloric absorption (small intestine) because drug typically acts on colon. Stimulant laxatives should not be used for more than 1-2 weeks because may cause an electrolyte imbalance and dependence for evacuation. [36] Abdominal cramps and diarrhea possible. Long-term use depletes potassium (cardiac and muscle effects). DO NOT USE if on digoxin or diuretics that deplete potassium. [36]	Increased Fecal Evacuation
Taraxacum officinale	Dandelion	Diuretic (only transient weight loss). Not for patients with a ragweed allergy or gallbladder/bile duct obstruction, or bowel obstruction	Increased Urination

Table contents adapted from Botanical Medicine, The Handbook of Clinically Tested Herbal Remedies, and The Handbook of Nonprescription Drugs

Other Miscellaneous Herbal Agents

Other agents that have been used for weight loss include: calcium, Guggul (Commiphora), and Willow bark (Salix alba). Kidney bean extract and mung bean extract's suggested weight loss mechanism is to block absorption of dietary carbohydrates through intestinal walls. Beta-sitosterol, phosphatidylserine, and theanine are suggested to block the release of cortisol which encourages fat storage in the body. Conjugated linoleic acid and pyruvate are both agents that alter fat/carbohydrate absorption and can both cause GI upset. [36] Green coffee contains caffeine and is a fat absorption blocker.

Medications Used Off-label for Weight Loss

There are many medications that are not FDA approved for the treatment of obesity, but prescribers take advantage of their common side effect of weight loss help their patients achieve weight loss goals. This off-label use can be seen generally using three types of drugs – antidiabetic medications, some serotonergic antidepressants, and some anticonvulsants.

Metformin is a common antidiabetic medication that is not FDA approved to treat obesity, but has been shown to produce modest weight loss. The mechanism for the weight loss is not really known, however.[51, 52, 53] Exenatide (Byetta, Bydureon) is a glucagon-like peptide-1 (GLP-1) agonist typically used to treat diabetes. It also increases satiety, slows gastric emptying and promotes weight loss.[51, 54] Pramlintide (Symlin) is another antidiabetic medication that promotes weight loss through increased satiety and is used off-label for obesity.[55] A newer class of antidiabetic medication, the selective sodium-dependent glucose cotransporter-2 inhibitors (SGLT-2 Inhibitors), have also been shown to produce weight loss in patients with Type II Diabetes. These include canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance). These agents increase urinary glucose secretion, leading to the loss of 200-300 kcal/day which may contribute to weight loss. [51, 52] There is no current evidence of these medications being used primarily for weight loss, but there may be an off-label use for these agents in patients with diabetes and obesity in the near future.

Increased serotonin concentrations centrally increases satiety by decreasing the amount of food consumed and prolonging the time between food intake.[56] For this reason, fluoxetine (Prozac) is a SSRI that can be used off-label for weight loss. Higher doses (60 mg) are generally used for weight loss than for depression.[6, 51, 53]

Finally, some anticonvulsants have been used in the treatment of obesity. These include topiramate (Topamax) and zonisamide (Zonegran). Multiple case reports and clinical trials have shown significant weight loss as a common side effect of topiramate.[53] For this reason, the combination of extended release topiramate and phentermine (Qysmia) was developed and now has an FDA indication for the treatment of obesity. The exact mechanism is not known but may be due to decreased appetite and satiety.[51, 53] Zonisamide is also known to cause significant weight loss. It is thought it might help to regulate appetite through effects on serotonin and dopamine[51, 53]

Alabama Law Pertaining to the Dispensing of Controlled Weight Loss Medications

The state of Alabama has regulations for the prescribing of controlled medications for weight loss. The Alabama Board of Medical Examiners Administrative Code, Chapter 540-X-17 sets forth guidelines and standards for the utilization of controlled substances for weight reduction. Although this code was written for doctors, there are many rules pharmacists must take note of.

Table 6. Controlled Weight Loss Medications
• Belviq® (lorcaserin)* • Qsymia® (phentermine and topiramate)* • Fastin® (phentermine) • Adipex® (phentermine) • Suprenza® (phentermine) - Discontinued • Tenuate® (diethylpropion) • Bontril® (phendimetrazine) • Ionamin® (phentermine resin) – Not Available • Didrex® (benzphetamine) *Exceptions to these rules apply to these medications

Before a prescription can be prescribed for any of the medications in Table 6, a patient should have at least one of the following: [57, 58]

- Body Mass Index (BMI) ≥ 30
- BMI > 25 with at least one comorbidity factor
- Male patients: measurable body fat content ≥ 25% of total body weight
- Female patients: measurable body fat content ≥ 30% of total body weight
- Male patients: waist circumference ≥ 40 inches
- Female patients: waist circumference ≥ 35 inches

There are many stipulations pharmacists must pay close attention to upon receipt of a prescription for weight loss/management. No Schedule II controlled substance may be prescribed for the purpose of weight loss. [57, 58] Therefore, when receiving a prescription for any schedule II amphetamine, or any amphetamine-like or sympathomimetic drug, the pharmacist must ensure the intended purpose is not for the treatment of obesity. Also, none of the above medications in Table 6 may be called into the pharmacy. Nevertheless, they may be written or e-prescribed. [57, 58] Only a doctor of medicine (MD) or doctor of osteopathy (DO) may prescribe any Schedule III, IV or V controlled substance medication for weight management except for Belviq and Qsymia (Physician Assistant, Certified Registered Nurse Practitioner or Certified Nurse Midwife may also prescribe these). [57, 58] The maximum days' supply allowed for each of these agents is 35 days, and no refills are allowed. At the end of the prescription, the patient must be seen by the practitioner and new prescription written. Again, the exception to this rule is Belviq and Qsymia. The first prescription for these medications should not have a refill, but after that prescription has been filled and the patient has been seen for evaluation, the new prescription may be written for up to 5 refills in a six-month period. It is key to note this stipulation applies to the brand name drugs Belviq and Qsymia only. Refills are not allowed for generic substitutes or for the individual prescriptions of phentermine and topiramate (in the case of Qsymia). [57, 58]

Because the medications in this section are all controlled substances, it is good practice for pharmacists to be vigilant in assessing their patients for any sign of abuse or diversion of the medication. If this is a concern contact would need to be made with the prescriber and discontinuation of the medication should be discussed.

Conclusion

Obesity is a highly prevalent medical condition affecting more than one-third of Americans. It is defined as an abnormal or excessive fat accumulation that may impair health. As the most accessible health care professional, pharmacists can play an active role in recognizing and counseling patients on weight management. Knowing the poor outcomes that stem from excess body weight, pharmacists have the tools to educate patients on FDA-approved prescription and OTC products, lifestyle modifications, and available programs which help patients meet their health goals and prevent the morbidity of obesity.

References

1. Adult Obesity Facts [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2016 Sep 1 [updated 2016 Sep 1; cited 2017 July 6]. Available from: https://www.cdc.gov/obesity/data/adult.html
2. Obesity and overweight [Internet]. Washington (DC): World Health Organization [updated 2016 June; cited 2017 July 6]. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/
3. Adult Obesity Prevalence Maps [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2017 April 10 [updated 2017 April 10; cited 2017 July 6]. Available from: https://www.cdc.gov/obesity/data/prevalence-maps.html
4. Body Mass Index: Considerations for Practitioners [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2013 May 17 [cited 2017 July 6]. Available from: https://www.cdc.gov/obesity/downloads/bmiforpactitioners.pdf
5. Defining Adult Overweight and Obesity [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2016 June 16 [updated 2016 June 16; cited 2017 July 6]. Available from: https://www.cdc.gov/obesity/adult/defining.html
6. Sheehan AH, Chen JT, Yanovski JA, Calis KA. *Obesity*. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 10th ed. New York: McGraw-Hill Medical; c2016. P.2385-402.
7. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation [Internet]. Geneva, Switzerland: World Health Organization; 2008 December 8-11 [cited 2017 July 17]. Available from: http://apps.who.int/iris/bitstream/10665/44583/1/ 9789241501491_eng.pdf
8. 2013 Guideline. The American College of Cardiology, American Heart Association Task Force on Practice Guidelines, The Obesity Society. 2013 AHA/ACC/TOS Guideline for the management of overweight and obesity in adults. Circulation [Internet]. 2014 June 24 [cited 2017 Jul 5];129(Supplement):S1-S45. Available from: http://ovidsp.tx.ovid.com/sp-3.25.0a/ovidweb.cgi?&S=OOKMFPFONBDDCKADNCGKAHIBDLBAAA00&Link+Set=S.sh.22.24.28.38%7c1%7csl_10
9. Stephanie W. What is the waist-to-hip ratio? [Internet]. San Francisco (CA): healthline; 2017 Apr 26 [cited 2017 July 17, 2017]. Available from: http://www.healthline.com/health/waist-to-hip-ratio#overview1
10. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, Coutinho T, Jensen MD, Roger VL, Singh P, Jimenez FL. Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality. Ann Intern Med. 2015;163(11):827-35.
11. Wade M. The Risks of Belly Fat – and How to Beat Them [Internet]. New York (NY): Medscape; [cited 2017 July 17]. Available from: http://www.webmd.com/diet/obesity/features/the-risks-of-belly-fat#1
12. Cerhan JR, Moore SC, Jacobs EJ, Kitahara CM, Rosenberg SR, Adami HO, Ebbert JO, English DR, Gapstur SM, Giles GG, Horn-Ross PL, Park Y, Patel AV, Robien K, Vainio EW, Willett WC, Wolk A, Jacquotte ZJ, Hartge P, Bernstein L, Gonzalez AB. A Pooled Analysis of Waist Circumference and Mortality in 650,000 Adults. Mayo Clin Proc. 2014 March; 89(3):335-45.
13. Genes and obesity [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2013 May 17 [cited 2017 July 6]. Available from: https://www.cdc.gov/genomics/resources/diseases/obesity/obesedit.htm
14. Diseases and Conditions Obesity: Risk factors [Internet]. Scottsdale (AZ): Mayo Clinic; 2015 June 10 [cited 2017 July 6]. Available from: http://www.mayoclinic.org/diseases-conditions/obesity/basics/risk-factors/con-20014834
15. Caprio S, Daniels SR, Drewnowski A, Kaufman FR, Palinkas LA, Rosenbloom AL, Schwimmer JB. Influence of Race, Ethnicity, and Culture on Childhood Obesity: Implications for Prevention and Treatment: A consensus statement of Shaping America's Health and the Obesity Society. ADA Diabetes Care 2008 Nov; 31(11):2211-21.
16. Ali ZA. Insulinoma [Internet]. New York (NY): Medscape; [updated 2016 Feb 21; cited 2017 July 6]. Available from: http://emedicine.medscape.com/article/283039-overview
17. Ali ZA. Insulinoma Clinical Presentation [Internet]. New York (NY): Medscape; [updated 2016 Feb 21; cited 2017 July 6]. Available from: http://emedicine.medscape.com/article/283039-clinical
18. Kam K. The Facts on Leptin: FAQ [Internet]. New York (NY): Medscape; 2010 March 11 [cited 2017 July

6]. Available from: http://www.webmd.com/diet/obesity/features/the-facts-on-leptin-faq#1
19. Zelman KM. The Truth About HGH for Weight Loss [Internet]. New York (NY): Medscape; 2010 [cited 2017 July 6]. Available from: http://www.webmd.com/diet/features/the-truth-about-hgh-for-weight-loss#1
20. Health Risks of Being Overweight [Internet]. Bethesda (MD): National Institutes of Health; 2015 Feb [cited 2017 July 6]. Available from: https://www.niddk.nih.gov/health-information/weight-management/health-risks-overweight
21. Effects of Obesity [Internet]. Stanford (CA): Stanford HEALTH CARE; [cited 2017 July 6]. Available from: https://stanfordhealthcare.org/medical-conditions/healthy-living/obesity.html
22. Eka A, Chen AF. Patient-related medical risk factors for periprosthetic joint infection of the hip and knee. Ann Transl Med. 2015 Sep; 3(16):233.
23. Malinzak RA, Ritter MA, Berend ME, Meding JB, Davis KE. Morbidly obese, diabetic, younger, and unilateral joint arthroplasty patients have elevated total joint arthroplasty infection rates. J Arthroplasty. 2009 Sep; 24 (6 Suppl): 84-8.
24. Chen J, Cui Y, Li X, Miao X, Wen Z, Xue Y, Tian J. Risk factors for deep infection after total knee arthroplasty: a meta-analysis. Arch Orthop Trauma Surg. 2013 May; 133(5): 675-87.
25. Ogunbode AM, Fatiregun AA, Ogunbode OO. HEALTH RISKS OF OBESITY [Internet]. Bethesda (MD): Ann Ib Postgard Med [Internet]. 2009 Dec [cited 2017 July 6]; 7(2): 22-25. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4111009/
26. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD. Pharmacological management of obesity: an endocrine society clinical practice guideline. J Clin Endocrinal Metab [Internet]. 2015 Feb 1 [cited 2017 Jul 5];100(2):342- 362. Available from: https://academic.oup.com/jcem/article/100/2/342/2813109/Pharmacological-Management-of-Obesity-An-Endocrine
27. National Heart, Lung, and Blood Institute. Managing overweight and obesity in adults: systematic evidence review from the obesity expert panel, 2013. U.S. Department of Health & Human Services [Internet]. 2013 [cited 2017 Jul 5]. Available from: https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/obesity-evidence-review.pdf
28. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta- analysis of randomized clinical trials. J Acad Nutr Diet [Internet]. 2015 Sep [cited 2017 Jul 5];115(9):1447-1463. Available from: http://www.sciencedirect.com/science/article/pii/S2212267215002592?via%3Dihub
29. Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, Ball GDC, Busse JW, Thorlund K, Guyatt G, Jansen JP, Mills EJ. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. JAMA [Internet]. 2014 Sep 3 [cited 2017 Jul 5];312(9):923-933. Available from: http://jamanetwork.com/journals/jama/fullarticle/1900510
30. Miller WC, Koceja DM, Hamilton EJ. A meta-analysis of the past 25 years of weight loss research using diet, exercise, or diet plus exercise intervention. Int J Obes [Internet]. 1997 [cited 2017 Jul 5];21:941-947. Available from: http://www.optimalhealthpartner.com/A_Archive/MetaAnalysis_Miller.pdf
31. Alabama Hospital Association, Alabama Public Health, and Blue Cross Blue Shield of Alabama. Scale Back Alabama [Website]. www.scalebackalabama.com. Accessed 2017 June 26.
32. Blue Cross Blue Shield of Alabama. Walking Works Program [Website]. https://www.bcbsal.org/web/health/walkingworks.html. Accessed 2017 June 26.
33. Real Appeal, Inc. Real Appeal [Website]. https://realappeal.com/. Accessed 2017 June 26.
34. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012 Feb;95(2):297-308.
35. Orlistat, Lorcaserin, Qsymia, Contrave, Liraglutide, Bontril, Phentermine, Diethylpropion, Benzphetamine In: DRUGDEX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ (cited: 6/30/2017).
36. Miller SJ, Bartels CL. Overweight and obesity. In: Krinsky DL, Ferreri SP, Hemstreet BA, Hume AL, Newton GD, Rollins CJ, Tietze KJ. Handbook of nonprescription drugs: An interactive approach to self-care. 18th

ed. Washington D.C: The American Pharmacists Association; 2015. p. 487-508.
37. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, Kim DD, Dunayevich E; COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010 Aug 21;376(9741):595-605.
38. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, Kim D, Dunayevich E; COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring) 2013 May;21(5):935-43.
39. Smith SR, Fujioka K, Gupta AK, Billes SK, Burns C, Kim D, Dunayevich E, Greenway FL. Combination therapy with naltrexone and bupropion for obesity reduces total and visceral adiposity. Diabetes Obes Metab 2013 Sep;15(9):863-6.
40. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004 Jan;27(1):155-61.
41. Sjöström L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, Krempf M. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. Lancet 1998 Jul 18;352(9123):167-72.
42. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, Raether B, Anderson CM, Shanahan WR. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012 Jul;20(7):1426-36.
43. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, Bays H, Shanahan WR; Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010 Jul 15;363(3):245-56.
44. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, Day WW. Effects of low- dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet 2011 Apr 16;377(9774):1341-52.
45. Hadler AJ. Sustained-action phendimetrazine in obesity. J Clin Pharmacol J New Drugs 1968 Mar-Apr;8(2):113-7.
46. Cercato C, Roizenblatt VA, Leança CC, Segal A, Lopes Filho AP, Mancini MC, Halpern A. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects. Int J Obes (Lond) 2009 Aug;33(8):857-65.
47. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med 2015 Jul 2;373(1):11-22.
48. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. URL: http://www.clinicalpharmacology.com. Updated June 2015.
49. Barrett M. The handbook of clinically tested herbal remedies. Vol. 2. Binghamton (NY): The Haworth Press, Inc; c2004. 1435 p.
50. Eskinazi D, Blumenthal M, Farnsworth N, Riggins CW, editors. Botanical medicine: Efficacy, quality assurance, and regulation. Larchmont (NY): Mary Ann Liebert, Inc; 1999.
51. Metformin. Exenatide. Pramlintide. Canagliflozin. Dapagliflozin. Empagliflozin. Fluoxetine. Topiramate. Zonisamide. In: Micromedex [AUHSOP Intranet]. Greenwood Village, CO: Thomson Reuters. [updated 2017; cited 2017 June 29]. Available from: http://www.micromedexsolutions.com/micromedex2/librarian/
52. Triplitt CL, Repas T, Alvarez C. Chapter 74: Diabetes Mellitus. Pharmacotherapy: A Pathophysiologic Approach [Internet], 10e. Eds. Joseph T. DiPiro, et al. New York, NY: McGraw-Hill, 2017. [cited 2017 June 29]. Available from: http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146065891#1138162836
53. Moyers SB. Medications as adjunct therapy for weight loss: approved and off-label agents in use. J Am Diet Assoc [Internet]. 2005 Jun [cited 2017 June 29];105(6):948-959. Available from:

http://www.sciencedirect.com/science/article/pii/S0002822305003214
54. Triplitt C, Solis-Herrera C. GLP-1 receptor agonists: practical considerations for clinical practice. Diabetes Educ [Internet]. 2015;41(Suppl 1):32S-46S. Available from: http://xt5bv6dq8y.search.serialssolutions.com/OpenURL_local?sid=Entrez:PubMed&id=pmid:26450217
55. Smith SR, Aronne LJ, Burns CM, Kesty NC, Halseth AE, Weyer C. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. Diabetes Care [Internet]. 2008 Sep 3;31(9):1816-23. Available from: http://care.diabetesjournals.org/content/31/9/1816
56. Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic drugs: effects on appetite expression and use for the treatment of obesity. Drugs [Internet]. 2007;67(1):27-55. Available from: https://link-springer-com.spot.lib.auburn.edu/article/10.2165/00003495-200767010-00004
57. Guidelines and Standards for the Utilization of Controlled Substances for Weight Reduction, Alabama Board of Medical Examiners Administrative Code. Chapter 540-X-17 (2012).
58. Alabama Board of Pharmacy [Internet]. Birmingham (AL); c2016 [cited 2017 June 28]. FAQ Weight Loss Management; [about 1 screen]. Available from: http://www.albop.com/FAQ.aspx#WeightLoss_Medications