

Oregon Health Resources Commission



Medical Management of Obesity

**MedTAP Report
June 2007**

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Health Resources Commission

The State of Oregon's Health Resources Commission (HRC) is a volunteer commission appointed by the Governor. The HRC provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use MedTAP or subcommittees, the members to be

approved by the commission. The appointees must have the appropriate expertise to develop a medical technology assessment. All MedTAP and subcommittee deliberations are open, where public testimony is encouraged. MedTAP or subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 1993 ORS 442.583 statute authorized the creation of the MedTAP that specifically directs the HRC to encourage the rational, responsible and appropriate allocation and use of health technology in Oregon. The HRC MedTAP report will be used to inform and influence decision makers, including consumers, through the collection, analysis, synthesis, and dissemination of information concerning the use, effectiveness and cost of health technologies.

In the spring of 2006 the HRC appointed an Obesity Management MedTAP to perform an evidence-based review and two reports on:

1. The use of Bariatric Surgery for the treatment of Morbid Obesity in adults
2. The Medical Management of Obesity in comparison to Bariatric Surgery

Members of the subcommittee consisted of a Medical Director from an Oregon physician-owned liability carrier, a Cardiologist, an Endocrinologist, the Medical Director of the Health Services Commission, the Medical Director for Oregon Medicare, a Registered Dietician, a Nurse Practitioner, a State Epidemiologist, a Pediatrician and a Pharmacist. The subcommittee held six meetings for the report on Medical Management of Obesity. All meetings were held in public with appropriate notice provided.

MedTAP members developed and finalized key questions for the review of Medical Management of Obesity specifying patient populations, interventions to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was

specifically sought for subgroups of patients based on co-morbidities, age, and other demographics.

The AHRQ's systematic report, "Pharmacological and Surgical Treatment of Obesity" Evidence Report/Technology Assessment: Number 103 was completed in July, 2004, circulated to subcommittee members and posted on the web. The AHRQ report was a summation of systematic reviews through 2004 and served as a basis for this report. However, there has been considerable literature since then; the MedTAP subcommittee used the EPC's standardized methods to review and grade the medical literature through January 2007. The subcommittee met on January 25, 2007 to review the document and by consensus agreed to adopt the AHRQ's report. The MedTAP report was finalized at the June 15, 2007 HRC meeting. Time was allotted for public comment, questions and testimony at each meeting.

This report does not recite or characterize all the evidence that was discussed by the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Health Services Commission (HSC), public and private health plans, and the public in general.

The Health Resources Commission will seek medical evidence for new developments in obesity management. Working cooperatively with Oregon Health Policy and Research (OHPR) Data Unit, the commission will obtain Oregon data needed to monitor the utilization of Bariatric Surgery and its effects on the health system. Substantive changes will be brought to the attention of the Health Resources Commission who may choose to reconvene an Obesity Management MedTAP.

The full AHRQ's report, *Pharmacological and Surgical Treatment of Obesity* is available on the Office for Oregon Health Policy & Research Medical Technology Evaluation web site. Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website:

http://www.oregon.gov/DAS/OHPPR/HRC/MedTap_page.shtml

You may request more information including copies of the draft report, minutes and tapes of subcommittee meetings, from:

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Quality of the Evidence:

For quality of evidence the Obesity Management MedTAP took into account the number of studies, the total number of patients in each study, the length of the study period, and the end points of the studies. Statistical significance was an important consideration. The subcommittee utilized the AHRQ's ratings of "good, fair or poor" for grading the body of evidence. Poor evidence was excluded. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency and power of the body of evidence relevant to that question.

Key Questions:

- 1. What is the evidence for the effectiveness of non-surgical treatments (pharmacological, dietary, behavioral, and/or physical activity) in improving objective outcomes for obesity such as sustained weight loss; waist/hip ratio; diabetes prevention, improvement or reversal; hyperlipidemia; hypertension; cardiovascular disease; mortality; obstructive sleep apnea; metabolic syndrome; or non-alcoholic fatty liver disease (NAFLD)**
- 2. What is the evidence for the effectiveness of combination of non-surgical treatments?**
- 3. What are the adverse effects associated with non-surgical treatments in patients?**

4. Are there any subgroups of patients in which the effectiveness of non-surgical treatments are paramount?
5. What is the evidence for effectiveness of non-surgical treatments in prevention of weight gain for children and adults?
6. What is the effectiveness and cost-effectiveness of treatments of obesity measured in \$/QALY (quality adjusted years)?

Inclusion criteria:

1. Populations:

a. Adults with obesity (BMI \geq 28)

$$\text{BMI} = \frac{\text{weight in pounds}}{\text{Height in inches}^2} \times 703$$

BMI 25-30: Overweight

BMI 30-40: Obese

BMI \geq 40: Morbidly Obese

b. Children (<18)

BMI 85th-94th Percentile for their age and sex = At risk for obesity

BMI \geq 95th Percentile for their age and sex = Obese

2. Exclusions

a. Secondary types of obesity are excluded (e.g. hypothyroidism, Cushing's)

3. Interventions

a. Dietary

i. Low calorie diet (LCD)

ii. Very low calorie diet (VLCD)

iii. Low carbohydrate

iv. Low fat

v. Glycemic index

vi. Protein sparing

b. Pharmacological

i. Bupropion (Wellbutrin)

ii. Diethylpropion

iii. Exenatide (Byetta)

iv. Fluoxetine (Prozac)

v. Phenteramine

vi. Sibutramine (Meridia)

vii. Topiramate (Topamax)

viii. Xenical (Orlistat)

ix. Zonisamide

- c. Behavioral**
 - i. Self monitoring**
 - ii. Stimulus control**
 - iii. Cognitive restructuring**
 - iv. Nutrition education**
 - v. Group dynamics**
 - vi. Psychotherapy**
- d. Physical Activity**
 - i. Exercise**
 - ii. Non-exercise activity thermogenesis (NEAT)**
- e. Combination of pharmaceutical, dietary, behavioral, and physical activity**
- 4. Outcomes**
 - a. Sustained weight loss (1 or 2 years)**
 - b. Sustained decreased waist/hip ratio**
 - c. Prevention, reduction, resolution, or reduced use of medications or treatment of:**
 - i. Diabetes Type 2**
 - ii. Hyperlipidemia**
 - iii. Hypertension**
 - iv. Mortality**
 - v. Cardiovascular events**
 - vi. Obstructive sleep apnea**
 - vii. Metabolic Syndrome**
 - viii. Non-alcoholic fatty liver disease (NAFL-D)**
 - d. Quality of life (QOL)**
- 5. Safety and Adverse Effects:**
 - a. Mortality**
 - b. Morbidity**
 - i. Drug dependence on anorexants**
 - ii. Anxiety/depression**
 - iii. Alternative addiction**
 - iv. Nutritional (e.g. anemia, metabolic bone disease, and vitamin deficiency)**
 - v. Cholelithiasis**
 - vi. Gout**
 - vii. Telogen effluvium**

Clinical Overview

Prevalence

Obesity underlies a wide range of serious chronic conditions. The increased prevalence of obesity among both children and adults in the US has received much publicity. Despite the calls for action at various levels, the obesity epidemic is progressive. Obesity has reached rampant proportions in the US with only one third of the US population now being of normal weight. BMI data for the US show over 64% of US adults are classified as obese (BMI ≥ 30) or overweight (BMI between 25 and 29.9).¹ The prevalence of obesity has increased by 61% in the last decade and has shown no sign of slowing down. This increase has affected all racial groups and both genders. Much of this increase has been among younger individuals, including children, with grave implications for the future. Among the young, 13% of children aged 6-11 years and 14% of adolescents age 12-19 years were overweight in 1999, representing a tripling of prevalence of overweight in these age groups over the previous 20 years. Overweight children are more likely than children with healthy weights to be overweight or obese as adults. Moreover the adverse health effects only get more severe with age and lead experts in obesity to refer to pound/years analogous to pack/years with smoking. Also alarming is the rate of morbid obesity: BMI ≥ 40 .² Thus, it is recommended that the fourth vital sign be a calculation of BMI as part of health maintenance with weight loss therapy prescribed for all patients who have a BMI >25 .

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1995, 2005

(*BMI ≥ 30 , or about 30 lbs overweight for 5'4" person)

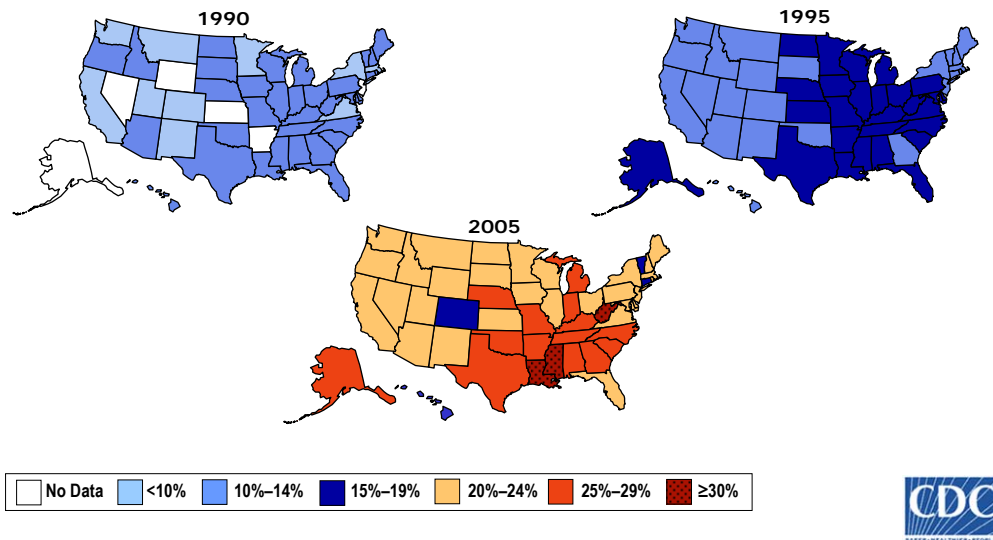


Figure 1

Causes

¹ National Centers for Health Statistics, CDC. Prevalence of overweight and obesity among adults: US, 1999-2000. Washington, DC: National Centers for Health Statistics, CDC

² Flegal KM, Carroll MD, Odgen CL, et al. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* 2002; 288:1723-7.

There are multiple mechanisms contributing to the vulnerability to obesity including genetic, developmental, and environmental factors that are likely to interact in diverse ways among individuals to produce the behavioral phenotype of overeating.³ Adoption twin, and family studies have consistently noted that obesity has a strong heritable component with 30%-70% of variability in body weight or fat mass being genetically determined.⁴ Pima Indians living in Arizona have been compared with distant relatives living in Mexico who are much more physically active and eat a diet 50% lower in fat. The Mexican Pimas average 57 pounds lighter than their Arizona counterparts and few have diabetes.⁵

Our environment has contributed to the exponential increase of obesity in this country. The “perfect storm” has been created by the societal change of fast junk foods, vending machines, eating out, super-sized portions, displacement of fruits and vegetables, decreased physical activity, increased sedentary life style, and change in body perception to accept “obesity” as a normal part of aging. Another more salutary environmental trend contributing to increased rate of overweight and obesity in the US is the decline in the prevalence of smoking in recent years. One quarter of the increase in prevalence of overweight for men in the past 10 years and one-sixth of the increase for women is attributable to smoking cessation.⁶ Yet the health benefits of smoking cessation far outweigh the negative consequences of weight gain. Smoking cessation related weight gain can be minimized if cessation is accompanied by a moderate increase in exercise.⁷

Small changes in energy balance can result in major changes in weight. For example, if an average adult were to consume 120 calories a day, just 10 potato chips, without any change in physical activity, they would put on one pound of weight in a month or 12 pounds in a year. It is the accumulative effect of many small changes in our eating and physical activity patterns that has led us to the obesity epidemic we have today.

The discrepancy between the successes of the metabolic treatment of the consequences of obesity and the failure of behavioral treatments to prevent or reverse obesity highlight the fact that this condition is not only a metabolic disorder, but also a brain disorder. Consideration of the mental component of obesity should be a key target in the treatment of obesity to facilitate compliance and minimize relapse. The American Psychiatric Association DSM-V task force is recommending that some forms of obesity such as binge, emotional, and nocturnal eating are driven by excessive motivational drive for food and should be included as a mental disorder in DSM-V.⁸ DSM-IV already recognizes other eating disorders such as anorexia and bulimia as mental disorders, but does not recognize obesity despite its devastating medical and psychological consequences. Obesity is characterized by compulsive consumption of food and the inability to restrain from eating

³ Friedman JM Modern science versus the stigma of obesity *Nat Med* 2004; 10:563-569.

⁴ Vogler GP, Sorensen Ti, Stunkard AJ, et al. Influence of genes and shared family environment on adult BMI assessed in an adoption study by a comprehensive path model. *Int J Obes Relat Metab Disorder* 1995; 19:40-45.

⁵ Gibbs WW Gaining on fat. *Sci Am* 1996; 275:88-94.

⁶ Fiegel KM, Troiana RP, Kucamarskir RJ, et al. The influence of smoking cessation on the prevalence of overweight in the US *NEJM* 1995; 333:1165-1170

⁷ Kawachi I, Troisi RJ, Rotnitzky AG, et al. Can physical activity minimize weight gain in women after smoking cessation? *Am J Public Health* 1996; 86:999-1004

⁸ Volkow ND, O’Brien CP Issues for DSM-V: Should obesity be included as a brain disorder? *American Journal of Psychiatry* May 2007; 164:5.

despite the desire to do so. These symptoms are remarkably parallel to those described in DSM-IV for substance abuse and drug dependence which has led some to suggest that obesity may be considered a “food addiction.”⁹

Combinations of diet therapy, behavior modification, prescribed exercise programs, and pharmacotherapy in various combinations are widely used and generally accomplish some degree of weight loss. Unfortunately, the weight loss is usually transient. This report will access the effectiveness of prevention of obesity as summarized in the AHRQ systematic review on Screening and Interventions for Obesity in Adults and Children.¹⁰

Prevention of Obesity

In an effort to improve children’s obesity rates, many states and municipalities have passed or are considering passage of laws to improve nutrition standards for school lunch programs and ban sweetened beverages from school vending machines. The Surgeon General has recommended action to ensure that meals offered through the school breakfast and lunch programs meet nutrition standards.

The second major target for public policy intervention against obesity concerns increasing physical activity. Experts have called for improved infrastructure for exercising in the community, particularly creating and implementing public policy related to the provision of safe and accessible sidewalks, walking and bicycle paths, stairs and daily physical education in schools for all children. Clinicians are being urged to stress the importance of physical activity at medical visits, and to encourage a reduction in television viewing and other “screen time,” which has been shown to increase snacking, portion size, percentage of calories from fat, and overall calories¹¹

Economic Impact of Obesity

Healthcare costs from obesity, now estimated at \$92.6 billion/year, account for 9.1% of the total US health expenditures.¹² As the prevalence of obesity has increased in the US (33% increase in past decade), it is expected that obesity will likely overtake tobacco as the leading preventable cause of mortality.¹³ The cornerstone of obesity treatment remains lifestyle and behavioral modifications in diet and physical activity.

Many providers are hesitant to address weight loss with their patients, as they feel that significant weight loss is not possible through medical means. While it is true that consistent massive weight loss is achievable only with bariatric surgery¹⁴, there is

⁹ Cota D, Tschop MH, Horvath TL, Levine AS Cannabinoids, opioids, and eating behavior: the molecular face of hedonism? *Brain Res Rev* 2006; 51:85-107

¹⁰ National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in adults. The Evidence Report. NIH Publication No 98-4083. Xxx: NIH 1998

¹¹ Finkelstein EA, Ruhm CJ, Kosa KM. Economic causes and consequences of obesity. *Ann Review Public Health*, 2005; 26: 239-257.

¹²Finkelstein EA, Fiebelkorn IC, Wang G. National medical spending attributable to overweight and obesity: how much and who’s paying? *Health Affairs(Milwood)* 2003; [Suppl W3]:219-226.

¹³ Mokdad AH, Marks JS, Stroup DF, et al. Actual cause of death in the United States 2000, *JAMA* 2004;291”1238-1245.

¹⁴ Weaver, KW Bariatric Surgery *Health Resources Commission MedTAP Report* October 2006 p. 19

increasing evidence that medically significant weight loss can be achieved with nonsurgical methods. One recent example is found in the results of the Diabetes Prevention Program in which a moderate average weight loss (7% of body weight) coupled with moderate exercise (150 minutes per week of moderate activity such as walking) was sustained over a period of 3 years in a large cohort. These modest changes were associated with a nearly two thirds reduction in diabetes risk, compared to a one-third risk reduction of diabetes for metformin.¹⁵

Medical Complications of Obesity

Obese and overweight individuals are at increased risk for chronic conditions including type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, obesity related glomerulopathy, non-alcoholic steatorrhea hepatitis, osteoarthritis, and cardiovascular disease,¹⁶ as well as for several major causes of death, including cardiovascular disease, several types of cancer, and diabetes. Obesity is a stronger predictor of mortality and morbidity than either poverty or smoking.¹⁷ Obesity accounts for about 70% of hypertension and 90% of diabetes, both of which account in turn for the majority of end-stage renal disease (ESRD). Sleep apnea, respiratory impairment, osteoarthritis, diminished mobility, gall bladder disease and social stigmatization are all common complications of obesity.¹⁸

Morbidly Obese

The morbidly obese (BMI ≥ 40) patient who presents for surgical evaluation has participated in multiple combinations of medical interventions with variable success and with weight regain commonly occurring after treatment cessation. There are differences between the anticipated long-term risks of non-operative interventions including progressive weight gain and its effect on organ systems vs. the short-term and potentially life-threatening operative risk and complications.

With the growth in the use of bariatric surgery has come increasing scrutiny of its safety. Obesity poses a long-term rather than a short-term health risk. The “elective” nature of these surgeries demands a low risk. While laparoscopic procedures have appealed to patients, they are challenging to perform and have a considerable learning curve. Media exposure of less invasive procedures has heightened the public’s awareness, yet reports of adverse outcomes, the closing of bariatric surgery programs because of perceived safety problem, and the sense that inexperienced surgeons are involved in this procedure has made evaluation of bariatric surgical safety paramount.

¹⁵ Knowler WC, Barrett-Conner E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *NEJM* 2002;346:393-403

¹⁶ McTigue KM, Harris R, Hemphill B, et al. Screening and Interventions for Obesity in Adults: Summary of the evidence for the US Preventive Services Task force. *Ann Int Med* 2003;139:933-49.

¹⁷ Peeters A, Varendregt JJ, Willekens F, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Ann Intern Medicine* 2003;138:24-32

¹⁸ McTigue KM, Harris R, Hemphill B, et al. Screening and Interventions for Obesity in Adults: Summary of the evidence for the US Preventive Services Task force. *Ann Int Med* 2003;139:933-49

The desirability for prevention of morbid obesity and application of effective medical intervention for morbid obesity is recognized. Effective treatment of morbid obesity is challenging and is expected to require major advances in pharmacotherapy as well as appropriate changes in public policy. The Longitudinal Assessment of Bariatric Surgery (LABS) is a National Institutes of Health (NIH)-funded consortium of six clinical centers and a data coordinating center working in cooperation with NIH scientific staff to plan, develop, and conduct coordinated clinical, epidemiological, and behavioral research in the field of bariatric surgery. Topics include improving patient safety, more detailed identification of optimal candidates for specific bariatric surgical procedures, responses of specific co-morbidities to surgical intervention, and the mechanism of action of the different surgical procedures.

Summary of Results

Key Question 1 ***What is the evidence for the effectiveness of non-surgical treatments (pharmacological, dietary, behavioral, physical activity) in improving objective outcomes for obesity such as : sustained weight loss; decreased waist/hip ratio; diabetes prevention, improvement, or reversal; hyperlipidemia; hypertension; mortality; cardiovascular disease; obstructive sleep apnea; metabolic syndrome; or non-alcoholic fatty liver disease (NAFL-D) .***

Pharmacological therapy

The outcome of interest specified by pharmaceutical researchers was weight loss. However, excess weight is associated with other health outcomes such as diabetes mellitus type 2, hypertension, sleep apnea, osteoarthritis, hyperlipidemia, etc. They endeavored to assess treatments by comparing their efficacy on these outcomes. Very few of the pharmaceutical studies reported these outcomes, making it not feasible to make across-study comparisons addressing the control of co-morbidities.

The AHRQ Systematic Review summarized 78 medication studies that reported on sertraline (1), zonisamide (1), orlistat (49), bupropion (5), topiramate (9), and fluoxetine (13).¹⁹ Of the medications assessed three had up-to-date existing meta-analyses (sibutramine, phentermine, and diethylpropion), and others had a sufficient number of new studies to justify a new meta-analysis (orlistat, topiramate, fluoxetine, and bupropion). In order for a trial to be included in analysis, the associated publication(s) had to report on weight loss, one control or placebo group, provide data prior to the crossover point if the trial was a crossover design, and contain sufficient statistical information for the calculation of a mean difference at 6 months and/or 1 year follow-up.

¹⁹ Paul G. Shekel Morton SC, Maglione M, Maggard M, et al. *AHRQ Evidence Report/Technology Assessment #103. Pharmacological and Surgical Treatment of Obesity. Southern California-RAND Evidence Based Practice Center*

A recent meta-analysis of sibutramine efficacy reported a mean different in weight loss (compared to placebo) of 3.43 kg at 6 months and 4.45 kg at 12 months.²⁰ Orlistat mean weight loss was 2.5 kg at 6 months and 2.75 kg at 12 months. Phentermine showed loss of 3.60 kg at 6 months vs. diethylpropion that showed 3.01 kg at 6 months (only borderline statistical significance).²¹ Fluoxetine showed a mean weight loss compared to placebo of 4.74 kg at 6 months and 3.05 kg at 12 months. Bupropion was 2.8 kg at 6 months. Only 6 studies of topiramate (5 as abstracts) revealed a loss of an additional 6.5% of baseline body weight. One eligible study assessed the efficacy of zonisamide for weight loss. At 4 months the zonisamide group lost an average of 6.0% baseline body weight compared to 1.0% for placebo patients. Metformin safely and effectively reduced centripetal obesity in non-diabetic subjects (5.9 kg at 7 months) and reduced heart disease risk factors such as fasting insulin, leptin, and LDL cholesterol.²² There were no direct comparisons of weight loss medications. Sibutramine, orlistat, phentermine, diethylpropion, fluoxetine, topiramate and metformin, all promote weight loss when given along with recommendations for diet. Sibutramine and orlistat are the two most studied drugs.

Metabolic syndrome is a constellation of clinical findings (central obesity, dyslipidemia, hypertension, and elevated blood sugar) that substantially increases risk of coronary artery disease. In Canada, the incidence of metabolic syndrome in a family practice population is men or women age 40-60 is 33%.²³ More than one-third of obese individuals who sought weight loss treatment met the criteria for metabolic syndrome. Prevalence differed by age, sex and ethnicity. Moderate weight loss markedly reduced the odds of metabolic syndrome in this sample.²⁴

Non-alcoholic fatty liver disease (NAFL-D) has been associated with metabolic disorders of central obesity, dyslipidemia, hypertension, and hyperglycemia. Metabolic syndrome, obesity, and insulin resistance are major risk factors in the pathogenesis of NAFL-D. NAFL-D refers to a wide spectrum of liver damage, ranging from simple steatosis to advance fibrosis and cirrhosis. About 20% of the asymptomatic NAFL-D progresses to fibrosis. NAFL-D treated by gastroplasty and significant weight loss improves metabolic abnormalities and hepatic lesions in long-term observations.²⁵

²⁰ Areterburn DE, Crane PK, Veenstra DL. The efficacy and safety of sibutramine for weight loss: a systematic review. *Arch Intern Med.* 2004;164:994-1003.

²¹ Li A, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med.* 2005;142:532-46/

²² Glueck CJ, Fontaine RN, Wang P, et al. Metformin reduces weight, centripetal obesity, insulin, leptin, and low density lipoprotein cholesterol in nondiabetic, morbidly obese subjects with body mass index greater than 30. *Metabolism* 2001 Jul;50(7):856-61.

²³ Kakafika AI, Mikhailidis DP, Karagiannis A, et al. The role of endocannabinoid system blockade in the treatment of the metabolic syndrome. *J Clin Pharmacol* 2007 May;47(5):642-52.

²⁴ Phelan S, Wadden TA, Berkowitz RI, et al. Impact of weight loss on metabolic syndrome *Int J Obes (Lond)*. 2007 Mar 13; [Epub ahead of print]

²⁵ Jaskiewicz S, Raczynska, Rzepko R, et al. Nonalcoholic Fatty Liver Disease Treated by Gastroplasty *Digestive Diseases and Sciences* January 2006; 51(1):21-26.

Exenatide (Byetta), an incretin mimetic agent, has an agonist activity at glucagon-like peptide-1 (GLP-1) receptors. It enhances insulin secretion, suppresses glucagon secretion, slows gastric emptying, and decreases food intake. It was approved by the FDA as adjunct therapy to oral antidiabetic medications. The drug has a moderate effect on fasting plasma glucose, postprandial plasma glucose, and HbA1c. The ability of the incretin mimetic exenatide to improve glycemic control and reduce body weight was assessed over 82 weeks in patients with type 2 diabetes failing to achieve glycemic control with maximally effective doses of metformin.²⁶ In addition, exenatide treatment produced clinically significant improvements in cardiovascular risk factors after 82 weeks.²⁷ Exenatide has a high incidence of GI tract adverse effects such as nausea and vomiting. It slows gastric emptying which may affect the absorption of oral medications

The amount of extra weight loss attributable to all of these medications is modest (< 5 kg at 1 year) and no evidence indicates that any particular drug promotes more weight loss than another drug. While sustained moderate weight loss (5% of body weight) can significantly influence obesity-associated risk factors for poor health outcome the longest studies followed patients for two years. All of these drugs have side effects. The choice of drug may be made on an individual basis, based on tolerance to the expected side effects.

Table 1. Comparison of Weight Loss Drugs

Medication	Source of data	Weight loss assessed at:	Mean weight loss (95% CI)	Mechanism of action	Major side effects
Sibutramine (Meridia®) *	Existing meta-analysis of 24 RTCs	52 weeks	-4.45 kg	Inhibits serotonin and norepinephrine reuptake	<ul style="list-style-type: none"> • Cardiovascular: abnormal ECG, hypertension, palpitations (0.3% Sibutramine caused palpitations leading to withdrawal in 0.3% of treated patients (Lean, 1999).), tachyarrhythmia (0.4%) • Gastrointestinal: constipation (11.5%), loss of appetite (13%), xerostomia (17%) • Neurologic: headache (30%), Insomnia (10%)
Orlistat (Xenical®) *	AHRQ meta-analysis of 23 RTCs	52 weeks	-2.76 kg (- 3.31, -2.20)	Inhibits the intestinal lipase reversibly. At therapeutic doses, orlistat inhibits dietary fat absorption by 30%.	<ul style="list-style-type: none"> • Gastrointestinal: abdominal discomfort, abdominal pain, defecation urgency, increased frequency of defecation, steatorrhea.

²⁶ Ratner RE, Maggs D, Nielsen LL, Stonehouse AH, et al., Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2006 Jul;8(4):419-28.

Fluoxetine (Prozac®)	AHRQ meta-analysis of 9 RCTs	52 weeks	-3.15 kg (- 5.82, - 0.48)	Inhibits serotonin reuptake	<ul style="list-style-type: none"> Cardiovascular: prolonged QT interval Gastrointestinal: indigestion, loss of appetite, nausea, xerostomia Neurologic: asthenia, insomnia, insomnia, somnolence, tremor Reproductive: abnormal ejaculation, Impotence, decreased libido
Phentermine* (Fastin®)	Meta-analysis of 9 RCTs	2 to 24 weeks	- 3.6kg (- 6.0, - 0.6)	The exact mechanism is not yet established, although it may involve other CNS actions or metabolic effects.	<ul style="list-style-type: none"> Cardiovascular: increased blood pressure (mild), palpitations - rapid (mild), cardiac dysrhythmia, cardiomyopathy Gastrointestinal: constipation, nausea, stomach cramps, vomiting,
Bupropion (Wellbutrin®)	AHRQ meta-analysis of 3 RCTs	24 to 52 weeks	- 2.77 kg (- 4.5, - 1.0)	Inhibits weakly the neuronal uptake of dopamine, norepinephrine, and serotonin but does not inhibit monoamine oxidase .	<ul style="list-style-type: none"> Cardiovascular: hypertension (2% to 4%), tachyarrhythmia (11%) Gastrointestinal: constipation (5% to 10%), disorder of taste (2% to 4%), nausea (13% to 24%), pharyngitis (3%to 11%), xerostomia (17% to 26%) Neurologic: confusion (8%), dizziness (6% to 11%), Headache (25% to 34%), insomnia (11% to 20%), tremor (3% to 6%) Psychiatric: agitation (2% to 9% anxiety (5% to 7%), hostile behavior (6%) Reproductive: disorder of menstruation (5%
Zonisamide (Zonegran®)	1 RCT	16 weeks	5% of pre-treatment weight loss	The exact method by which zonisamide exerts its anticonvulsant effect is unknown. Zonisamide is known to exert a dose-dependent biphasic dopaminergic and serotonergic activity. This is thought to be the mechanism of weight loss in epileptic patients.	<ul style="list-style-type: none"> Gastrointestinal: abdominal pain (2%), diarrhea (3%), indigestion (2%), loss of appetite (7%), nausea (3%), taste sense altered (2%) Neurologic: ataxia (5%), confusion (3%), dizziness (6%), insomnia (3%), memory impairment (4%), nystagmus (2%), paresthesia (3%), somnolence (10%), inability to concentrate (4%) Psychiatric: agitation (5%), depression (3%)
Exenatide (Byetta)	2 RCTs 326 diabetic patients	30 weeks	-2.8 kg	Incretin mimetic	<ul style="list-style-type: none"> Subcutaneous injection GI: Nausea, vomiting, diarrhea Hypoglycemia rare
	92 diabetic patients	82 weeks	-5.3 kg		

Metformin (glucophage)	Observational Study	27 weeks	5.9 kg overall weight loss, but specifically centripetal obesity with decreased waist to hip ratio. Also reduction in cardiac risk factors of serum insulin, leptin, and LDL cholesterol	Insulin-sensitizing	<ul style="list-style-type: none"> • Nausea/ vomiting • Anorexia • Diarrhea • Lactic acidosis • Metallic taste • Rash
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* FDA approval for obesity treatment

Dietary Therapy

An increasing number of men and women in the US are attempting to lose weight.²⁸ Popular diets have become increasingly prevalent and controversial. More than 1000 diet books are now available with many popular ones departing from mainstream medical advice. Although some diets are based on long-standing medical advice and recommend restriction of portion sizes and calories (e.g., Weight Watchers), a broad spectrum of alternatives has evolved. Some plans minimize carbohydrate intake without fat restriction (e.g., Atkins diet), many modulate macronutrient balance and glycemic load (e.g., Zone diet), and others restrict fat (e.g., Ornish diet). A 1 year randomized trial of the dietary component of the Atkins, Zone, Weight Watchers, and Ornish plans to determine their real clinical effectiveness and sustainability for weight loss and cardiac factor reduction was undertaken.²⁹ A single center trial reported a total of 160 participants randomly assigned to these diets. Mean (SD) weight loss at 1 year was **2.1 kg** (4.8) for Atkins (21 [53%] participants completed, $p=0.009$), **3.2 kg** (6.0) for Zone (26[65%] participants completed, $p=0.002$), **3.9 kg** (4.9) for Weight Watchers (26[85%] participants completed, $p <0.001$), and **3.3 kg** (7.3) for Ornish (20 [50%] participants completed, $p=0.007$). Greater effects were observed in study completers. Each diet significantly lowered LDL/HDL ratio by 10% (all $p <0.05$) with NS effects on BP or glucose at 1 year. For each diet decreasing levels of total/HDL cholesterol, C-reactive protein, and insulin were significantly associated with weight loss (mean $r=0.36$, 0.37 , and 0.39 respectively) with no significant difference between diets ($p=0.48$, $p=0.57$, $p=0.31$, respectively). The paper concluded each popular diet modestly reduced body weight and several cardiac risk factors at 1 year.

Medically supervised diet and exercise programs provide weight loss treatment to approximately 13% of obese women and 5% of obese men. However, obese participants in

²⁸ Serdula MK, Mokdad DF, Galuska DA, et al .Prevalence of attempting weight loss and strategies for controlling weight. *JAMA* 1999; 282:1353-1358.

²⁹ Dansinger JL, Gleason JA, Griffith JI, et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for weight loss and heart disease risk reduction. *JAMA* January 2005; 293:43-52.

diet and exercise programs rarely achieve a BMI in the normal range, and because weight lost is often regained there is the perception that nothing is accomplished by participation in such programs. Numerous studies have documented improvements in indicators of health with modest weight loss, which if maintained over several years may be clinically significant.

A multicenter randomized parallel-group trial was conducted over 2 years to evaluate the largest providers of commercial weight services in the US.³⁰ At one year 150 (71%) in the commercial group and 159 (75%) in the self-help group completed the study. In the intent-to-treat analysis mean (SD) weight loss of participants in the commercial group was greater than in the self-help group at 1 year (-4.3 kg [6.1] vs. -1.3 kg [6.1] respectively $p < 0.001$) and at 2 years (-2.9 kg [6.5] vs. -0.2 kg [6.5] respectively $p < 0.001$) Waist circumference ($p = 0.003$) and BMI ($p < 0.001$) decreased more in the commercial group. Changes to blood pressure, lipids, glucose, and insulin levels were related to changes in weight in both groups, but between-group differences in biological parameters were not significant by year 2.

Another systematic review comparing eDiets.com, Health Management Resources (HMR), Jenny Craig, LA Weight Loss, Medifast, Take Off Pounds Sensibly (TOPS), OPTIFAST, Overeaters Anonymous, and Weight Watchers was reported in 2005.³¹ Weight Watchers reported a loss of 3.2% of initial weight at 2 years. One RCT and several case series of medically supervised very low calorie diet (VLCD) programs found that patients who completed treatment lost approximately 15%-25% of initial weight. These programs were associated with high costs, high attrition rates, and the possibility of gaining 50% of the lost weight in 1 to 2 years, especially if they lacked a prolonged maintenance phase. Commercial interventions available over the internet produced minimal weight loss. Although organized self-help programs produced minimal weight loss; they are not-for-profit and are at no cost to the patients. These programs are conducted by lay persons, all of whom have struggled with their weight or with eating problems. They especially provide support for patients with emotionally triggered eating disorders.

A Cochrane systematic review of low fat diets concluded that fat restricted diets are no better than calorie restricted diets in achieving long term weight loss in overweight or obese people.³²

Variability in dietary weight loss trials may be partially attributable to differences in hormonal response. Reducing glycemic load may be especially important to achieve weight loss among individuals with high insulin secretion. A low glycemic load diet has beneficial effects on high-density lipoprotein cholesterol and triglyceride concentrations independent of effect on low-density lipoprotein cholesterol concentration.³³

³⁰ Heshka, S, Anderson JW, Atkinson, RL, et al. Weight loss with self-help compared with a structured commercial program. *JAMA* April 2003;389:1792-98.

³¹ Tsai AG, Wadden TA. Systematic Reviews: An evaluation of major commercial weight loss programs in the US. *Annals of Internal Medicine*

³² Pirozzo S, Summerbell C, Cameron C, et al. Advice on low-fat diets for obesity. *The Cochrane Database of Systematic Reviews* 2006 Issue 2

³³ Ebbeling CB, Leidig MM, Feldman HA, et al. Effects of a Low-Glycemic Load vs. Low-Fat Diet in Obese Young Adults *JAMA*, 2007;297:2092-2102

VLCDs providing ≤ 800 kcal/day have been used since the 1970s for rapid weight loss. Previous reviews of the literature have disagreed concerning the relative efficacy of VLCDs vs. LCDs for achieving long term weight loss. This systematic review revealed VLCDs induced significantly greater short-term weight losses than LCDs ($16.1\% \pm 1.6\%$ vs. $9.7\% \pm 2.4\%$ of initial weight respectively; $p=0.0001$) but similar long-term losses ($6.3\% \pm 3.2\%$ vs. $5.0\% \pm 4.0\%$, respectively, $p.0.2$). Attrition was similar with VLCD and LCD regimens. They concluded that in the US the use of liquid meal replacements as part of a 1000-1500 kcal/d diet may provide an effective and less expensive alternative to VLCDs. In Europe, VLCDs are used with less intensive medical supervision than in the US, which reduces the cost of this approach.

The mainstay for weight loss in dietary therapy is to follow a hypo-caloric diet (500 kcal/day deficit) regardless of the distribution of calories amongst food groups. This should produce ~ 1 lb weight loss/week. Further benefit for lipid lowering is to reduce fat intake to $\leq 30\%$ of the calories.

Behavioral Therapy

An essential component of behavioral therapy is to assess the patient for co-morbid psychiatric illnesses that need special treatment. Special sub-groups of obese patients who engage primarily in binge, nocturnal, or emotional eating should be recognized and treated more intensely. Epidemiological data suggest an association between obesity and depression that is stronger in women than in men. A self-reported study on 9125 respondents revealed that obesity (≥ 30 BMI) was associated with significant increases in lifetime diagnosis of major depression (OR 1.21; 95% CI 1.09-1.59), bipolar disorder (OR 1.47; 95% CI, 1/12-1.93) and panic disorder or agoraphobia (OR 1.27; 95% CI 1.01-1.60). Obesity was associated with significantly lower lifetime risk of substance use disorder (OR, 0.78; 95% CI 0.65-0.93). They concluded that obesity is associated with a 25% increase in odds of mood and anxiety disorders and 25% decrease in odds of substance use disorders. Many female morbidly obese patients have a history of physical or sexual abuse in their past.

A systematic review of psychological interventions for overweight or obese patients included trials that fulfilled the following criteria: 1) they were RCTs of a psychological intervention vs. a comparison intervention, 2) one of the outcome measures of the study was weight change, 3) participants were followed for at least 3 months, 4) the study participants were adults (18 years or older) who were overweight or obese (BMI >25) at baseline. A total of 36 studies involving 3495 participants assessed behavioral and cognitive-behavioral weight reduction strategies. The hallmark of behavioral therapy for obesity was self-monitoring of eating behavior, but techniques of stimulus control, self-reward, cognitive restructuring, nutrition education, and physical activity were also emphasized. Psychotherapy, relaxation therapy, and hypnotherapy were assessed in a small number of studies. Behavior therapy was found to result in significantly greater weight reductions than placebo when assessed as a

stand-alone weight loss strategy. When behavior therapy was combined with a diet/exercise approach and compared with diet/exercise alone, the combined intervention resulted in a greater weight reduction. Increasing the intensity of the behavioral intervention significantly increased the weight reduction. The authors concluded that people who are overweight benefit from psychological interventions, particularly behavioral and cognitive-behavioral strategies to enhance weight reduction. Other psychological interventions have been less rigorously evaluated for their efficacy as weight loss treatments.

Table 2. Summary of Findings from Prior Systematic Reviews and AHRC Updated Searches of Obesity Treatment Efficacy

Intervention Type	Evidence Source	Months of Follow-up		RCTs	Treatments Compared with Control	Weight Change: Intervention Group (kg)		Weight Change: Control Group (kg)	
		Range	Median	Number	Number	Range	Mean	Range	Mean
Counseling and behavioral therapy	U.S. NIH	12 to 60	12	29	54	8 to -21.6	-5.7	1.9 to -8.8	-3.3
	U.K. NHS	12 to 60	12	24	51	5.4 to -12.9	-4.5	1.4 to -10.6	-3.0
	CTFPHC	24 to 60	24	6	12	2.7 to -9.2	-3.3	-0.2 to -4.5	-2.1
	Updated searches (1)	12 to 54	12	12	22	9.2 to -17	-3.7	0.88 to -5.8	-2.0
	Updated searches (2)	12 to 54	12	13	24	9.2 to -17.9	-4.6	0.88 to -12.3	-2.6
Pharmacotherapy (orlistat or sibutramine)	<i>BMJ Clin Evid</i>	0.5 to 24	NA	17	NR	NR	NR	-2.5 to -4.4	NR
	Updated searches	6 to 12	6	10	11	-3.3 to -13.1	-6.5	-2.8 to -5.8	-4.0
Surgery	U.S. NIH	12 to 48	24	5	7	-9.7 to -159	-76.0	NA	
	U.K. NHS	12 to 48	30	6	8	-9.7 to -57.9	-45.1	NA	
	CTFPHC	24 to 60	36	4	9	-17 to -45.5	-29.9	NA	
	Updated searches	18 to 18	18	2	4	-34 to <-46	-40.0	NA	

Data reflect weight loss RCTs that have at least 1 year of follow-up; the longest follow-up reported is shown. Only counseling and pharmacotherapy trials that provided data on treatment effect with and without adjustment for control are included. Weight maintenance studies are not shown. Surgery data reflects only current procedures (gastric bypass, adjustable gastric banding, vertical banded gastroplasty); because trials compare 2 techniques (i.e., no comparison to non-surgical control), results are unadjusted for control. Results of updated searches for counseling results are shown with (1) and without (2) inclusion of a trial combining alternative counseling strategies with pharmacotherapy. Weight loss for sibutramine and orlistat is different from that in Table 1, as a result of different inclusion criteria for this meta-analysis.

BMJ Clin Evid = British Medical Journal's Clinical Evidence; CTFPHC = Canadian Task Force on Preventive

Physical Activity and Exercise

Exercise is an important component of behavioral weight control interventions, and exercise may be most effective for weight control when combined with modifications to energy intake. Clinicians should initially encourage overweight and obese adults to adopt at least 150 minutes of moderate-intensity exercise per week (30 min×5 d/wk), because this level of exercise has been shown to improve health-related outcomes. Higher levels of exercise, however, may be necessary to enhance long-term weight loss and to facilitate weight loss maintenance. It is now recommended that exercise be progressively increased to approximately 300 minutes per week (60 min×5 d/wk) to optimize the impact of exercise on body weight regulation. Adoption of this high level of exercise may be challenging, however, and therefore clinicians should counsel patients to incorporate lifestyle approaches for exercise to maximize adherence. Use of a pedometer may facilitate goal-setting and self-monitoring of exercise and are critical components of effective behavioral interventions.

Due to serious co-morbidities including cardiovascular risk factors, an appropriate level of medical screening should be implemented before recommending exercise to previously sedentary, overweight individuals. It is also important to consider the stages of motivational readiness for change in order for the clinician to match exercise intervention recommendations to the stage of readiness of the patient. The five stages of readiness to accept an exercise program are:

- 1) Pre-contemplation
- 2) Contemplation
- 3) Preparation
- 4) Action
- 5) Maintenance

Following the screening and readiness for change evaluation, an exercise prescription may be provided that takes the individual's previous level of activity, interests, time constraints, and physical impairments into account. A summary of recommendations for exercise is listed below (Table 2). See Appendix A for an example of a progressive exercise prescription for overweight adults.

TABLE 3. Summary of Recent Recommendations for Exercise³⁴

Organization/agency	Year of recommendation	Minimum recommended duration of exercise	Minimum recommended intensity of exercise	Desired health outcome
Centers for Disease Control and Prevention and the American College of Sports Medicine	1995	30 min on most days of the week	Moderate intensity	Improved health outcomes
Surgeon general's report on physical activity and health	1996	30 min on most days of the week	Moderate intensity	Improved health outcomes
American College of Sports Medicine	2001	150 min/wk	Moderate intensity	Improved health outcomes
		200–300 min/wk	Moderate intensity	Long-term maintenance of weight loss
Institute of Medicine	2002	60 min/d	Moderate intensity	Prevent weight gain, and accrue additional weight-independent health benefits
International Association for the Study of Obesity	2003	45–60 min/d	Moderate intensity	Prevention of weight regain
		60–90 min/d	Moderate intensity	Prevent the transition to overweight or obesity

Non-Exercise Activity

Non-exercise activity thermogenesis (NEAT) is the energy expenditure of all physical activities other than volitional sporting-like exercise. NEAT includes all the activities that render us vibrant, unique, and independent beings such as working, playing, and dancing. Because people of the same weight have markedly variable activity levels, it is not surprising that NEAT varies substantially between people by up to 200 kcal per day. Evidence suggests that low NEAT may occur in obesity, but in a very specific fashion. Obese individuals appear to exhibit an innate tendency to be seated for 2.5 hours per day more than sedentary lean counterparts. If obese individuals were to adopt the lean type they could potentially expend an additional 350 kcal per day.³⁵ Obesity was rare a century ago

³⁴ Jackicic JM Exercise in the treatment of obesity, Department of Health, Physical and Recreation Activity, Weight Management Research Center, University of Pittsburg.

³⁵ Levine JA, VanderWeg MW, Hill JO, et al. Non-exercise activity thermogenesis: The crouching tiger hidden dragon of societal weight gain *Arterioscler Thromb Casc Biol* April 2006 <http://www.atvbaha.org>

and the chair-enticing environment to which those with an innate tendency to sit, did so, and became obese. To reverse obesity we need to develop individual strategies to promote standing and ambulating time by 2.5 hours per day. This would require the re-engineering of our work, school, and home environments to render active living the option of choice.

For many people the majority of the working day is spent sitting in front of a computer screen. These authors postulated that a vertical work station that allows an obese individual to work whilst walking is associated with significant and substantial increases in energy expenditure over seated work. Fifteen sedentary individuals with obesity (mean BMI 32 ± 2.6) underwent measurements of energy expenditure at rest, seated working in an office chair, standing and whilst walking at a self-selected speed using the vertical work station. Mean energy expenditure whilst seated at work in an office chair was 72 ± 10 kcal/hr, whereas the energy expenditure whilst walking-and-working at a selected velocity of 1.1 ± 0.4 mph was 191 ± 29 kcal/hour. The mean increase in energy expenditure for walking-and-working, over sitting, was 119 ± 25 kcal/hour. If obese individuals were to replacing sitting computer-time with walking computer time by 2-3 hours per day for a 5 day week, and if other components of energy balance were constant, weight loss of 20-30 kg/year would occur.³⁶

Key Question 1

The Obesity Management MedTAP agrees by consensus that:

- ***There is good evidence for the short term (6-24 months) modest effectiveness of non-surgical treatments (pharmacological, dietary, behavioral, and physical activity) for weight loss. (-4 to -5 Kg.***
- ***There is no evidence for long term sustained weight loss for non-surgical treatments of obesity.***

Key Question 2 What is the evidence for combined therapy for obesity?

An AHRQ summary of systematic reviews on screening and interventions for obesity in adults compared data on studies with at least 1-year follow-up.³⁷ Successful interventions typically included 2 to 3 components (diet, exercise, and behavioral therapy). Trials designed to maintain weight loss showed some success. Pharmacotherapy or counseling interventions produced modest (generally 3-5 kg) weight loss over at least 6-12 months. Counseling was most effective when intensive and combined with behavioral therapy.

³⁶ Levine JA, *Mayo Clinic US*, The energy expenditures of using a “walk and work” desk for office-workers with obesity. *Br J. Sports Med.* May 15, 2007 e-published.

³⁷ McTigue K, Harris R, Hemphil B, Lux L, Sutton S, Bunton AJ, Lohr KN. Screening and Interventions for Obesity in Adults. Summary of the Evidence. Originally published in *Ann Intern Med* 2003;139(11):933-49. Agency for Healthcare Research and Quality, Rockville, MD.
<http://www.ahrq.gov/clinic/3rduspstf/obesity/obessum.htm>

Maintenance strategies helped retain weight loss. Weight reduction improved blood pressure, lipids, and glucose metabolism and decreased diabetes incidence. Most of the studies on cost-effectiveness of weight loss strategies were conducted outside the US.^{38,39}

Self-reported data by successful weight loss patients has shown that approximately 20% of overweight individuals are successful at long-term weight loss when defined as losing at least 10% of initial body weight and maintaining the loss for at least 1 year. The National Weight Control Registry (NWCR) provides information about the strategies used by successful weight loss “maintainers” to achieve and maintain long-term weight loss. NWCR members have lost an average of 33 kg and maintained the loss for more than 5 years. To maintain their weight loss, members report engaging in high levels of physical activity (approximately 1 hour/day); eating a low calorie, low-fat diet; eating breakfast; self-monitoring weight; and maintaining a consistent eating pattern across weekdays and weekends.⁴⁰

Early prevention and treatment of childhood and adolescent obesity requires the combined family oriented dietary-behavioral-physical activity intervention for success both in the short- and longer-term. The results from a parallel study of obese adolescents revealed a significant difference in body weight, BMI change, cholesterol, LDL and fitness for those on a combined program to the controls.⁴¹

Key Question 2

³⁸ Yates J, Murphy C. A cost benefit analysis of weight management strategies. *Asia Pac J Clin Nutr*. 2006;15 Suppl:74-9

³⁹ Avenell A, Broom J, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess*. 2004 May;8(21):iii-iv, 1-182.

⁴⁰ Wing R, Phelan S Long-term weight loss maintenance *Am J Clin Nutr* 2005 Jul;82(1 Suppl):2225-55

⁴¹ Nemet D, Barkan S, Epstein Y et al. Short- and long-term beneficial effects of a combined dietary-behavioral-physical activity intervention for the treatment of childhood obesity. *Pediatrics* 2005 Apr;115(4):e443-9

The Obesity Management MedTAP agrees by consensus that:

- *Successful interventions typically included 2 to 3 components (diet, exercise, and behavioral therapy).*
- *Successful patients with significant sustainable weight loss have in common the following:*
 - *High physical activity*
 - *Low calorie and low fat diets*
 - *Do not skip breakfast*
 - *Self monitor their weight*
 - *Have consistent eating pattern across weekdays and weekends.*
- *The most successful approach to childhood obesity requires the combined family oriented dietary-behavioral-physical activity intervention for both short- and longer-term weight loss.*

Key Question 3 *What is the evidence for the adverse effects of weight loss?*

The major drug adverse effects are covered in Table 1. Regardless of how the weight is lost the following adverse effects are noted:

- 1) An up to 28% incidence of symptomatic cholelithiasis, although obesity itself renders a patient a 10-30% chance of lifetime cholelithiasis. This risk is greater with rapid weight loss (e.g., VLCD or bariatric surgery).⁴²
- 2) An increased risk of gout, especially with those with already elevated uric acid.
- 3) A 2-3% risk of telogen effluvium (the temporary reversible thinning of the hair.)

Key Question 3

The Obesity Management MedTAP agrees by consensus that:

- *The FDA approved weight loss drugs*
 - *Sibutramine, phentermine, and diethylpropion have cardiovascular side effects of palpitations and hypertension*
 - *Orlistat has gastrointestinal side effects of diarrhea and hypermotility*
- *Significant weight loss from any method has the potential of:*
 - *Symptomatic cholelithiasis (28%)*
 - *Gout*
 - *Telogen effluvium*

Key Question 4 *What is the evidence for the effective treatment, either medical or surgical, of subgroups of obesity such as type*

⁴² Hoy MK, Heshka S, Allison DB, et al. Reduced risk of liver function test abnormalities and new gallstone formation with weight loss on 800 kcal formula diets.

2 diabetics?

Obesity is the most important modifiable risk factor for type 2 diabetes mellitus and most patients with diabetes are obese. It is well known that excess bodyweight induces or aggravates insulin resistance, which is a characteristic feature of type 2 diabetes. Recent data suggest that lifestyle interventions in patients with impaired glucose tolerance results in a reduction in the conversion to overt diabetes, which is greater than the effect of early intervention with drugs such as metformin or acarbose. The prevention of diabetes has been shown to be associated with the extent of the weight loss. Weight loss by any means is followed by an improvement of metabolic control and associated risk factors. The most appropriate recommendation for obese patients with type 2 diabetes is a nutritionally balanced, moderately hypocaloric diet with a reduced intake of saturated fat and an increase in physical activity. If this standard approach is only partly or not successful, additional strategies such as weight-lowering drugs, very low calorie diets for limited periods of up to 12 weeks, and for morbidly obese patients, bariatric surgery should be considered. There is growing agreement that due to the low success rate of conventional therapies and the overwhelming benefit from weight loss, more aggressive strategies may be appropriate to achieve weight reduction in obese patients with type 2 diabetes.⁴³

The prospective long-term Swedish Obese Subjects (SOS) Study involved obese subjects who underwent gastric surgery and contemporaneously matched, conventionally treated obese control subjects. At 10 years the weight had decreased by 16.1% in the bariatric surgery patients as compared to an increase of 1.6% in the controls ($p < 0.001$). Two and 10 year rates of recovery from diabetes, hypertriglyceridemia, low levels of HDL, hypertension, and hyperuricemia were more favorable in the surgery group than in the control group, whereas recovery from hypercholesterolemia did not differ between the groups. The surgery group had lower 2 year and 10 year incidence rates of diabetes than the control group, although differences between the groups in the incidence of hypercholesterolemia and hypertension were undetectable. Specifically at 2 years the incidence of diabetes was 1% for surgery patients compared to a 8% incidence for controls and at 10 years 7% (surgery) vs. a 24% (control) $p < 0.001$.

⁴³ Hauner H. Managing type 2 diabetes mellitus in patients with obesity *Treat Endocrinol* 2004;3(4):223-232.

Key Question 4

The Obesity Management MedTAP agrees by consensus that:

- ***Pharmacological studies have generated the most evidence for weight loss effect on co-morbidities such as:***
 - ***Cardiac risk factors***
 - ***Diabetes prevention, improvement, or reduction in medications***
 - ***Metabolic syndrome***
- ***Weight loss by any means improves metabolic control and associated risk factors greater than metformin or acarbose.***
- ***Bariatric surgery at 10 years significantly resolves or improves diabetes in those patients with diabetes at the time of surgery. The new onset of diabetes was significantly reduced in the bariatric surgery group compared to the control group.***

Key Question 5

What is the evidence for effectiveness of non-surgical treatments in prevention of weight gain for children and adults?

There are social and environmental causes of the obesity and diabetes twin epidemics. Many small changes in our environment have made it more difficult for Americans to be physically active and eat in a healthy way. The ubiquity of high-calorie snacks within easy reach, eating fast foods instead of meals at home, super-size portions, and new communities designed so that it's necessary to drive rather than walk are important contributors. Although this is a societal problem, experience addressing other health hazards such as tobacco has demonstrated that health care providers are opinion leaders in the policy arena. Until recently, the evidence supporting health systems-based weight management has been sparse.

The US Preventive Services Task Force recommends⁴⁴:

- (1) Weight assessment
 - (2) Intense multi-disciplinary interventions including counseling with periodic contact and reinforcement.
 - (3) Promotion of regular physical activity
 - (4) Limitation of caloric intake
- (See Appendix B)

⁴⁴ U.S. Dept. of Health and Human Services, AHRQ US Preventive Services Task Force. Recommendation on Screening and Intervention to Prevent Obesity in Adults. <http://www.ahrq.gov/clinic/uspsstf/uspsobes.htm>

Managing overweight in older children and adolescents presents a special challenge. The majority of overweight children will become overweight adults and experience a shortened life expectancy with higher rates of disease and higher health care costs. A strategy of early intervention and prevention allows targeting of children at increased long-term risk for obesity when treatment is most likely to be successful. It is critical at the onset that physicians, parents, and children have mutually agreeable goals. A good initial goal is no weight gain, which in association with an increase in height will result in a decreased BMI. A 5% reduction in body weight can provide substantial health benefits. Further improvement can be obtained with increase physical activity and behavior modification.⁴⁵

A Cochrane systematic review found that lifestyle modifications which include a decrease in sedentary activities and a family-centered approach to a healthful diet appear to be the most promising intervention to treat and prevent childhood overweight.⁴⁶ Promoting healthful lifestyles in schools and communities as well as increasing public awareness can help to reduce overweight in children and adolescents.⁴⁷

Both state and national policy initiatives have been proposed or enacted to address the increasing obesity rate in the US. These approaches focus on two major areas: food and activity. Policies which address the types of foods eaten by Americans include education initiatives regarding portion sizes, based on research that serving sizes for both foods eaten away from home and for food prepared at home have increased substantially in the past decades⁴⁸

Oregon's Public Health Data on Obesity

Sixty per cent of Oregon adults in 2005 have reported BMI's that classify them as either overweight (36%) or obese (24%). Among Oregon teens, 25% of 8th graders reported a BMI that would classify them as overweight or at risk for overweight, as did 25% of 11th graders.⁴⁹ Almost 32% of Oregon children aged 2-5 years receiving services from the Women's Infant and Child (WIC) nutrition program were overweight or at risk for it as compared to a national average of 30%.

In 2005 only 26% of adult Oregonians ate five or more servings of fruits or vegetables daily and only 56% of adult Oregonians met the relatively minimal CDC recommendations for physical activity (≥ 30 minutes of vigorous exercise at least 3 days/week.) Among adolescents and younger kids, the recommendation from the 2005 Dietary Guidelines for Americans is for 60 minutes of physical activity most (≥ 6) days of the week. In Oregon only 58% of 8th graders and 49% of 11th graders meet these minimum recommendations.

⁴⁵ Schwimmer JB Managing Overweight in Older Children and Adolescents *Pediatric Annals* January 2004 33(1):39-44.

CD Summerbell, E Waters, LD Edmunds, S Kelly, T Brown, KJ Campbell Interventions for preventing obesity in children *Cochrane Review*

⁴⁷ Stokes BL Overweight in Children and Adolescents. *AAFP Home Study Clinical Update* 336.

⁴⁸ Finkelstein EA, Ruhm CJ, Kosa KM. Economic causes and consequences of obesity. *Ann Review Public Health*, 2005; 26: 239-257.

⁴⁹ In youngsters < 18 "overweight" is defined by a BMI for age and sex > 95th percentile; "at risk of overweight" is defined by a BMI between the 85th and 95th percentiles.

On the food side only 18% of 11th graders report eating five or more servings of fruits or vegetables a day, while 28% report drinking seven or more soft drinks per week.

In order to better understand how to address the problem of obesity for Oregon children, the Governor's office and the Oregon Health Policy Commission asked the Physical Activity and Nutrition Program at the Public Health Division of the Department of Human Services to review the data on childhood obesity in Oregon and the effectiveness of various approaches to prevention. The goal of this review was to develop a set of recommendations that would translate into legislation and policy.⁵⁰

The top three recommendations selected were:

1. Establish minimum standards for foods sold in schools
2. Establish minimum standards for Physical Education and monitor implementation.
3. Establish a statewide Obesity Prevention and Education Program.

Key Question 5

The Obesity Management MedTAP agrees by consensus that:

- ***Intensive counseling (defined as contact more than once a month during the first 3 months of treatment) is of benefit when combined with regular physical activity and caloric restriction.***
- ***Counseling without these other modalities is not effective.***
- ***To help an obese patient lose weight and keep it off, periodic contact and reinforcement with behavioral therapy have been associated with sustained weight loss after follow-up of 60 Months***
- ***In older children and adolescents a 5% reduction in body weight can provide substantial health benefits. Further improvement can be obtained with increase physical activity and behavior modification***
- ***Promoting healthful lifestyles in schools and communities as well as increasing public awareness can help to reduce overweight in children and adolescents***

Key Question 6

What is the effectiveness and cost-effectiveness of treatments of obesity measured in \$/QALY (quality adjusted years)?

⁵⁰ http://egov.oregon.gov/DAS/OHPPR/HPC/docs/2007/ChildhoodObesityStudyReport_final.pdf

An AHRQ Summary of Systematic Reviews on Screening and Interventions for Obesity in Adults compared data on studies with at least 1-year follow-up.⁵¹ Successful interventions typically included 2 to 3 components (diet, exercise, and behavioral therapy). Trials designed to maintain weight loss showed some success. Pharmacotherapy or counseling interventions produced modest (generally 3-5 kg) weight loss over at least 6-12 months. Counseling was most effective when intensive and combined with behavioral therapy. Maintenance strategies helped retain weight loss. Weight reduction improved blood pressure, lipids, and glucose metabolism and decreased diabetes incidence. Most of the studies on cost-effectiveness of weight loss strategies arose outside the US.^{52,53}

Cost Effectiveness

An Australian study⁵⁴ used modeling and projection to assess the cost effectiveness of several strategies for prevention of diabetes in patients with impaired glucose tolerance: intensive diet and behavior modification, group behavior modification, general practitioner advice, media campaign to the public, and obesity surgery. The effectiveness of each intervention in preventing non-insulin dependent diabetes (NIDDM) was taken from published literature. Costs and savings were projected forward for 25 years with inflation adjustment. They reported a cost of US \$8900 net cost per life year saved for surgery, and a net savings for intensive dietary program, media campaign, and behavior therapy for overweight men.

This study has limited application primarily because the study is based on projections rather than actual costs and the Australian health system is very different in design and cost structure from the American system. Surgical costs were taken from published hospital program cost surveys and did not include projected costs for complications. Surgical benefit was calculated assuming that 87% of patients would lose 50% of excess weight. Possible benefits for prevention or amelioration of conditions other than diabetes were not considered.

A second study⁵⁵ analyzed the five-year cost-benefit of bariatric surgery on type 2 diabetics in France, Germany, and England. This study had a more robust predictive model. The comparison group included type 2 diabetics on conventional care. Conventional care assumed modest weight loss the first year, with return to baseline weight during years two

⁵¹ McTigue K, Harris R, Hemphil B, Lux L, Sutton S, Bunton AJ, Lohr KN. Screening and Interventions for Obesity in Adults. Summary of the Evidence. Originally published in *Ann Intern Med* 2003;139(11):933-49. Agency for Healthcare Research and Quality, Rockville, MD. <http://www.ahrq.gov/clinic/3rduspstf/obesity/obessum.htm>

⁵² Yates J, Murphy C. A cost benefit analysis of weight management strategies. *Asia Pac J Clin Nutr*. 2006;15 Suppl:74-9

⁵³ Avenell A, Broom J, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess*. 2004 May;8(21):iii-iv, 1-182.

⁵⁴ Segal et al. *Health Promotion International* Vol 13 #13, 1998

⁵⁵ Ackroyd et al *Obesity Surgery* Vol 16; 2006

through five. Cost estimates for surgery included direct costs and anticipated cost of complications. Cost of diabetes treatment was determined from payment databases for each country. Cost saving were projected from reduction in diabetes treatment costs due to weight loss. Quality of life improvements assumed an inverse linear relation between BMI and quality of life. BMI reductions for banding or bypass surgery were within the ranges observed in the SOS data. This study projected cost savings in France and Germany, and a modest cost increase in England. The projected cost in England was £1927/QALY.

The study has inherent limitations because it used cost projections rather than actual costs and included patients age 60 or older (higher cost of care than for younger patients). Applicability of this European study's findings to the US healthcare system is further limited by major differences in the healthcare delivery and payment systems.

The issue of cost effectiveness of bariatric surgery in the US remains unanswered.

Key Question 6

The Obesity Management MedTAP agrees by consensus that:

- ***Control patients who have supervised diet and exercise lose -2.6 kg at one year.***
- ***Sibutramine or orlistat add only -2.5 kg sustainable weight loss at 6 months. If these drugs are discontinued weight gain returns.***
- ***Behavioral counseling adds only -2 kg sustainable weight loss at 1 year.***
- ***Bariatric surgery produces the following weight loss at 18-36 months post-operatively:***
 - ***US(NIH) -76.0 kg***
 - ***UK(NHS) -45.1kg***
 - ***Canada -29.9 kg***
 - ***US(recent) -40.0 kg***
- ***The impact of bariatric surgery in Type 2 Diabetes shows an acceptable cost-benefit analysis.***
- ***The results from foreign countries cannot be generalized to the US because of different social, cultural, and medical systems.***
- ***The cost-benefit analysis for surgical or non-surgical therapy of obesity has not been answered for the US.***

Philosophical Conclusions

This document has addressed the ever increasing problem of obesity in our society. Surgical and non-surgical treatments have been discussed in great detail. Surgical treatment will only be appropriate for a small segment of obese people and the long term results of

non-surgical treatments, regardless of the modality, are minimal and discouraging to say the least.

If, indeed, the obesity epidemic in our country is to be halted or even slowed the approach must be societal. Education of an entire population about good nutrition and appropriate physical activity must become pervasive. The “temptations” of fast food; the advertising of high caloric, low nutrition foods especially to children; immediate access to these foods in schools and homes; and the ever increasing number of restaurant meals must be addressed.

Some of the attempts that have shown promise include:

1. Nutrition education to children at an early age
2. Removal or appropriate contents of vending machines in schools
3. Decreasing “screen time” for children and adults
4. Increasing opportunities for exercise in our daily lives, especially in schools
5. “Zero tolerance” for the ridicule/teasing of the obese, especially children
6. Eliminating inappropriate advertising of “junk” foods, especially to children and adolescents
7. Educating our entire population about the health consequences of obesity and the positive aspects of exercise.

Conclusion

It is the decision of the Obesity Management MedTAP that:

- 1) Obesity is a chronic disease as defined by the World Health Organization, National Institutes of Health, Centers for Disease Control and Prevention, and the American Dietetic Association***
- 2) Modest weight reduction (4-5 kg) by any method improves blood pressure, lipids, and glucose metabolism and decreases diabetes incidence.***
- 3) Pharmacotherapy interventions produced modest (generally 3-5 kg) weight loss over at least 6-24 months, but were not sustained after discontinuation of the drugs.***
- 4) Counseling was most effective when intensive and combined with behavioral therapy. Maintenance strategies support sustained weight loss.***
- 5) The morbidly obese patient has a 10-fold weight reduction with bariatric surgery compared to non-surgical treatment.***
- 6) Long-term RCTs of obesity treatments in populations with obesity related illness are needed to include an evaluation of risk factors, morbidity, quality of life and economic evaluation.***
- 7) Research is needed to explore types of exercise, diet or behavior that prevent obesity in adults.***

APPENDIX A

Example of a progressive exercise prescription for overweight adults				
Treatment week	Intensity of exercise	Frequency d/wk	Duration of exercise⁵⁶	Total exercise (min/wk)
1	Moderate ⁵⁷	5	20	100
2	Moderate	5	20	100
3	Moderate	5	20	100
4	Moderate	5	20	100
5	Moderate	5	30	150
6	Moderate	5	30	150
7	Moderate	5	30	150
8	Moderate	5	30	150
9	Moderate	5	40	200 ⁵⁸
10	Moderate	5	40	200
11	Moderate	5	40	200
12	Moderate	5	40	200
13	Moderate	5	40	200
14	Moderate	5	40	200
15	Moderate	5	50	250
16	Moderate	5	50	250
17	Moderate	5	50	250
18	Moderate	5	50	250
19	Moderate	5	50	250
20	Moderate	5	50	250
21	Moderate	5	60	300
22	Moderate	5	60	300
23	Moderate	5	60	300
24	Moderate	5	60	300

⁵⁶ Duration can be performed in multiple sessions throughout the day with each session being at least 10 min in duration

⁵⁷ Moderate intensity = 40%–59% of heart rate reserve, 55%–70% of maximal heart rate, or rating of perceived exertion of 12–13

⁵⁸ Participant should be encouraged to maintain at least 150 min of exercise/wk if unable to achieve goals of 200 min/wk or more.

APPENDIX B

US Preventive Services Task Force Recommendations:

- 1) Weight assessment is a key first step. The U.S. Preventive Services Task Force (USPSTF)⁵⁹ recommends that clinicians screen all adult patients for obesity by calculating a body mass index (BMI=weight in kgs/height in meters²) and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults (BMI > 30.)
- 2) Intense, multi-disciplinary interventions in light of evidence from multiple studies revealed that intensive counseling (defined as contact more than once a month during the first 3 months of treatment) is of benefit when combined with regular physical activity and caloric restriction. Counseling without these other modalities is not effective. Many of the successful programs were multi-disciplinary and involved nutritionists and other ancillary staff. These combined programs resulted in a sustained weight loss of 3-5 kg more than controls after one year.⁶⁰ To help an obese patient lose weight and keep it off, periodic contact and reinforcement with behavioral therapy have been associated with sustained weight loss after follow-up of 60 months.⁶¹
- 3) Promote regular physical activity. The Institute of Medicine recommends at least one hour of moderate to vigorous activity each day to promote weight control.⁶² In addition, resistance training increases muscle mass.
- 4) Limit caloric intake. Although physical activity is paramount, a patient would have to run 10 miles to work off the 1,100 calories that he would get from a half-pound cheeseburger and large fries. Caloric restriction in association with a physical activity and behavioral program promoted weight loss regardless of whether the diet was low fat or low carbohydrate. “When it comes to weight control, calories *do* count – not the proportions of carbohydrate, fat and protein in the diet,” according to the Secretaries of Agriculture and Health and Human Services. However a low-fat diet < 30% of calories from fat and <300 mg cholesterol is recommended due to potential beneficial effects on lipids.⁶³

⁵⁹ U.S. Dept. of Health and Human Services, AHRQ US Preventive Services Task Force. Recommendation on Screening and Intervention to Prevent Obesity in Adults. <http://www.ahcpr.gov/clinic/uspsstf/uspsobes.htm>

⁶⁰ Jain A, et al. What works for obesity: a summary of the research behind obesity interventions. *BMJ Publishing Group* 2004

⁶¹ McTigue KM, et al. Summary of the Evidence: Screening and interventions for obesity in adults. <http://www.afcpr.gov/clinic/3reduspstf/obesity/obessum.htm> What works for obesity: a summary of the research behind obesity interventions

⁶² Brooks GA, et al. Chronicle of the IOM physical activity recommendation: how a physical activity recommendation came to be among dietary recommendations. *Am J Clin Nutr.* 2004 May;79:921S-930S.

⁶³ NIH Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults; 2000. http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_b.pdf

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