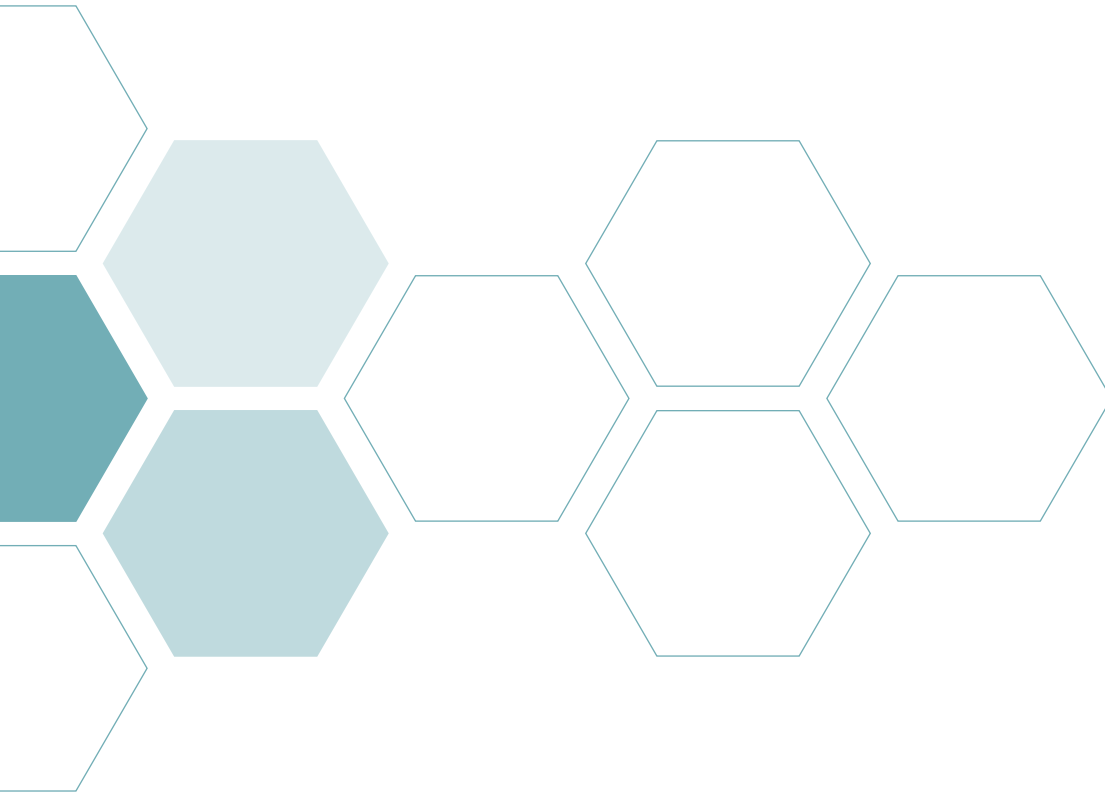


# Management of Obesity: Considerations in Managed Care Medicine



JOURNAL of MANAGED CARE MEDICINE



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## TABLE OF CONTENTS

<b>Management of Obesity: Considerations in Managed Care Medicine</b> Bartolome Burguera, MD, PhD; Angela Fitch MD, FACP, FOMA, Diplomate ABOM; Gary M. Owens, MD; Dhiren Patel, PharmD, CDE, BC-ADM, BCACP; Vicente T. San Martin, MD . . . . .	4
<b>Key Points</b> . . . . .	4
<b>Introduction</b> . . . . .	4
<b>What is Obesity?</b> Bartolome Burguera, MD, PhD and Vicente T. San Martin, MD . . . . .	4
<b>What Causes Obesity?</b> Gary M. Owens, MD . . . . .	4
<b>The Problem of Obesity</b> Bartolome Burguera, MD, PhD and Vicente T. San Martin, MD . . . . .	5
<b>The Consequences of Obesity</b> Bartolome Burguera, MD, PhD and Vicente T. San Martin, MD . . . . .	5
<b>Cost of Obesity in the United States</b> Gary Owens, MD . . . . .	6
<b>Recommendations for Weight Loss</b> Bartolome Burguera, MD, PhD and Vicente T. San Martin, MD . . . . .	7
<b>Why 5 to 10 percent?</b> Dhiren Patel, PharmD, CDE, BC.ADM.BCACP . . . . .	7
<b>Benefits of Modest Long-Term Weight Loss</b> Dhiren Patel, PharmD, CDE, BC.ADM.BCACP . . . . .	8
<b>Treatment of Obesity</b> Angela Fitch, MD, FACP, FOMA, Diplomate ABOM. . . . .	13
<b>Maintaining Weight Loss for the Long Term</b> Bartolome Burguera, MD, PhD and Vicente T. San Martin, MD. . . . .	16
<b>Considerations for Policy-Makers, Clinicians, Payers, and Employers</b> Gary M. Owens, MD . . . . .	17
<b>Overall Conclusions</b> . . . . .	18
<b>Authors</b> . . . . .	19
<b>References</b> . . . . .	19

# Management of Obesity: Considerations in Managed Care Medicine

Bartolome Burguera, MD, PhD; Angela Fitch MD, FACP, FOMA, Diplomate ABOM; Gary M. Owens, MD; Dhiren Patel, PharmD, CDE, BC-ADM, BCACP; Vicente T. San Martin, MD

## Key Points

- Obesity is a chronic disease with major consequences.
- More than 70 percent of the United States (U.S.) population is either overweight or suffer obesity.
- There are genetic, biologic, environmental, and behavioral reasons for obesity.
- The economic and social costs of obesity are staggering.
- Modest weight loss results in significant morbidity and mortality benefits and may be cost effective.
- Losing 5 to 10 percent of starting weight is considered clinically meaningful after modest weight loss.
- Helping patients achieve modest weight loss requires a multimodal approach of lifestyle modifications and anti-obesity medication.
- Anti-obesity medication is needed in many cases to overcome the biologic defense of the weight set point.
- With anti-obesity medications, patients are able to achieve modest weight loss almost twice as often as without the use of medication.
- Obesity must be treated like other chronic diseases with chronic holistic treatment.
- Various stakeholders need to find better ways to support modest weight loss and prevent more Americans from suffering overweight or obesity.
- Managed care and employers should be supporting modest weight loss by providing coverage for weight loss programs, chronic anti-obesity medications for appropriate patients to address underlying physiology encouraging weight regain, and long-term maintenance programs.

## Introduction

OBESITY IS A CHRONIC, RELAPSING, MULTIFACTORIAL, neurobehavioral disease resulting in adverse metabolic, biomechanical, and psychosocial consequences.<sup>1</sup> The medical and financial burden of obesity significantly affects individuals, health care providers, employers, payers, and society. Much of this burden is due to the increased risk of multiple comorbidities, which result in substantial excess health care costs and increased morbidity and mortality. Obesity is also known to carry significant deleterious effects on the quality of life and work productivity of the affected individuals. This supplement provides an extensive overview of the problem of obesity, the benefits of modest weight loss, and why various stakeholders are affected by and should address the issue.

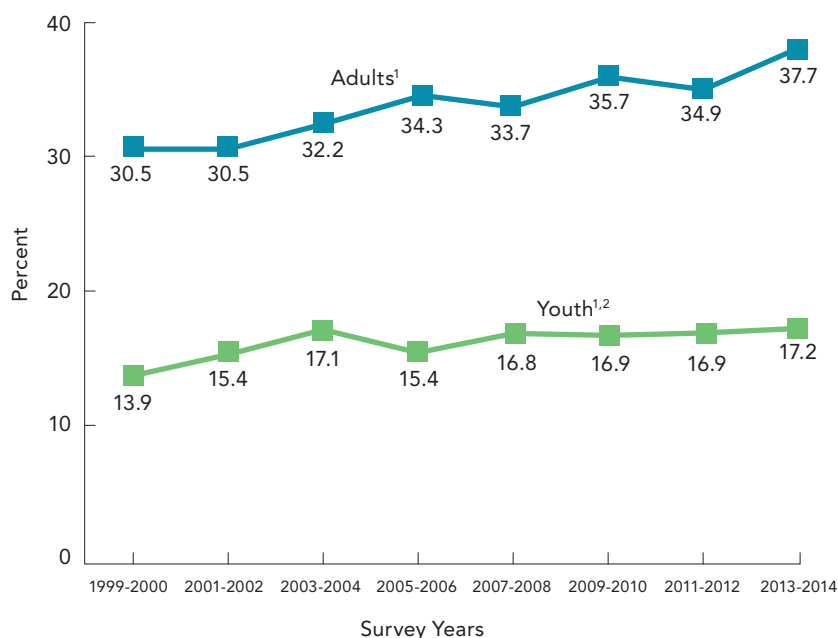
## What is Obesity?

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.<sup>1</sup> Body mass index (BMI), calculated as weight in kilograms (kg) divided by height in meters squared, is one of the most commonly used measurements to characterize excess body weight, although it has limitations in defining individual health status. Overweight is a BMI greater than or equal to 25 kg/m<sup>2</sup> and obesity is defined as a BMI greater than or equal to 30 kg/m<sup>2</sup>.<sup>1</sup> By these measures, more than 70 percent of the adult population in the United States (U.S.) is overweight or has the disease of obesity.<sup>2</sup>

## What Causes Obesity?

Obesity is often stigmatized and viewed as the result of eating too much and a sedentary lifestyle; his-

Exhibit 1: Obesity Prevalence Trends in the U. S. from 1999-2014<sup>11</sup>



torically, obesity management has focused on telling persons suffering obesity to consume fewer calories and engage in more physical activity to achieve a more normal weight and body composition.<sup>3</sup> A 2012 online poll found that 61 percent of U.S. adults believed that “personal choices about eating and exercise” were responsible for the high rates of obesity.<sup>4</sup> However, scientific evidence indicates that the etiology of obesity is more complex than solely being an imbalance between energy intake and energy output. Genetic, neuroendocrine, environmental and behavioral interactions each play a contributing aspect in weight gain.<sup>5,6</sup> The cerebral adipostat or weight set point that receives hormonal and metabolic signals from the periphery dictates how much an individual needs to eat.

The genetic heritability of obesity is estimated to be 40 to 70 percent.<sup>7,8</sup> Apart from genetics, certain uncommon neuroendocrine causal factors for obesity include hypothyroidism, Cushing’s disease, growth hormone deficiency, and hypothalamic causes.<sup>6</sup> From an environmental and behavioral perspective, various structural changes that have occurred in society have created obesogenic conditions with easy availability of high-caloric density, low-quality food; sedentary lifestyle because of mechanized work and transportation and electronic media; and changes in family dynamics, parental nurturing and eating habits.<sup>9</sup> In addition, a number of commonly

prescribed medications are known to cause weight gain, including psychoactive drugs, anti-hyperglycemic medications (insulin, sulfonylureas, glitazones), antiepileptic drugs, and hormonal agents.<sup>10</sup>

### The Problem of Obesity

Obesity is a chronic disease of epidemic proportions in the U.S. and worldwide; the worldwide prevalence of obesity has nearly tripled since 1975 and is expected to continue to increase at an alarming rate.<sup>11,12</sup> The National Center for Health Statistics recently reported a U.S. obesity rate of 39.6 percent in adults and 18.5 percent in children.<sup>11</sup> There has been a 30 percent increase in adult obesity and a 33 percent increase in childhood obesity since 1999 (Exhibit 1).<sup>11</sup> In 2011, Wang and colleagues projected that by 2030 over 50 percent of adults in the U.S. will have the chronic disease of obesity.<sup>13</sup> Another analysis projected that 57 percent of U.S. children and teens will suffer obesity by age 35 if current trends continue.<sup>14</sup> Among high-income countries, the U.S. has the highest prevalence of obesity.<sup>13</sup> These trends are particularly alarming because obesity is associated with serious consequences that will ultimately stress the health care systems of the U.S. and the world from both a clinical and cost standpoint.

### The Consequences of Obesity

The biomedical and psychosocial consequences

of obesity have substantial implications for the health and well-being of the U.S. population. As the prevalence of obesity continues to increase, so does the prevalence of its associated comorbidities. The expanding set of chronic medical conditions which are known health consequences of obesity include metabolic syndrome, type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, coronary heart disease, stroke, myocardial infarction, atrial fibrillation, heart failure, obstructive sleep apnea, asthma, non-alcoholic fatty liver disease (NAFLD), osteoarthritis, various cancers, and others.<sup>1,6,15-22</sup> The risk for developing all these comorbidities correlates with body mass index (BMI).<sup>1</sup> For example, the risk of developing T2DM increases by 20 percent for each 1 kg/m<sup>2</sup> increase in the BMI over 27.2 kg/m<sup>2</sup>.<sup>23</sup> Additionally, urinary incontinence, gallbladder disease, gastroesophageal reflux, polycystic ovary syndrome (PCOS) and related infertility, depression, reduced quality of life, functional impairment, and impaired self-esteem occur as a result of obesity.<sup>1,18,19,24</sup>

Obesity causes a substantial burden on a personal level. It is associated with significantly lower generic and obesity-specific health-related quality of life (HRQOL).<sup>25</sup> This decreased HRQOL is more noticeable in those individuals with Class III obesity (BMI  $\geq$  40 kg m<sup>2</sup>) and those seeking bariatric surgery, suggesting that low HRQOL may provide motivation in these patients to undergo an invasive intervention.<sup>25</sup> Obesity-related health problems can impair physical health status and impose functional limitations on daily activities. Patients with obesity who are not able to move around at an intensity and frequency required to lose weight or prevent weight gain are at a greater risk of experiencing mobility disability; those patients with impaired mobility experience restrictions in activities at home, work, school, and in the community, which translates into a negative impact on their HRQOL.<sup>26</sup> An important contributor to impaired mobility is obesity-related pain, which can affect the global sense of well-being. Evidence from cross-sectional studies has shown a relationship between obesity and conditions known to cause pain, such as osteoarthritis and low back pain.<sup>27</sup> When bodily pain scores were compared with published data of several chronic conditions, individuals with obesity reported significantly greater body pain, than did those with depression, congestive heart failure, or human immunodeficiency virus; only patients with migraine headaches had a higher score.<sup>28</sup> Dissatisfaction with body image, low self-esteem, weight bias and weight stigmatization can also add to the psychological distress

in individuals with obesity, thus further affecting well-being in a negative manner.<sup>29</sup>

Perception of weight discrimination appears to be another important determinant of overall well-being among individuals with obesity. Research spanning several decades has documented consistent weight discrimination in a variety of settings, including employment, health care, schools, the media, and interpersonal relationships.<sup>30</sup> Individuals with obesity are often expected to be less successful and are unfairly viewed as having less leadership potential than normal-weight individuals; this translates into a lower possibility of being employed and into lower wages in comparison to normal-weight peers.<sup>31,32</sup> In the health care setting, perceived weight discrimination often causes individuals with obesity to be reluctant to seek medical help, not only for weight reduction but also for any health-related problems. Weight discrimination accounts for approximately 40 percent of the negative psychological effects associated with obesity.<sup>33</sup>

Beyond the QOL of life issues, obesity is associated with large decreases in life expectancy and increases in early mortality, similar to those seen with smoking.<sup>34</sup> In fact, it has been suggested that the steady increase in life expectancy during the past two centuries may come to an end because of the increasing prevalence of obesity.<sup>35</sup> Obesity is associated with increased risk in all-cause and cardiovascular disease (CVD) mortality.<sup>15,36-38</sup>

Just having excess weight also increases risk. In 2015, high BMI (>25 kg/m<sup>2</sup>) was estimated to have contributed to four million deaths globally, which represented 7.1 percent of the deaths from any cause among adults; CVD and T2DM were the leading causes of BMI-related deaths, contributing to 2.7 and 0.6 million deaths, respectively.<sup>15</sup>

### Cost of Obesity in the United States

There are many studies that have attempted to quantify the total medical costs attributable to obesity. It is sometimes difficult to determine how much obesity directly contributes to overall medical costs, especially in individuals with multiple comorbidities. However, several studies have attempted to quantify these costs, both direct and indirect.

In 2014, the global economic impact of obesity was estimated to be \$2.0 trillion (U.S.) or 2.8 percent of the global gross domestic product (GDP).<sup>39</sup> The direct medical costs of conditions causally related to obesity in the U.S. were estimated to be a staggering \$427.8 billion in 2016.<sup>40</sup> This is a significant increase from 1998 when costs attributed to obesity were estimated at \$78.5 billion per year and in 2012 when they were \$190.2 billion.<sup>41,42</sup> While

not all of the costs for treating chronic conditions can be directly related to obesity, it is clear that obesity is a major driver of the prevalence of various chronic diseases and is, therefore, a driver of substantial excess costs.

In an analysis of Medical Expenditure Panel Survey (MEPS) data, the per capita annual costs attributable to obesity were estimated to be 36 percent higher than patients without obesity for Medicare, 47 percent for Medicaid, and 58 percent for private payers.<sup>43</sup> For Medicare, the increased spending over individuals without obesity was over \$600 per person driven largely by increased non-inpatient services and prescription medications.<sup>43</sup> For private payers, the spending increase from 1998 to 2006 was statistically significant for each type of service and ranged from \$284 for prescription medications to \$443 for inpatient services per person. The authors noted that these increases represent 82 percent and 90 percent increases in costs, respectively, compared with people of normal weight.<sup>43</sup> These numbers should be particularly important to consumers and employer groups as these increased costs are ultimately reflected in the premiums paid by the fully-insured individuals and the direct cost paid by self-funded employers.

In addition to the direct medical costs associated with obesity, there are also a number of indirect costs associated with the disease. These include loss of productivity as measured by absenteeism (costs due to employees being absent from work for obesity-related health reasons) and presenteeism (decreased productivity of employees while at work), as well as disability and premature mortality and their impact on families and the economy.<sup>44-47</sup> The indirect costs dwarf the direct medical costs of obesity at \$988 billion to \$1.42 trillion or 8.2 percent of the GDP (2014).<sup>40</sup>

Obesity, but not overweight, is associated with a significant increase in absenteeism, from 1.1 to 1.7 extra days missed annually compared to normal-weight employees.<sup>45</sup> Obesity-attributable absenteeism among American workers costs the nation an estimated \$3.38 to \$8.65 billion per year.<sup>45-47</sup> Obesity also increases workers' compensation claims and related lost workdays. It imposes a considerable financial burden, accounting for 6.5 to 12.6 percent of total absenteeism costs in the workplace. One estimate placed the costs at \$506 per year per employee with obesity.<sup>47</sup>

Disability-related costs of obesity are also an impact to society. Disability-adjusted life years, or DALYs, combine years lost due to premature mortality with partial years lost due to reduced productivity. DALYs are an aggregate measure of the total impact that a particular disease or condition has on a population level.<sup>48</sup> The calculation of the economic

impact of obesity in 2014 based on DALYs was \$543 billion.<sup>48</sup>

Premature mortality is a significant social cost of obesity. For young Americans, obesity makes an individual 1.41 times more likely to experience death due to any cause.<sup>35</sup> Even when metabolically healthy, individuals with obesity have increased risk for events compared with metabolically healthy normal-weight individuals.<sup>49</sup> Considerable controversy exists about the precise calculation of the monetary value of premature death. Generally, the accepted range is between \$3.2 million and \$13.7 million, depending on the analytic approach used.<sup>50,51</sup> Regardless of the actual amount used, the economic impact of premature death caused by obesity is a large societal burden.

### Recommendations for Weight Loss

Several obesity management guidelines suggest a multifactorial approach to the treatment of obesity, with comprehensive lifestyle modification as the foundation for weight loss and using adjunctive anti-obesity pharmacotherapy and/or bariatric surgery when appropriate.<sup>18,19,22</sup> These guidelines recommend an initial weight loss of 5 to 10 percent of starting body weight within the first six months for those who have overweight or obesity.

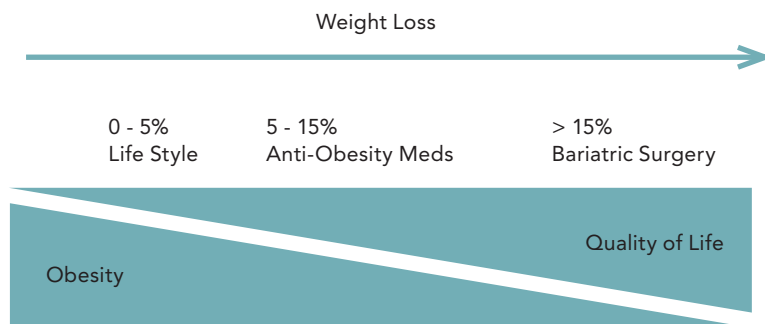
### Why 5 to 10 percent?

There are several reasons why modest weight loss (defined as 5 - 10% of baseline weight) is advocated by weight loss experts and management guidelines. Foremost, there is a significant body of evidence that this degree of weight loss improves health outcomes and reduces risk for several chronic diseases. Each of these benefits will be discussed in further detail in subsequent sections. Additionally, modest weight loss is achievable with lifestyle modification with or without pharmacotherapy.<sup>52,53</sup> Among adults with overweight or obesity, the FDA approved anti-obesity agents [orlistat (Xenical<sup>®</sup>, Alli<sup>®</sup>), lorcaserin (Belviq<sup>®</sup>), naltrexone-bupropion (Contrave<sup>®</sup>), phentermine-topiramate extended release (Qsymia<sup>®</sup>), and liraglutide 3mg (Saxenda<sup>®</sup>)] compared with placebo, are associated with achieving at least a 5 percent weight loss at 52 weeks.<sup>54-58</sup> Phentermine-topiramate and liraglutide 3 mg are associated with the highest odds of achieving at least a 5 percent weight loss.<sup>58</sup> Modest weight loss does not require expensive bariatric surgery or other major interventions. Lastly, modest weight loss goals allow a patient to have success, which can motivate them to pursue additional weight loss.

Obviously, losing 5 to 10 percent of body weight is just a starting point for many patients. For those



Exhibit 2: Impact of Weight Loss on Quality of Life



with severe or greater obesity (BMI > 35 kg/m<sup>2</sup>), additional weight loss would be beneficial and likely a goal.<sup>59</sup>

### Benefits of Modest Long-Term Weight Loss

Each of the areas of benefit from modest long-term weight loss are discussed in the following pages. This is not an exhaustive review of every available trial but is a general overview. The specific benefits of bariatric surgery are not included here since the focus is on modest weight loss.

### Quality of Life

Weight loss is associated with improved QOL measures. In a systematic review of U.S. literature, weight loss of 5 percent or greater from non-bariatric surgery interventions resulted in improvements primarily in physical domains of HRQOL.<sup>60</sup> Some trials have found that in addition to improvements in physical function, improvements in HRQOL from weight loss through lifestyle changes or medications appear to be driven also by improvements in psychosocial factors and depression.<sup>61-64</sup> Treatment with the combination of bupropion and naltrexone produced a significant improvement in the Montgomery-Åsberg Depression Rating Scale score after body-weight losses of 4 percent at week 12 and 5.3 percent at week 24 in patients with obesity and major depressive disorder.<sup>64</sup> In another trial, a 6 to 7 percent weight loss led to a positive change in self-perceived health status.<sup>65</sup> Weight loss with liraglutide 3 mg, lorcaserin, or phentermine/topiramate combined with diet and exercise improves HRQOL as assessed with the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and Medical Outcomes Study Short Form (SF-36) measures.<sup>63,66-68</sup> In a three-year trial with liraglutide 3 mg with diet and exercise, both the IWQOL-Lite total score and physical compo-

nent score of the SF-36 demonstrated an association between greater HRQOL improvement with higher weight loss.<sup>66</sup> Importantly, this trial demonstrated long-term improvement in HRQOL with sustained weight loss. Overall, weight loss can improve HRQOL and improvements appear to parallel the amount of weight lost (Exhibit 2).

### Diabetes

Modest weight loss achieved through lifestyle interventions is particularly effective for reducing the risk of developing T2DM. The Diabetes Prevention Program showed that intensive lifestyle interventions (including individual counseling and motivational support on diet, exercise and behavior modification) resulting in an average of 7 percent loss of starting body weight, and that 150 minutes of exercise weekly reduced the risk of developing diabetes by 58 percent.<sup>69</sup> Lifestyle interventions were compared to metformin (850 mg bid) in the Diabetes Prevention Program; it reduced the risk by 31 percent. Metformin can induce a modest weight loss ( $2.06 \pm 5.65\%$ ) and reduces insulin resistance.<sup>70</sup> To prevent one case of diabetes during a period of three years, 6.9 persons would have to participate in a lifestyle-intervention program and 13.9 would have to receive metformin.<sup>71</sup> Prevention or delay of diabetes with lifestyle intervention or metformin has been shown to persist for at least 10 years after stopping the intervention (34% for lifestyle, 18% for metformin).<sup>69</sup> This was despite some weight regain in the lifestyle group in the Diabetes Prevention Program.

Liraglutide 3 mg has also been shown to reduce risk of developing T2DM when used over three years in adults with prediabetes (2% rate of developing diabetes vs 6% in placebo group).<sup>72</sup> A National Heart Lung Blood Institute (NHLBI) expert review noted that in adults with overweight and



obesity at risk for T2DM, average weight losses of 2.5 to 5.5 kg at two or more years reduces the risk for developing T2DM by 30 to 60 percent.<sup>18</sup>

For those patients who have already developed T2DM, a 2 to 5 percent weight loss results in modest reductions in fasting plasma glucose concentrations and lowering of hemoglobin A1C (A1C) by 0.2 to 0.3 percent.<sup>18</sup> Weight loss of 5 to 10 percent is associated with A1C reductions of 0.6 to 1.0 percent and reduced need for diabetes medications.<sup>18,73</sup> Over time, even with continued intervention, some weight regain will typically occur in patients; partial weight regain is associated with an increase in A1C, but A1C values can remain below pre-intervention levels and the reduction remains clinically meaningful.<sup>74</sup>

### *Cardiovascular Disease*

Evidence for the impact of weight reduction on cardiovascular disease (CVD) is not as clear-cut as for T2DM. Obesity has significant negative impact on CVD risk via its maladaptive effects on individual CVD risk factors and cardiac structure and function.<sup>75</sup> Weight loss can improve cardiovascular parameters and risk factors. In a small two-year trial, modest weight loss was associated with decreased left ventricular (LV) mass and carotid intima-media thickness and significant improvement in LV diastolic and systolic function.<sup>73</sup> Over the course of the study, partial weight regain diminished the maximal observed beneficial effects of weight loss; however, cardiovascular parameters measured at two years still showed a net benefit compared with baseline. Modest weight loss has also been shown to significantly improve CVD risk factors including glucose, lipids, and markers of inflammation such as high-sensitivity C-reactive protein (hsCRP) in those who have overweight or obesity with T2DM and those who already have CVD.<sup>73,75,76</sup>

Despite positive effects on CVD risk factors, some studies have shown that weight loss in individuals with overweight and obesity, who already have CVD, is associated with increased mortality. Other CVD studies show a better prognosis with a higher BMI (the obesity paradox), and some studies actually suggest that purposeful weight loss may not be beneficial and may even be detrimental in patients with CVD diseases.<sup>77-80</sup> Yet, other studies show benefits in CVD-related mortality. A meta-analysis of 12 studies found that intentional weight loss was associated with lower all-cause mortality, cardiovascular mortality, and major adverse cardiac events in those with CVD.<sup>81</sup> The difference among all the studies appears to be intentional weight loss versus unintentional. The meta-analysis supports the benefit

of intentional weight reduction in patients with overweight or obesity and CVD.

### *Blood Pressure*

Modest weight loss has been shown to decrease blood pressure. In adults with overweight or obesity with elevated CVD risk (including T2DM and hypertension), there is a dose-response relationship between the amount of weight loss achieved for up to three years by lifestyle intervention alone or combined with orlistat and the lowering of blood pressure.<sup>18</sup> Estimates for how much reduction of blood pressure occurs with modest weight loss varies. A NHLBI expert review found that a 5 percent weight loss resulted in a modest mean reduction in systolic and diastolic blood pressure of approximately 3 and 2 mmHg, respectively.<sup>18</sup> At less than a 5 percent weight loss, there are more modest and more variable reductions in blood pressure. A systematic review found that weight loss with lifestyle intervention alone lowers lower blood pressure approximately 1 mm Hg per kilogram lost.<sup>82</sup> A Cochrane review found that a mean weight loss of 4 kg with lifestyle modification resulted in a mean systolic blood pressure reduction of 4.5 mm Hg and diastolic blood pressure of 3.2 mm Hg.<sup>83</sup> As for anti-obesity medications, weight loss with orlistat, phentermine/topiramate, and liraglutide 3mg in patients with overweight and obesity has been shown to modestly reduce blood pressure.<sup>84</sup> For example, orlistat reduced systolic blood pressure as compared to placebo by 2.5 mm Hg (mean difference) and diastolic blood pressure by 1.9 mm Hg.<sup>84</sup> Liraglutide 3 mg reduced systolic and diastolic by mean 2.8 mm Hg and 0.9 mm Hg and phentermine/topiramate by 3.1 mm Hg and 1.4 mm Hg, respectively.<sup>76,85</sup> The combination of bupropion and naltrexone can cause a transient increase of around 1.5 mm Hg in mean systolic and diastolic blood pressure but is followed by a reduction to baseline with weight loss.<sup>86,87</sup> Overall, weight loss with lifestyle changes or anti-obesity medications leads to a modest blood pressure reduction.

### *Lipids*

In adults with overweight or obesity with or without elevated CVD risk, there is a dose-response relationship between the amount of weight loss and the improvement in lipid profile.<sup>18,88</sup> The amount of weight loss needed for improvement varies by lipid. At a 3 kg weight loss, a weighted mean reduction in triglycerides of at least 15 mg/dL is observed.<sup>18</sup> At a 5 to 8 kg weight loss, LDL-C reductions of approximately 5 mg/dL and increases in HDL-C of 2 to 3 mg/dL are achieved.<sup>18</sup> Compared with higher amounts of lost

weight, a less than 3 kg weight loss produces more modest and more variable improvements in triglycerides, HDL-C, and LDL-C.<sup>18</sup> Among adult individuals with overweight-obesity and T2DM an 8 percent weight loss at one year and a 5.3 percent weight loss over four years results in greater average increases in HDL-C (2 mg/dL) and greater average reductions in triglycerides compared to no weight loss.<sup>18</sup>

### **Obstructive Sleep Apnea**

Weight loss is recommended for all patients with overweight or obesity with obstructive sleep apnea (OSA) because modest weight reduction has been shown to improve this condition.<sup>89-91</sup> Additionally, over a five-year period, moderate but sustained weight reduction can prevent the progression of the disease or even cure mild OSA in patients who are overweight.<sup>92</sup> A 10 percent or greater weight loss can also lower the amount of positive airway pressure treatment needed to treat OSA.<sup>89</sup>

### **Osteoarthritis**

Osteoarthritis (OA) affects weight-bearing joints in people who have obesity and is a major cause of knee replacement surgery in patients who have this condition for a long time. Weight loss is recommended by the American College of Rheumatology and European League Against Rheumatism guidelines for OA management.<sup>93</sup> Modest weight loss has been shown to reduce symptoms of OA and improve physical functioning.<sup>94-97</sup> Each pound of weight lost results in a fourfold reduction in the load exerted on the knees per step which accumulated over thousands of steps per day is clinically meaningful.<sup>98</sup> Long-term maintenance of weight loss has also been shown to lead to preservation of reduced symptoms and may slow progression of the disease.<sup>94,95,97</sup>

### **Gout**

Weight loss is typically recommended to manage gout in those who have overweight or obesity because serum uric acid levels correlate with BMI.<sup>99-101</sup> Weight loss can improve serum uric acid levels, help patients achieve serum uric acid target levels, and reduces gout attacks.<sup>102</sup> A weight loss of greater than 7 kg results in a beneficial effect on uric acid levels and a greater than 3.5 kg loss showed beneficial effects on gout attacks at medium-term/long-term follow-up based on six studies.<sup>102</sup> Rapid weight loss, such as from bariatric surgery, can provoke gout attacks.<sup>103,104</sup>

### **Cancer**

Overweight and obesity are associated with increased risk of at least 13 types of cancer - menin-

gioma, multiple myeloma, adenocarcinoma of the esophagus, and cancers of the thyroid, postmenopausal breast, gallbladder, stomach, liver, pancreas, kidney, ovaries, uterus, and colorectal.<sup>105</sup> These cancers account for about 40 percent of all cancers diagnosed in the U.S. in 2014, according to the latest Vital Signs report by the Centers for Disease Control and Prevention (CDC).<sup>106</sup> Approximately 630,000 people in the U.S. were diagnosed with a cancer associated with overweight and obesity in 2014.<sup>107</sup>

The prevention of excess body fatness reduces the risk of cancers of the colon and rectum, esophagus (adenocarcinoma), kidney (renal cell carcinoma), breast in postmenopausal women, and endometrium.<sup>105</sup> In addition, for middle-aged adults, there is sufficient evidence in humans that the absence of excess body fatness reduces the risk of cancers of the gastric cardia, liver, gallbladder, pancreas, ovaries, thyroid, meninges, and bone marrow.<sup>105</sup> There is also limited evidence that the absence of excess body fatness reduces the risk of fatal cancer of the prostate, cancer of the breast in men, and diffuse large B-cell lymphoma.<sup>105</sup>

Evidence on weight loss and reduction in risk of cancer is more limited.<sup>108</sup> Although the mechanisms driving the association between body weight and multiple types of cancer are not totally understood, weight loss results in altered gene expression of adipokines and inflammatory markers in subcutaneous adipose tissue which are postulated to be related to cancer development.<sup>109</sup> Inflammatory marker changes include decreases in leptin, tumor necrosis factor alpha, and interleukin 6. Modest weight loss significantly lowers serum estrogens and free testosterone, which have been shown to be associated with a decrease in postmenopausal breast cancer risk, and reduces C-reactive protein and leptin levels which also may reduce risk.<sup>110-112</sup> These findings support weight loss for breast cancer risk reduction.

### **Nonalcoholic Fatty Liver Disease**

Nonalcoholic fatty liver disease (NAFLD) is closely associated with obesity and insulin resistance which leads to liver accumulation of triglycerides and free fatty acids. Modest weight loss decreases the amount of fat found in the liver and improves insulin resistance but may not necessarily reverse NAFLD.<sup>113</sup> Loss of at least 3 to 5 percent of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10 percent) may be needed to improve necroinflammation seen in nonalcoholic steatohepatitis (NASH).<sup>114</sup> The more dramatic weight loss with bariatric surgery has been shown to significantly improve underlying fatty liver disease.<sup>115</sup>

### *Urinary Incontinence*

Chronic obesity can weaken pelvic muscles, making it harder to maintain bladder control leading to urinary incontinence. A few studies have shown that weight loss can improve symptoms of urinary incontinence.<sup>116,117</sup> In one trial in women, a loss of 8 percent reduced weekly urinary incontinence episodes by 47 percent.<sup>117</sup> Even when women in this trial only lost 1.6 percent of body weight (about 3 pounds), they had 28 percent fewer episodes.<sup>117</sup>

### *Reduced Need for Medications*

Because of the consequences of the disease, those with obesity tend to be on more medications and have higher medication costs.<sup>43,118-121</sup> In one trial, 52 percent of individuals with obesity were taking medications compared with only 36 percent of a randomly selected reference population and had higher total annual medication costs.<sup>119</sup> In one analysis, attributable cost of overweight and obesity accounted for 23 percent of spending on all medications, with 16 percent attributable to obesity alone.<sup>121</sup>

Reduced medication use is another benefit of modest weight loss. The Look Ahead investigators found that a 7 percent weight loss resulted in reduced blood pressure medication use at one- to four-year follow-up in 5,145 adults with overweight or obesity and T2DM.<sup>74</sup> A mean 5 percent weight loss achieved over four years by lifestyle intervention in adults with overweight or obesity and T2DM was associated with a reduction in newly prescribed lipid-lowering medications compared with controls.<sup>122</sup> In another trial, the need to add additional therapy to control blood pressure was reduced by 23 percent in patients with overweight and mild hypertension who only had a net loss of 2 to 3 kg over 4.5 years of follow-up.<sup>123</sup> Relative weight loss of 10 percent or greater may be necessary to reduce costs of medication for CVD and T2DM among subjects with such treatment at baseline.<sup>124,125</sup> Not all studies show a statistically significant reduction in medication costs with weight loss; this may be due to a lack of a systematic approach to reducing medication use or continued need for various therapies to reduce CVD risk.<sup>126,127</sup>

Although modest weight loss may reduce the need for some medications and reduces risk of weight-related disease, it does not eliminate CVD risk. Many of these patients who have been successful losing weight loss are still at risk and will likely require agents such as aspirin, statins, anti-hypertensives, anti-diabetics, or other medications for CVD risk reduction.

### *Other Benefits*

Weight loss is recommended as first-line treatment for managing the insulin-resistance seen in polycys-

tic ovary syndrome (PCOS). Weight loss improves many features of PCOS and may prevent future reproductive and metabolic complications.<sup>128,129</sup> Preconception weight loss in those with patients with PCOS who also have overweight or obesity is also recommended before infertility treatment is initiated; 7 percent weight loss leads to higher ovulation rates compared to oral contraceptive pretreatment.<sup>130,131</sup>

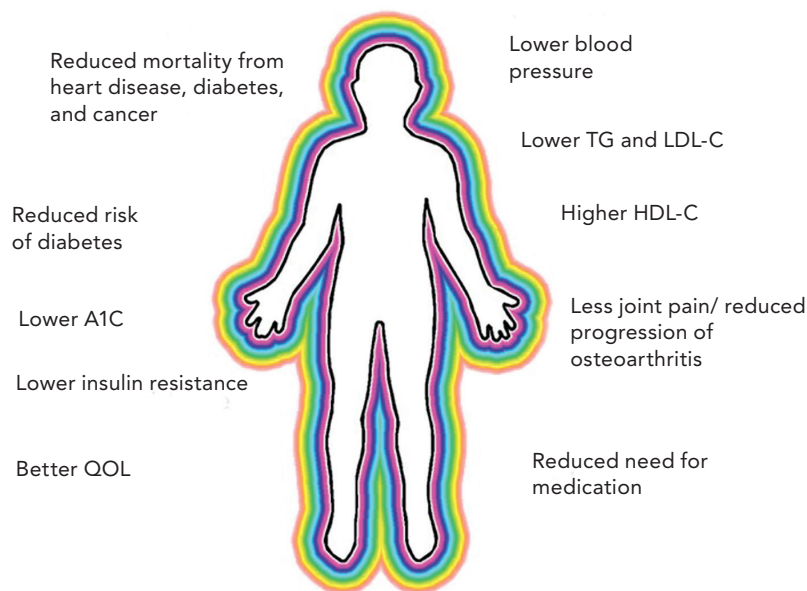
Weight loss of an average of  $13 \pm 7.7$  kg reduced gastroesophageal reflux disease (GERD) symptoms and the amount of weight lost correlated with improvements in symptom scores.<sup>132</sup> In another trial, mean weight loss of 4.0 kg improved GERD symptom scores by 75 percent from baseline.<sup>133</sup>

### *Impact of Weight Loss on Mortality*

As already discussed, there are significant data to show that weight loss impacts various metabolic parameters and other disease consequences of obesity, but the ultimate question about weight loss is whether it impacts the most important outcome, mortality. In a systematic review, women with obesity-related illnesses, who had intentional weight loss, irrespective of the amount of weight lost, had an associated reduced risk of death, CVD death, cancer and diabetes-related death.<sup>134</sup> Weight loss appeared more beneficial if achieved within one year. In this same systematic review, men with general illness who lost weight intentionally appeared to have a reduced risk of diabetes-related death, but there was no demonstrable effect on CVD mortality, and cancer mortality appeared increased.<sup>134</sup> Individual trials have shown mortality benefits of weight loss in men. In a prospective cohort study using a probability sample of the U.S. population, intentional weight loss was associated with 24 percent lower all-cause mortality rates among men and women.<sup>135</sup> The reduced risk was largely driven by persons who reported a weight loss of 1 to 9 kg. Intentional weight loss in patients with overweight or obesity who already have CVD is associated with only a nonsignificant trend for lower mortality.<sup>75</sup> Marked weight loss in those with CVD, with bariatric surgery, does result in improved mortality risk partially related to reduced CVD events.<sup>136,137</sup>

Weight loss appears to be especially important in reducing mortality in those who already have T2DM. In a study of men and women, diabetes treatment associated weight loss produced an approximately 25 percent reduced mortality rate.<sup>138</sup> In a 12-year follow-up of the Swedish Malmo Prevention Trial, a net 2.8 percent decrease in BMI reduced risk for death from heart disease and all-cause mortality by 50 percent in men with im-

Exhibit 3: Benefits of 5% to 10% Weight Loss



paired glucose tolerance (IGT).<sup>139</sup> In observational cohort studies, adults with overweight or obesity and T2DM who intentionally lost 9 to 13 kg had a 25 percent decrease in mortality rate compared to weight-stable controls.<sup>18,140</sup> Lastly, metformin treatment was associated with decreased mortality and myocardial infarction-related mortality in the UK Prospective Diabetes Study over 10 years.<sup>141</sup>

Weight lost more quickly (i.e., within a year) in an epidemiological framework may be beneficial with respect to risk of mortality.<sup>134</sup> Losing a larger amount of weight (more than 9 Kg) does not seem to have an additional effect on mortality compared with a less than 9 kg weight loss, indicating that it is likely to be the weight loss itself that may be beneficial in reducing risk of death.<sup>134</sup> Exhibit 3 provides a visual overview of the benefits of modest weight loss.

#### Cost-Effectiveness of Modest Weight Loss

Aside from the morbidity and mortality benefits of modest weight loss, managed care and employer decision makers may wonder if programs or treatments to help their members lose weight are cost effective. There are a few studies examining the cost-effectiveness of lifestyle and pharmacotherapy interventions. The majority of cost-effectiveness data published on weight loss is with bariatric surgery because of the substantial upfront costs of these procedures.

A recent systematic review of the literature showed that for individuals with a BMI over 40 kg/

m<sup>2</sup> a 5 percent weight reduction would save \$2,137 in medical costs annually.<sup>142</sup> For those with BMIs of 35 kg/m<sup>2</sup>, the same percentage reduction would save \$528 in medical costs annually.<sup>142</sup>

An Australian analysis found that two diet programs (DASH and low-fat) used in a population suffering overweight or obesity had incremental cost-effectiveness ratios (ICERs) of AUS\$12,000 – \$13,000 per DALY. This was a cost savings of AUS\$68,000 to \$130,000. The authors did note that neither diet intervention reduced the body weight-related disease burden at a population level by more than 0.1 percent and that the modest weight loss during the interventions, post-intervention weight regain, and low participation limited the health benefits.<sup>143</sup>

An economic model of diet and exercise over six years for people with impaired glucose tolerance done in the United Kingdom found a high initial cost per additional quality-adjusted life year (QALY), but by the sixth year the cost per QALY was £13,389.<sup>134</sup> This analysis did not include cost savings from diseases other than T2DM, and is therefore conservative. The initial high incremental cost per additional QALY of £113,905 occurs because of the initial investment in lifestyle change therapies in the intervention group, but the initial expenditures are subsequently offset by reduced T2DM disease treatment costs for the intervention group.

In a United Kingdom health technology assessment, orlistat was found to be cost effective when



used in primary care for weight loss in those patients with obesity-related disease. Compared with lifestyle advice, the mean ICER for orlistat ranged between £970 and £59,174.<sup>144</sup> An Australian cost-effectiveness analysis found that one year use of orlistat targeting Australian adults with obesity but without obesity-related disease was not cost effective using a lifetime horizon for costs and health outcomes and a health sector perspective for costs.<sup>145</sup> This analysis found that orlistat use reduced body weight-related disease burden at the population level by 0.1 percent. As with the diet analysis discussed previously, the authors noted that modest weight loss during the interventions, rapid post-intervention weight regain, and low adherence limited the health benefits of orlistat treatment. It is important to note that therapy with anti-obesity medication is not recommended currently in the U.S. for those patients who are overweight without obesity-related disease.<sup>19</sup>

In a cost-effectiveness analysis of three commercial weight loss programs (Weight Watchers, Vtrim, Jenny Craig) and anti-obesity medications (phentermine/topiramate extended release, lorcaserin, and orlistat), Weight Watchers and phentermine/topiramate extended-release (Qsymia<sup>®</sup>) were the two most cost-effective strategies for nonsurgical weight loss compared with lorcaserin and orlistat.<sup>146</sup> Naltrexone/bupropion (Contrave<sup>®</sup>) nor liraglutide 3mg (Saxenda<sup>®</sup>) were not included in this analysis because they were not yet FDA approved at the time of the analysis. A recent cost-effectiveness analysis of phentermine/topiramate showed an incremental cost-effectiveness ratio (ICER) of \$48,340 per QALY gained.<sup>147</sup> An ICER of less than \$50,000 per QALY gained is considered beneficial. No specific cost-effectiveness studies were identified for naltrexone/bupropion or liraglutide 3 mg.

Targeting high-risk individuals with weight loss medications is likely to be more cost effective than treating lower-risk individuals. Avenell and colleagues concluded that given the combination of the costly implications of obesity, especially CVD and T2DM, interventions targeted toward high-risk individuals with obesity (e.g., those with diabetes, prediabetes, hypertension, high risk for CVD, or those who have severe obesity) are likely to be cost effective.<sup>134</sup> This strategy of targeting high-risk patients for treatment with pharmacotherapy is reflected in the management guidelines.<sup>18,19</sup>

Yet, there is still much work to be done. Considering the impact of obesity on health care costs, the literature has a relative paucity of articles comparing the impact of medical versus surgical treatment of obesity and comparative effectiveness studies of the various medical therapies, both pharmacologic and

non-pharmacologic, are lacking.

### *Modest Weight Loss Conclusion*

Overall, patients do not have to lose a dramatic amount of weight or completely resolve their obesity to benefit from weight loss. As expert obesity guidelines advocate, modest (5-10%) loss of baseline weight leads to substantial obesity-related disease benefits and mortality benefit.

### **Treatment of Obesity**

Helping patients achieve modest weight loss requires a multimodal approach. Lifestyle changes including changes in nutritional quality, quantity and timing, alteration in physical activity, and changing eating, sleeping and other behaviors are necessary to combat the current obesogenic environment. The current literature supports success being achieved in a statistically greater percentage of patients when anti-obesity pharmacotherapy and/or surgery are added.<sup>148</sup> The focus of this section is pharmacotherapy.

### *Impact of Pharmacotherapy on Physiology of Weight Control*

The physiology of human weight control is complicated and modulated by a complex pathway of neurotransmitters between the brain, gut and adipose tissue. This pathway serves to protect the human body from weight loss by causing an increase in appetite and an improvement in metabolic efficiency as weight loss occurs. As changes are made in the amount of calories consumed, the human body decreases the amount of calories burned as a protective mechanism to maintain the weight set point. The more weight one desires to lose, the more changes one must make to continue weight loss and the more appetite increases. Pharmacotherapy helps to tip the balance in the neuroregulatory pathways in favor of continued weight loss. Anti-obesity medications, with the exception of orlistat, reduce appetite and decrease cravings. Medications can help keep patients on track with eating behavior changes. For behavior change to stick and become a habit, humans must be rewarded for their efforts. Medications in effect help to increase our reward for the amount of change being made and thus help to create healthier habits over time.

### *Medications for Effective Obesity Treatment*

As noted previously, there are medications that allow patients to reach the 5 to 10 percent weight loss goal at almost twice the rate they would be able to do without medication. Current evidence supports starting medication treatment earlier and continuing medication treatment indefinitely, similar to other

chronic diseases such as hypertension and diabetes. Pharmacotherapy is currently indicated for patients with a BMI greater than or equal to 30 or BMI greater or equal to 27 with an obesity-related comorbidity such as pre-diabetes, sleep apnea, T2DM, CVD, hypertension or nonalcoholic steatohepatitis.<sup>18,19,22</sup> Some basic tenants of anti-obesity medications are given in Exhibit 4.

### *Sympathomimetics*

Phentermine is the most commonly prescribed medication to treat obesity and is in the class of medication defined as sympathomimetics. It has been available since the 1950s and is FDA approved for “short-term use”, usually interpreted as 12 weeks. Since that time, numerous studies and society guidelines support the off-label safety and efficacy of using phentermine longer term.<sup>149</sup> It suppresses appetite by norepinephrine agonism in the hypothalamus. There are multiple doses and dosing frequency patterns used that are personalized to patient response and needs. Other sympathomimetics occasionally used are diethylpropion and phendimetrazine. These medications are inexpensive but can have side effects that can make them hard to tolerate for certain patients. Anxiety, poor sleep, dry mouth, and increased heart rate can be limiting factors. These medications should not be used in patients with active CVD or uncontrolled hypertension.

### *Orlistat (Xenical®)*

Orlistat is an inhibitor of gastrointestinal lipase. The gastrointestinal side effects of flatulence and greasy oily stool leakage can deter its use. It has to be used in conjunction with a low fat diet or these side effects are much worse. Low fat diets are currently not the most widely recommended, so this can be challenging for clinicians and patients. Orlistat is FDA approved for use in pediatric patients ages 12 and older, which makes it unique among the anti-obesity medication class. There is also an over-the-counter version (Alli®), making it the most accessible medication.

### *Lorcaserin (Belviq®)*

Lorcaserin is a serotonin (5HT<sub>2C</sub>) receptor agonist and is thought to decrease food intake via activation of pro-opiomelanocortin (POMC) neurons in the hypothalamus. Three placebo-controlled trials of lorcaserin have demonstrated a 3.0 to 3.8 percent placebo subtracted weight loss and documented no adverse CV effects or valvulopathy that was concerning with previous nonspecific serotonin receptor agonists.<sup>150-152</sup> In patients with T2DM (A1C 7-10%), treatment with lorcaserin resulted in a 0.5

percent reduction in A1C.<sup>152</sup> Lorcaserin is well tolerated with very few side effects, making it easy to use in patients that may have trouble otherwise tolerating medications or those taking multiple medications already. It should be used with caution in patients taking antidepressants that also affect serotonin. It comes in a once a day controlled-release version and a twice a day short-acting version. The twice a day version may be helpful in patients that need an evening dose of medication to help combat night eating behavior, as other medications that are once a day may wear off in the evening when eating struggles may be the worst.

### *Phentermine/topiramate (Qsymia®)*

The combination of phentermine and topiramate extended release was approved for weight loss in 2012. Topiramate is a weak carbonic anhydrase inhibitor used to treat epilepsy, prevent migraine, and stabilize mood. Topiramate may reduce compulsive or addictive food craving as it has been studied in binge eating disorder and found to affect behavior change by decreasing binge eating frequency.<sup>153</sup> Topiramate also has a side effect of dysgeusia, a condition that modifies the taste of food, making it less desirable.

Two randomized, controlled trials of phentermine/topiramate demonstrated greater than 8.5 percent placebo-subtracted weight loss at one year.<sup>154,155</sup> The medication is well tolerated and side effects of topiramate, such as word finding issues and numbness and tingling of the extremities, are manageable if they occur. Topiramate also makes carbonated beverages taste bad. This side effect is especially useful for patients wishing to eliminate sugar-sweetened carbonated beverages that add to excessive weight gain. The once a day sustained-release nature of the medication may improve adherence. While all anti-obesity medications are contraindicated in pregnancy, topiramate, in particular, can increase the risk of orofacial clefts and pregnancy testing regularly while on the medication is recommended.

### *Naltrexone/Bupropion (Contrave®)*

The combination of naltrexone and bupropion was approved for weight loss in 2014. The weight loss effect is based on the combined mechanisms of action on the hypothalamic melanocortin system and the mesolimbic dopamine reward system. Although studies demonstrate mild weight loss with bupropion monotherapy, naltrexone monotherapy has not been effective in treating obesity.<sup>156,157</sup>

Because naltrexone is a centrally acting opioid receptor antagonist, this medication cannot be used

#### Exhibit 4: Basic Tenets of Anti-Obesity Pharmacotherapy

- All anti-obesity medications are more effective than placebo in accomplishing a 5-10% clinically significant weight loss goal.
- Long term treatment with pharmacotherapy is necessary for long term results. Weight regain occurs when medications are discontinued much like hypertension returns when anti-hypertensives are discontinued unless substantial lifestyle changes have been accomplished in the interim.
- Pharmacotherapy should be tailored to the individual patient based on other co-morbid diseases, genetics, past medical history and more importantly individual response to treatment.
- Individual patients may respond differently to each medication. There are responders and non-responders to each medication for various reasons.
- With the exception of orlistat, all FDA approved weight loss medications reduce appetite, decrease cravings and help patients to achieve weight loss when physiological mechanisms are trying to promote weight gain.

in patients who are taking opioid medications for pain control. The most common side effect with the combination is nausea that tends to remit the longer the medication is continued but also can lead to discontinuation. The dose is titrated to minimize the side effect of nausea to a maximum dose of 32mg naltrexone and 360mg bupropion divided twice a day. This combination, which is given twice a day, is another option for those with night eating issues and could possibly be useful in patients with compulsive eating behavior or depressed emotional eating given bupropion is helpful in compulsive disorders and depression.

Four 56-week randomized, placebo-controlled trials were conducted comparing naltrexone/bupropion with placebo and found weight loss of 4.2 to 4.8 percent over placebo.<sup>87,158,159</sup> Another study in patients with diabetes showed a reduction in A1C of 0.5 percent compared to placebo.<sup>160</sup> This medication should not be used in patients with a history of seizure disorder or uncontrolled hypertension.

#### *Liraglutide 3mg (Saxenda®)*

The 3mg dose of liraglutide was approved in December of 2014 for the treatment of obesity. This is a higher dose of liraglutide (Victoza®) already approved for treatment of T2DM and more recently approved for prevention of cardiovascular disease in patients with T2DM. The 1.8 mg dose of liraglutide has been shown to reduce the risk of cardiovascular death in those with T2DM by 22 percent.<sup>161</sup> Liraglutide is unique among the anti-obesity medications as it is a once daily injection which has metabolic effects related to blood glucose metabolism. Lira-

glutide is a glucagon-like peptide-1 (GLP-1) agonist that shares 97 percent homology to native GLP-1. GLP-1 is a neuropeptide produced by the L cells in the intestine in response to food intake causing a decrease in glucose levels, delaying gastric emptying, and increasing satiety through stimulation of POMC neurons in the arcuate nucleus of the hypothalamus. Native GLP-1 increases are seen post bariatric surgery and are thought to be partially responsible for the successful outcome of surgery along with other neuroendocrine peptide alterations.

Randomized controlled trials have demonstrated a 6 percent placebo subtracted weight loss with liraglutide 3 mg daily.<sup>76,162,163</sup> A recent study also showed that T2DM was prevented in 80 percent of patients with prediabetes treated for three years with liraglutide 3 mg and prediabetes was reversed in 60 percent of these patients.<sup>76</sup> An estimated 86 million people in the U.S. have prediabetes and nine out of 10 do not know they have it. Currently, one of every three Medicare dollars goes to treat diabetes. Preventing diabetes through weight loss can therefore be a huge cost savings.

Liraglutide is well tolerated. Common side-effects are gastrointestinal, specifically nausea, which tends to subside over time. The medication is titrated weekly to reach the 3.0 mg dose to reduce the risk of substantial nausea. Dropout rates were low in studies with 72 to 78 percent completion rates, some of the highest completion rates for weight loss studies.

Given this is a subcutaneous injection, some patients may be averse to this method of delivery; however, with proper instruction, most patients do not find this prohibitive. Many patients actu-



ally like it as they take multiple oral medications already and do not wish to add another oral drug. This medication should not be used in patients with a history of pancreatitis or personal or family history of thyroid C-cell tumors. High cost, if not covered by insurance, is the biggest barrier to the selection of this agent.

Almost two-thirds of patients are able to be successful with a 5 percent weight loss with our most effective medications of liraglutide 3 mg and phentermine/topiramate.<sup>164</sup> This refutes the belief that medication for weight loss is not effective, which is held by the vast majority of the lay population and by many physicians as well. Many patients believe they should be able to lose weight effectively on their own without the use of medications or programs to help them. This is a popular belief that is validated by lack of coverage for medications and lack of prescribing them by physicians. Most patients do not believe they can treat their cancer or diabetes on their own and coverage for these medications is universal by most employers.

Pharmacotherapy has an ever-increasing role in the treatment of the chronic disease of obesity. We must change from a mindset centered on obesity as a character flaw to one of chemistry and the chronic disease model of effective care. Managed care coverage of medications to treat obesity for reducing the burden of other diseases and lowering health care and other costs to society is a must.

#### *Pharmacotherapy Conclusion*

Like other chronic diseases, obesity is treatable with a combination of lifestyle, pharmacotherapy and surgery. Using pharmacotherapy in conjunction with lifestyle modification, patients are able to achieve a 5 to 10 percent weight loss almost twice as often as without the use of medication.

#### **Maintaining Weight Loss for the Long Term**

Once a patient has lost weight, it is important to maintain the loss, which can be as difficult as losing the weight. Weight regain is very common after someone stops a weight loss program or anti-obesity medication because of the counter-regulatory hormone response to weight loss. Approximately 30 to 35 percent of lost weight is regained one year following intentional weight loss and 50 percent of patients will return to their baseline weight by the fifth year out from weight loss.<sup>165</sup> The health outcomes of weight loss followed by weight regain are not well understood, and more research is needed to determine whether health benefits achieved through weight loss persist despite partial or full weight regain.<sup>166</sup>

#### *Factors Associated With*

#### *Maintaining Weight Loss*

The National Weight Control Registry tracks over 10,000 adults who have lost at least 30 pounds and have kept it off for one year or longer (<http://www.nwcr.ws>). Approximately 20 percent of individuals are successful at long-term weight loss when defined as losing at least 10 percent of initial body weight and maintaining that loss for at least one year.<sup>167</sup>

Metabolic adaptations occur with weight loss that result in increased hunger and the desire to eat. In one study, at one year after initial weight reduction with a very low energy diet, levels of the circulating mediators of appetite including leptin, peptide YY, cholecystokinin, insulin, ghrelin, gastric inhibitory polypeptide, and pancreatic polypeptide did not revert to the levels recorded before weight loss.<sup>168</sup> Weight loss also lowers total daily energy expenditure from a disproportionately greater decrease in resting metabolic rate than would be predicted based on the decline in body mass and decreased thermic effect of food.<sup>169</sup> These metabolic adaptations can readily promote weight regain.

Another part of weight regain is attributable to an inability to maintain healthy eating and exercise behaviors over time.<sup>167</sup> The most frequently mentioned strategies used by participants in the National Weight Control Registry who have been successful at maintaining weight loss are shown in Exhibit 5.<sup>167,169,171</sup> Successful weight maintenance requires a lifelong commitment to healthful food selection, regular physical activity, and diligent weight monitoring. It also likely requires chronic medication use for many patients. Because of the pathophysiology of obesity and metabolic changes with weight loss, available data support the need for long-term use of weight loss medications in appropriate patients to support weight maintenance.<sup>22</sup> Overall, a chronic weight management plan is needed to help patients maintain clinically meaningful weight loss.

#### **Considerations for Policy-Makers, Clinicians, Payers, and Employers**

As it has been illustrated here, the economic and social implications of the obesity epidemic are substantial. Effective public health strategies to reduce the prevalence of obesity are urgently needed to attenuate the deleterious effects of high BMI on population health and quality of life. From the societal perspective, all stakeholders must do a better job to educate the public on the health risks and consequences of obesity. Even with that effort, it may take several years (or even generations) to see a change in the public attitude around this issue. Encouraging programs aimed at combating obesity at

**Exhibit 5: Successful Strategies for Preventing Weight Regain  
from the National Weight Control Registry<sup>167,169,171</sup>**

- Eat breakfast
- Monitor energy and fat intake
- Consume a low calorie/low fat diet
- Exercise daily (~1 hour daily of moderate intensity activity)
- Reduce sedentary activities
- Monitoring weight (at least weekly)
- Maintain a consistent eating pattern (no binges)
- Eat out less than 3x/week
- Take corrective action if weight begins increasing

the community and school level will be increasingly necessary. Stakeholders including payers, employers, health care providers, drug developers, and the food service industry will need to play a critical role in blunting the obesity trend. Unfortunately, under the current epidemiological scenario, there is no expectation that the obesity figures will plateau anytime in the near future. It will only be with a multi-faceted effort from all stakeholders that we will be able to change the relentless increase in the prevalence of obesity and its associated societal and economic cost.

As discussed previously, clinicians, payers, and employers must begin to think of obesity as a chronic disease much like that of other chronic debilitating diseases that are costly and affect patients' morbidity and mortality. Focusing on early treatment will allow for chronic disease modification. Much like we think of treating diseases such as inflammatory bowel disease and rheumatoid arthritis with disease-modifying agents early to prevent long-term complications, we should begin to think of pharmacotherapy for obesity in a similar light.

Clinicians are often unable to give adequate attention to obesity as a medical problem because they often need to manage multiple complex comorbid conditions in the short time that can be allotted to patients. Changes to primary care practice are needed to improve this issue; the moves to a medical home model with a more holistic approach to care may help address weight issues.

Many payers do not cover pharmacologic treatments for obesity, citing lack of comparative data, lack of outcomes, and the potential for misuse and cost as reasons for the benefit exclusion. Adequate comparative effectiveness data are not yet available to allow payers and policy-makers to select the most cost-effective agents for formularies but at least

some, if not all, of the FDA approved anti-obesity medications should be covered like for any other chronic disease. Treating obesity in the earlier stages may prevent patients from developing severe obesity and requiring expensive bariatric surgery. Given the benefits presented in this paper, managed care should be supporting a modest weight loss solution by providing coverage for weight loss programs, chronic anti-obesity medications for appropriate patients to address underlying physiology encouraging weight regain, and long-term maintenance programs.

Every employer must understand that they are already paying for the direct and indirect costs of overweight and obesity. Employers should be encouraging employees to engage in programs aimed at preventing and treating excess weight in order to reduce direct health care costs, workers' compensation claims and associated lost work days, absenteeism, and presenteeism. Large employers have been offering wellness/health promotion programs for several years aimed at getting employees to adopt healthful lifestyles. Those that target weight primarily encourage physical activity and making dietary changes but do not necessarily include referral for anti-obesity medications nor long-term weight maintenance strategies. Employer-based strategies can target several areas, including health benefit design and incentives to encourage healthy behavior, workplace environmental support for healthy lifestyles, culture of health at work, communication, and family and community engagement. Exhibit 6 provides some strategies for each of these target areas.<sup>172</sup>

Several large national employers have had significant success in showing positive outcomes with wellness/health promotion programs.<sup>172</sup> Smaller employers (those with fewer than 500 employees),

### Exhibit 6: Employer Strategies<sup>172</sup>

Area	Strategies
Health benefit design and incentives to encourage healthy behavior.	<ul style="list-style-type: none"> <li>• Lower premiums for employees who complete health risk assessment and a recommended health-coaching activity</li> <li>• Reimbursement for consultations with a registered dietician.</li> <li>• Cash, points, or prizes as a reward for regular physical activity or weight loss.</li> </ul>
Environmental support for healthy lifestyles.	<ul style="list-style-type: none"> <li>• Healthful on-site dining, catering and vending</li> <li>• Open stairwells, out of the way elevators, walking paths and signage marking distances and/or encouraging physical activity.</li> <li>• Break rooms with stretching aids.</li> <li>• Free filtered water.</li> <li>• Walking or active meetings.</li> <li>• Standing desks.</li> </ul>
Culture of health at work.	<ul style="list-style-type: none"> <li>• Strong visible leadership participation.</li> </ul>
Communications about health and wellness program offerings.	<ul style="list-style-type: none"> <li>• Site, team and/or individual competition to promote engagement.</li> <li>• Health champions (peer leaders).</li> <li>• Affinity groups.</li> <li>• Other strategies using the social environment at the workplace to promote health.</li> </ul>
Community and family connections.	<ul style="list-style-type: none"> <li>• Employee education and targeted communications.</li> <li>• Healthy dinners-to-go offered in employees' café.</li> <li>• Family and/or community access to company fitness facilities.</li> <li>• Corporate support of physical education, (e.g., schools, playgrounds and parks).</li> <li>• Weight loss program access for spouses and children.</li> </ul>

which represent the majority of U.S. employers, are far less likely to offer health promotion programs. Only 21 percent of a nationally representative sample of small employers offered weight management programs.<sup>173</sup> In addition to workplace wellness/health promotion programs, it would be prudent for employers to include coverage for obesity treatment in their benefit design to improve productivity and decrease health care spending while simultaneously creating a healthier workplace.

### Overall Conclusion

Given a multitude of biological and societal factors, the majority of the U.S. adult population struggles with overweight or obesity. Excess body weight causes significant health and financial burden on the individual, healthcare system, and society. Given the direct association of obesity with morbidity and mortality, it is clear that the current obesity epidemic, if left unchecked, will have catastrophic economic and clinical consequences in the U.S. A large body of evidence demonstrates the morbidity and mortality benefits of modest weight loss with lifestyle interventions and pharmacotherapy. Additionally, there is growing evidence demonstrating the positive financial impact of weight loss. Anti-obesity medication is needed in many cases because lifestyle interventions alone fail to produce adequate results given the biologic defense of the weight set

point. All involved stakeholders must consider and treat obesity as the chronic disease it is which requires chronic holistic treatment.

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