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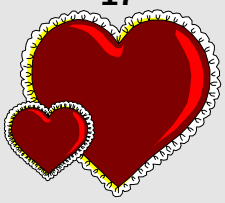

Happy Valentine's Day!

Pharmacoeconomic Analysis of Obesity Treatment

Executive Summary

Obesity is a chronic disease requiring lifelong treatment; it has been shown to be a risk factor for coronary heart disease, diabetes, osteoarthritis, gallbladder disease, and some cancers. At least one-third of the adult U.S. population is overweight, with the prevalence increasing over the past two decades. Thus, obesity is a serious public health concern.

The origins of obesity are multifactorial, reflecting genetic, environmental, cultural, socioeconomic, and physiological conditions; therefore, no single treatment can be effective for all obese individuals. Current obesity treatments consist of diet, exercise, behavior modification, surgical intervention, and pharmacological treatment alone or in combination.

Current pharmacological treatment for obesity consists of appetite suppressants, thermogenic agents, or agents that act locally in the gastrointestinal tract. Appetite suppressants are the most widely used agents and act centrally through catecholamine or serotonin pathways. Anorexiants available in the U.S. include: phendimetrazine, phentermine, mazindol, diethylpropion, phenylpropanolamine, dexfenfluramine, fenfluramine, and the selective serotonin release inhibitors (SSRIs). Due to limitations in long-term efficacy and toxicity data, the analyses in this document are limited to comparisons of dexfenfluramine, the combination of fenfluramine and phentermine, or fluoxetine added to a regimen of diet and exercise.

Due to the differences in weight reduction goals between active duty and non-active duty beneficiaries, this document includes two separate analyses. For the non-active duty population, the efficacy measure of interest is the percent of initial body weight lost. For active duty members, the pertinent question is whether the weight

loss is sufficient to meet the height/weight standard of that service. Therefore, the efficacy measure for active duty members begins with the achievable weight loss for each treatment, and is stratified by the amount of weight the person needs to lose to meet the height/weight standard.

Non-active duty population
The most cost-effective treatment regimen in the non-active duty population is a structured diet and exercise program. Adding dexfenfluramine to this regimen will result in enhanced effectiveness at an incremental annual cost (per person) of $67.96 per percent of initial body weight lost.

Active duty population
There are additional costs of treatment failure associated with the active duty population, namely those relating to replacing an obese service member. These costs are significant, and drive the model towards pharmacologic treatment of obese active duty members. The combination of fenfluramine and phentermine resin is the most cost-effective medication regimen for the active duty population within a range of obesity.

Limitations
While obesity is a chronic disease best portrayed by multi-year models, data limitations restrict these models to a one year time frame. Unfortunately, efficacy and toxicity data for these agents do not extend beyond one year, thus limiting the time frame of the models.

The future costs of treating cardiovascular disease, diabetes, arthritis, and other conditions attributable to obesity are not known, and could not be included in the models. If these data were available, their inclusion would increase the treatment failure cost, resulting in enhanced cost-effectiveness of pharmacologic treatment.

Many questions about the toxicities of these agents remain unanswered. Most importantly, the question of whether primary pulmonary hypertension is progressive with long-term use of anorexiants must be answered.

The data used in these models were obtained from clinical trials in obese civilians. Whether or not this data is generalizable to the active duty population is unknown. Controlled, clinical trials with active duty members are needed to completely answer this question.

Finally, an additional question remains with respect to active duty members: at what degree of obesity is it more cost-efficient to discharge the service member versus treating his/her obesity? This is a complex personnel question, beyond the scope of this analysis.

Summary
Uncertainties regarding anorexiant use remain:

- What is the long-term reduction in obesity-related diseases and concomitant costs?
- What is the risk of primary pulmonary hypertension with anorexiants used for longer than 1 year?

In addition, for the active duty population, the expense of treatment is borne by the Military Health Services System, while the benefits (fewer discharges due to obesity) accrue to the training arm of the services.

For these reasons, no definitive recommendations regarding anorexiant use in military beneficiaries are possible, and no changes are recommended for the Tri-Service Formulary.

Since safety and efficacy data beyond 1 year of treatment are not available, the long-term effectiveness of drug therapy for obesity cannot be accurately estimated. However, this analysis can be used at the local MTF in the absence of specific service policies to provide clinicians with additional information when evaluating individual patients.

Pharmacoeconomic Analysis of Obesity Treatment

Overview

Due to the differences in weight reduction goals between active duty and non-active duty beneficiaries, this document includes two separate analyses. For the non-active duty population, the efficacy measure of interest is the percent of initial body weight lost. For active duty members, the pertinent question is whether the weight loss is sufficient to meet the height/weight standard of that service. Therefore, the efficacy measure for the active duty members begins with the achievable weight loss for each treatment, and is stratified by the amount of weight the person needs to lose to meet the height/weight standard.

Introduction

Obesity is one of the most common disorders seen in clinical practice and can be defined in several ways, depending on the measurement system used. In general, obesity is an excess of adipose tissue. An accepted measure of adiposity is the body mass index (BMI, weight in kilograms/ height in meters squared) that correlates well with body fat percentage. BMI greater than the 85th percentile (a value of 28 for men or 27 for women, corresponds to a weight 20 percent above ideal weight) is considered obese. Table 1 delineates these values by height.

Table 1: Obesity and Ideal Body Weight

	Women [lb(kg)]		Men [lb(kg)]	
Height [in (cm)]	**Obese [lb (kg)]**	**Ideal Body Weight [lb (kg)]**	**Obese [lb (kg)]**	**Ideal Body Weight [lb (kg)]**
60 (152)	138 (63)	99 (45)	143 (65)	110 (50)
62 (157)	148 (67)	109 (50)	153 (69)	121 (55)
64 (163)	157 (71)	119 (54)	163 (74)	130 (59)
66 (168)	167 (76)	129 (59)	173 (79)	140 (64)
68 (173)	178 (81)	140 (63)	184 (84)	151 (68)
70 (178)	188 (85)	150 (68)	195 (89)	161 (73)
72 (183)	199 (90)	160 (73)	206 (94)	171 (78)
74 (188)	210 (95)	170 (77)	218 (99)	181 (82)
76 (193)	222 (101)	180 (82)	230 (104)	191 (87)
78 (198)	234 (106)	190 (86)	242 (110)	201 (91)

Note: *Obesity based on a body mass index of ≥ 27 for women and ≥ 28 for men.*
Ideal body weight (male) = 50 kg + [2.3 × (height in inches > 60 in)]
Ideal body weight (female) = 45 kg + [2.3 × (height in inches > 60 in)]

Obesity is a chronic disease with differing etiologies reflecting genetic, environmental, cultural, socioeconomic, and physiological con-ditions.[1-6] The recent discovery of an obesity gene will direct future research efforts, especially drug treatments for obesity. Lifelong treatment of obesity is indicated for many people. While a cure for obesity is not yet within sight, treatments with varying degrees of success are available. The National Institutes of Health (NIH) Consensus Development Conference on Obesity recommends that persons 20 percent or more above their ideal weight (BMI ≥ 27 for females, ≥ 28 for males) should be treated for obesity.[7]

An NIH Technology Assessment Conference report stated that one quarter to one third of Americans are overweight (with the prevalence increasing over the last two decades - Figure 1) and that being overweight affects health and longevity.[8] Obesity is associated with hypertension, hyperlipidemia, and non-insulin-dependent diabetes mellitus. In addition, excess weight increases the risk for gallbladder disease, coronary heart disease, gout, some types of cancer, and development of osteoarthritis of the

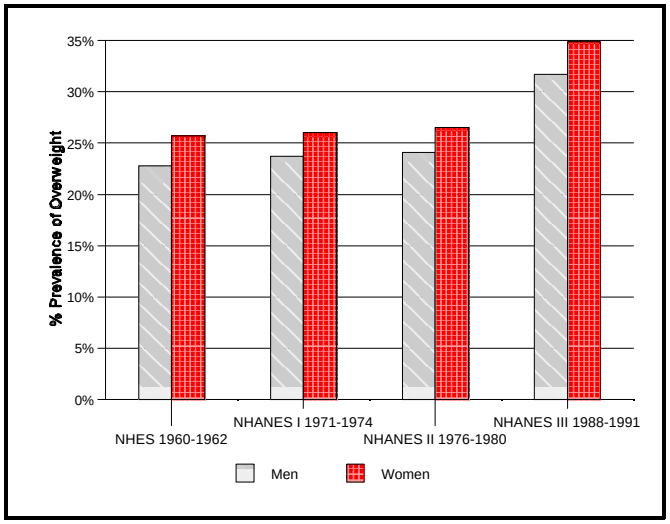

Figure 1: Age-adjusted prevalence of overweight for U.S. population, 20 to 74 years of age.

weight-bearing joints.[9-11] The direct costs of these obesity-related diseases were estimated to be $45.6 billion in 1990 in the U.S. (Figure 2).[12] Therefore, obesity must be considered a major contemporary public health concern.

Evidence has shown that even a modest weight loss will have a positive effect on blood pressure, insulin resistance, dyslipidemias, and orthopedic problems[13-17] (Table 2). Data from the Framingham study indicate that a weight loss of 10% of body weight may correspond to a 20% reduction in the risk of developing coronary artery disease.[17]

Current obesity treatments consist of diet, exercise, behavior modification, surgical intervention, and pharmacological intervention alone or in combination.[1] Due to the multifactorial origins of obesity, any treatment plan must be tailored to the individual's needs.[18] The challenge for health care providers is to identify those patients with obesity who are most likely to benefit from treatment and to provide them with the tools for long-term lifestyle change. An algorithm for obesity treat-ment, starting with the patient's request for treatment, is included as Appendix A.

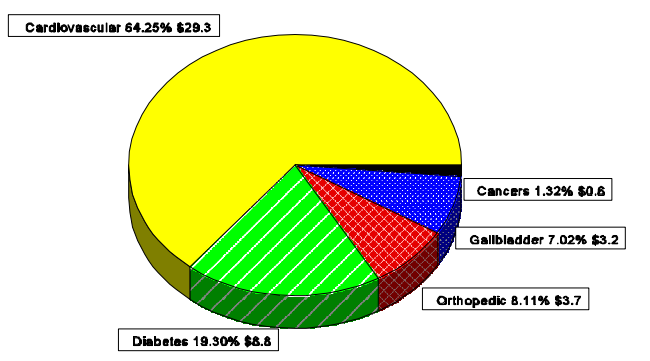

Figure 2: Direct costs of obesity in billions of 1990 dollars.

Pharmacologic treatment of obesity

An "ideal" pharmacologic agent for obesity treatment should possess several features[19]:

- safe and acceptable for long-term administration
- produce a dose-related reduction in body fat
- spare body protein
- free from significant side effects and abuse potential.

The "ideal" agent does not yet exist. Current pharmacologic treatment of obesity consists of appetite suppressant medications, thermogenic agents, or agents that act locally in the gastro-intestinal tract.[20-24]

Appetite suppressants are the most widely used agents and act centrally through catecholamine or serotonergic pathways.[25-26] The first anorexiant was dextroamphetamine, which acts by releasing catecholamine transmitters (norepinephrine and dopamine). The anorexiant effect of dextro-amphetamine is mediated by norepinephrine, while the euphoric and stimulant effects are mediated through dopaminergic pathways. Other catecho-laminergic anorexiants include: phendimetrazine, phentermine, mazindol, diethylpropion, and phenylpropanolamine. Drug research was then aimed at developing agents with greater anorectic effect and minimal stimulant and euphoric effects. Fenfluramine (Pondimin® and other brands) was developed in the 1970s and is a racemic mixture of dextro- and levorotatory stereoisomers. The l-isomer predominately affects catecholamines, while the d-isomer (dexfenfluramine) affects serotonin release and reuptake. Dexfenfluramine (Redux™)

has fewer unwanted effects when compared to fenfluramine, is twice as potent with respect to anorectic activity, and appears to be free from abuse potential.[27] While currently a controlled substance, application has been made to remove it from the controlled substances list. Phentermine (Ionamin® and other brands), also developed in the 1970s, is a centrally acting stimulant with greater anorexiant effect and less euphoric effect than dextroamphetamine. Phentermine acts by inhib-iting reuptake of norepinephrine. Fenfluramine, dexfenfluramine, and phentermine can cause a false positive test for amphetamines in urine drug tests using the ELISA method. More precise methodology, such as gas chromatography, can differentiate these agents from amphetamines. Dexfenfluramine and fenfluramine should not be used concomitantly with other serotonin enhancing agents including selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors, as the combination is potentially fatal.

An over-the-counter appetite suppressant, phenylpropanolamine, is approved by the Food and Drug Administration as an appetite suppressant, but long-term studies of its efficacy are lacking. Sibutramine (Meridia), a mixed serotonergic and catecholaminergic reuptake inhibitor, has been recommended for approval in the U.S.

Fluoxetine (Prozac®) is an SSRI that has a dose-related anorexiant effect.[28] This effect is most probably a class effect of the SSRIs, and not limited to fluoxetine alone. Serotonin is believed to regulate satiety, especially of carbohydrates.[29]

Thermogenic agents cause an increase in metabolic rate. Thyroid hormones were used in the past, but had significant toxicity and lean tissue (rather than adipose tissue) was lost. Since metabolic rate is modulated by catecholamines, drugs such as beta-agonists, ephedrine, and caffeine are being studied. Beta-agonists are effective at increasing the metabolic rate, but side effects of severe hand tremor and decreased exercise tolerance have restricted their use. A synergistic effect between ephedrine and

Table 2: Weighing the Risk[16]—Percent Increase in Risk by Level of Obesity

	Body Mass Index (BMI)									
	26	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**
Death/all causes (versus BMI < 19)		**60%**		**110%**			**120%**			
Death/heart disease (versus BMI < 19)		**210%**		**360%**			**480%**			
Death/cancer (versus BMI < 19)		**80%**					**110%**			
Type II diabetes (versus BMI 22-23)		**1,480%**		**2,660%**		**3,930%**		**5,300%**		
High blood pressure (versus BMI < 23)	**180%**			**260%**			**350%**			
Degenerative arthritis (versus BMI < 25)					**400%**					
Gallstones (versus BMI < 24)		**150%**			**270%**					
Neural birth defects (versus BMI 19-27)				**90%**						

caffeine has been confirmed in clinical trials; unfortunately, misuse of these agents (i.e., overdose) has resulted in significant morbidity and mortality.[26]

Several agents have been evaluated for their effect on the gastrointestinal tract. Bulk-forming agents have been used to produce feelings of satiety, but evidence to support this treatment is lacking. Cimetidine, a histamine H_2-receptor blocker, was studied in two European trials with equivocal results.

Storage of surplus nutrients converted to triglyceride in fat cells is regulated by the enzyme lipoprotein lipase. Orlistat (Xenical) is a lipase inhibitor with antiobesity and hypocholesterolemic activity. Short-term studies yielded positive results and long-term studies are underway, with approval anticipated in 1997.

Cessation of drug treatment results in weight regain, which is consistent with the chronicity of obesity and the interaction of genetics with environment. For appetite suppressants to be successful in establishing and sustaining weight loss, they must be used as chronic medications in the same manner as medications used to treat hypertension, hyperlipidemia, diabetes, asthma, or other chronic diseases.

I. Non-active duty population

This analysis compares various *appetite suppressant* medications to diet and exercise, as measured by sustained weight loss at 6 months to 1 year of treatment in non-active duty beneficiaries. The perspective of the analysis is that of the Department of Defense as payer of the health care benefit. The treatment regimens evaluated in this analysis include:

- Diet and exercise alone
- Dexfenfluramine 15 mg BID added to diet and exercise
- Fenfluramine 20 mg TID and phentermine resin 15 mg QD added to diet and exercise
- Fluoxetine 60 mg QD added to diet and exercise

Phenylpropanolamine, diethylpropion, and mazindol are not included because of a lack of long-term efficacy data.

The efficacy measure for the non-active duty population is the percent of initial body weight lost.

Assumptions

- All patients are participating in a structured obesity treatment program consisting of diet, nutritional counseling, exercise, and group sessions and are compliant with this program.
- Drug therapy is an adjunct to the overall obesity treatment program.
- Patients with eating disorders are excluded from the analysis.
- Noncompliance with the treatment regimen does not result in any increased cost to DOD, but will affect the effectiveness of the treatment. Dosing frequency of the treatment (i.e., QD, BID, TID) was used as the compliance modifier. Compliance was not further altered for multiple drug regimens (i.e., combination therapy).
- The only adverse effect from drug treatment that may incur a cost to DOD is primary pulmonary hypertension (PPH), which may result in hospitalization, heart-lung transplant, or death. If a person develops PPH, it is estimated that one hospitalization and 2 additional office visits will occur within 1 year for treatment of PPH. The probability of a heart-lung transplant is for the lifetime of the patient. PPH is associated with the use of dexfenfluramine, fenfluramine, and phentermine.[30-36]
- Treatment failure does not incur additional cost to DOD. Precise treatment failure costs are unknown for the general population in the treatment of obesity.
- 1 year cost of treatment model. While lifelong drug treatment may be needed, the safety and efficacy of these regimens beyond 1 year of treatment is not known, especially the incidence of adverse effects.
- Since the marginal cost of physician visits, laboratory tests, radiological studies,

hospitalizations, and emergency department visits are unknown for DOD, the CHAMPUS maximum allowable charge (CMAC) was used as a proxy. These values were varied by 5% to reflect the difference in rates across the country.

Table 3: Variable List

Variable	Point estimate	Range	Reference
Initial visit (IV)	$104.00	$98.80 - 109.20	CMAC*
Short follow-up visit-15 minutes (FU)	$31.25	$29.69 - 32.81	CMAC*
Dietary consult (Diet)	$25.00	$25.00 - 38.00	Weighted average of military medical treatment facilities
Rx dispensing fee (Disp)	$2.95	$2.80 - 3.10	37
Probability of developing PPH within 1 year on drug (pPPH)			38-40
• Dexfenfluramine	0.0039%	0.0023 - 0.0055%	
• Fenfluramine/Phentermine	0.0039%	0.0023 - 0.0055%	
• Fluoxetine	0	0	
• Diet & exercise alone	0	0	
Probability of hospitalization for PPH (pHOSP)	100%	70 - 100 %	Expert opinion
Cost of hospitalization for PPH (cHOSP)	$514	$488 - 540	CMAC*
Probability of heart-lung transplant (pTRANS)	100%	50 - 100 %	Expert opinion
Cost of heart-lung transplant (cTRANS)	$500,000	$475,000 - 525,000	CMAC*
Efficacy: % of initial body weight lost (% BW)			20, 41-51
• Dexfenfluramine	13.5%	8 - 30.7%	
• Fenfluramine/phentermine	15%	11.2 - 18.2%	
• Fluoxetine	1%	18.5% gained - 31.6% lost	
• Diet & exercise alone	5.6%	1.9 - 10.1%	
Dropout rate (Dr)			20, 41-51
• Dexfenfluramine	7.25%	0 - 7.8%	
• Fenfluramine/phentermine	4.38%	0 - 14%	
• Fluoxetine	16.03%	13 - 17.8%	
• Diet & exercise alone	4.10%	0 - 8.3%	
Compliance with treatment regimen (Comp)			52-55
• QD (Fluoxetine)	80%	73 - 87%	
• BID (Dexfenfluramine)	78%	70 - 85%	
• TID (Fenfluramine & phentermine)	62%	52 - 77%	

* CMAC = CHAMPUS Maximum Allowable Charge

Equation

Average cost effectiveness of drug A = C/E_A

$$C/E_A = \frac{\sum \text{Treatment costs} + \sum \text{Side effect costs} + \sum \text{Treatment failure costs} + \sum \text{Opportunity costs}}{\text{Effectiveness}_A}$$

$$\frac{[IV + (2 \times Diet) + (6 \times FU) + (4 \times Disp) + DC_A + pPPH\,[(pHosp \times cHosp) + (2 \times FU) + (pTrans \times cTrans)]]}{[\%\,BW_A \times Comp \times (1 - Dr_A)]}$$

Treatment costs

Side effect costs

Effectiveness

As previously mentioned in the assumptions section, there are no treatment failure or opportunity costs in the non-active duty population.

Key to abbreviations:
IV = Initial visit cost
Diet = Dietary consult cost
FU = Short follow-up visit cost
Disp = Prescription dispensing cost
DC_A = Drug acquisition cost for drug A
pPPH = Probability of developing primary pulmonary hypertension (PPH)
pHosp = Probability of hospitalization for PPH in 1 year
cHosp = Cost of hospitalization for PPH
pTrans = Probability of heart-lung transplant for PPH in 1 year
cTrans = Cost of heart-lung transplant
$\%\,BW_A$ = % of initial body weight lost at 6 months to 1 year on treatment_A
Comp = Compliance with dosing regimen
Dr_A = Dropout rate for drug A

Sensitivity Analysis

The model was tested for robustness to the variables and assumptions using univariate and multivariate sensitivity analyses. A Monte Carlo simulation was used for the multivariate sensitivity analysis. During this simulation, all variables were randomly varied throughout the ranges listed in Table 3 over 1000 trials.

The model was most sensitive to changes in the efficacy measure (% of initial body weight lost). Greater than 95 percent of the variance was attributable to this variable. Univariate analysis of the efficacy resulted in changes in the average cost-effectiveness ratio, but no change in the relative ranking of the treatments.

The Monte Carlo simulation afforded similar results as the univariate analysis, indicating that the model is robust to changes in the variables.

Results

Results obtained from 1000 trials in the Monte Carlo simulation are depicted in Table 4. The most cost-effective treatment regimen in the non-active duty population is a structured diet and exercise program.

An incremental cost-effectiveness (CE) analysis was performed on the results of the Monte Carlo

Table 4: Results of Monte Carlo Analysis for Non-Active Duty Population

Treatment	Average Cost/Effectiveness (using % initial body weight lost as the efficacy measure)	95% Confidence Interval
Diet & exercise alone	$6815.98	$6675.37 - $6956.60
Dexfenfluramine	$7202.25	$7075.75 - $7328.75
Fenfluramine/phentermine combination	$9041.38	$8965.35 - $9117.40
Fluoxetine	$129,316.02	$94,376.90 - $164,255.13

simulation. In an incremental CE analysis, the difference in total costs between two treatments is divided by the difference in effectiveness. The result is the incremental cost for an additional unit of effectiveness.

$$Incremental\ C/E = \frac{(TC_A - TC_B)}{(Eff_A - Eff_B)}$$

Results of the incremental analysis are portrayed in Table 5 and Figure 4. When compared to diet and exercise alone, the incremental cost for dexfenfluramine use is $67.96 per additional unit of effectiveness (% of initial body weight lost). This tells us that if more effectiveness is needed than diet and exercise can provide, the best buy is dexfenfluramine. The other treatment alternatives are more expensive, without conferring additional effectiveness (depicted as being outside the range of possibilities).

In Figure 3, the best option is the one with the greatest effectiveness for the lowest cost (i.e., the slope of the line from the origin is low and to the right). Any treatment regimen above this line has a higher cost with no increase in effectiveness, and is defined as outside the range of possibilities. Incrementally, the best option is diet and exercise alone. The next best buy is dexfenfluramine added to diet and exercise. The combination of fenfluramine and phentermine is less effective than dexfenfluramine, and costs almost as much. For this reason, the wise purchaser would bypass the combination of fenfluramine and phentermine in favor of dexfenfluramine. Fluoxetine's effec-tiveness is only slightly greater than the effectiveness of diet and exercise alone, but at a much higher cost. This puts fluoxetine outside the range of possibilities.

Limitations

This model looks at the cost of treatment over one year, with no cost of treatment failure. The most appropriate cost of treatment failure is the future cost of treating cardiovascular disease, diabetes, and other chronic conditions attributable to obesity. Unfortunately, the precise interplay among these factors is unknown, and therefore is not included in this model. If these factors were known, they would increase the cost of failure, resulting in enhanced cost-effectiveness of pharmacologic treatment.

Table 5: Incremental C/E Analysis for Non-Active Duty Population

Treatment	Total cost	Effectiveness	Incremental C/E
Diet & exercise alone	$354.57	5.70%	N/A
Dexfenfluramine *vs* Diet and exercise alone	$822.83	12.59%	$67.96
Fenfluramine/Phentermine *vs* Diet and exercise alone	$782.60	9.00%	$139.34 (Outside the range)
Fluoxetine *vs* Diet and exercise alone	$1,680.36	6.13%	$3083.23 (Outside the range)

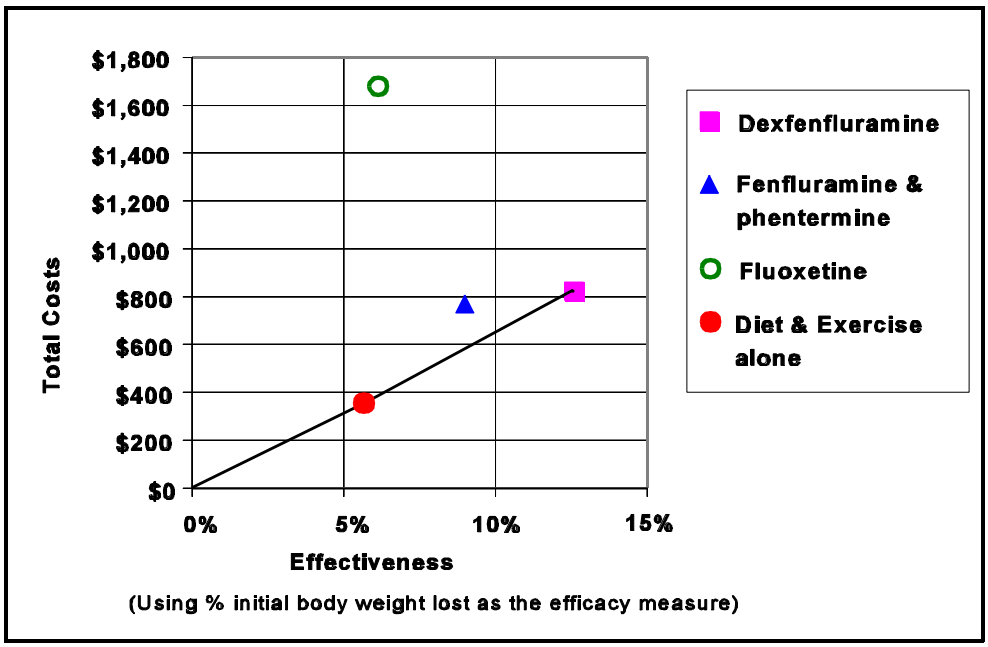

Figure 3: Incremental C/E of obesity treatment for non-active duty population

Obesity is a chronic disease and is best portrayed by a multi-year model. Unfortunately, data for the treatment regimens used in this analysis do not extend beyond a year's time. What is known is that if drug treatment is stopped, the weight is regained.

Conclusion

A structured diet and exercise program remains the treatment of choice for obesity in the non-active duty population. Adding dexfenfluramine to a regimen of diet and exercise will result in enhanced effectiveness (efficacy measured as percent initial body weight lost) at a cost of $67.96 per percent of initial body weight lost.

II. Active duty population

In 1995, 4273 enlisted members were separated from the military for obesity (personal communications: Bureau of Naval Personnel (PERS-60); Army Deputy Chief of Staff for Personnel; and Headquarters, USAF). The average cost of recruiting and training a replacement enlisted member is $40,283[*,56] (range $17,120 to $66,378; personal communication, Navy Recruiting Command), resulting in an overall cost to the Department of Defense of approximately $169 million. This does not include additional medical expenses resulting from the individual's obesity. In addition, this cost does not include those discharged members who were obese, but whose discharges were coded with other discharge codes. The $169 million spent on replacing obese enlisted personnel is an opportunity cost, money that could have been used in other programs, including obesity treatment.

The number of officers lost to obesity is much smaller (less than 5 percent of the total number), with greatly varying replacement costs. For this reason, the costs of replacing obese officer members are not included in this analysis.

Results from the 1995 DOD Survey of Health Related Behaviors showed that 11.9 to 22.6 percent of active duty members (stratified by age group) are overweight or obese. These people are in constant risk of not meeting the weight standards and discharge.[57]

The current weight standards for active duty members calculated as the body mass index (BMI) are shown in Table 6.[58-60] Since these standards are not based on the BMI, there is a range of BMI values for each service.

Table 6: Maximum Body Mass Index for Active Duty Members by Service

Service	Female	Male
Army	22-25	24-28
Air Force	25-26	28-30
Navy	26-28	27-29

This analysis compares various *appetite suppressant* medications to diet and exercise, as measured by sustained weight loss at 6 months to 1 year of treatment in enlisted members. The perspective of the analysis is that of the Department of Defense as both payer of the health care benefit and employer. The treatment regimens evaluated in this analysis include:

- Diet and exercise alone
- Dexfenfluramine 15 mg BID added to diet and exercise
- Fenfluramine 20 mg TID and phentermine resin 15 mg QD added to diet and exercise
- Fluoxetine 60 mg QD added to diet and exercise

Phenylpropanolamine, diethylpropion, and mazindol are not included because of a lack of long-term efficacy data.

In contrast to the analysis of obesity in the non-active duty population, the efficacy measure for the active duty population is the achievable weight loss with the treatment regimen, expressed in kilograms (kg). The achievable weight loss is stratified against the amount of weight the person needs to lose to meet the height/weight standard.

[*] As calculated in Monte Carlo simulation of 1000 trials.

Assumptions

- All patients are participating in a structured obesity treatment program consisting of diet, nutritional counseling, exercise, and group sessions and are compliant with this program.
- Drug therapy is an adjunct to the overall obesity treatment program.
- Patients with eating disorders are excluded from the analysis.
- Noncompliance with the treatment regimen does not result in any increased cost to DOD, but will affect the effectiveness of the treatment. The dosing frequency of the treatment (i.e., QD, BID, TID) was used as the compliance modifier. Compliance was not further altered for multiple drug regimens (i.e., combination therapy).
- The only adverse effect from drug treatment that may incur a cost to DOD is primary pulmonary hypertension (PPH), which may result in hospitalization, heart-lung transplant, or death. If a person develops PPH, it is estimated that one hospitalization and 2 additional office visits will occur within 1 year for treatment of PPH. The probability of a heart-lung transplant is for the lifetime of the patient and is assumed to be 100 percent for those patients developing PPH (range 50 to 100%). PPH is associated with the use of dexfenfluramine, fenfluramine, and phentermine.[30-36]
- Treatment failure results in administrative discharge and incurs replacement costs to the DOD (i.e., recruiting and training a new member and separation pay for some discharged members). Both the probability of and amount of separation pay included in the model is a weighted average, derived from Army data showing their discharges by length of service and pay grade (personal communication, Dept. of the Army, Deputy Chief of Staff for Personnel 05 Sep 1996). Since the same type of data was not available from the Air Force or Navy, it was assumed that the distribution of discharges by length of service and pay grade was similar to that seen in the Army.
- Treatment consists of an initial physician visit, 6 follow-up visits to the clinic, and 2 dietary visits in 1 year. The amount of time the member spent away from work for this treatment was assumed to be 2 hours for each appointment. The hourly wage used is a weighted average, derived from the Army data previously described. This amount was varied by 10 percent.
- 1 year cost of treatment model.
- Since the marginal cost of physician visits, laboratory tests, radiological studies, hospitalizations, and emergency department visits are unknown for DOD, the CHAMPUS maximum allowable charge (CMAC) was used as a proxy. These values were varied by 5% to reflect the difference in rates across the country.
- Costs based on only enlisted members, as they constitute the majority of discharges for obesity. The hourly wage is a weighted average, based on the demographics of personnel administratively separated for obesity.

Table 7: Variable List

Variable	Point estimate	Range	Reference
Initial visit (IV)	$104.00	$98.80 - 109.20	CMAC*
Short follow-up visit (FU)	$31.25	$29.69 - 32.81	CMAC*
Dietary consult (Diet)	$25.00	$25.00 - 38.00	Weighted average of military medical treatment facilities
Rx dispensing fee (Disp)	$2.95	$2.80 - 3.10	37

Variable	Point estimate	Range	Reference
Probability of developing PPH (pPPH)			38-40
• Dexfenfluramine	0.0039%	0.0023 - 0.0055%	
• Fenfluramine/Phentermine	0.0039%	0.0023 - 0.0055%	
• Fluoxetine	0	0	
• Diet and exercise alone	0	0	
Probability of hospitalization for PPH (pHOSP)	100%	70 - 100 %	Expert opinion
Cost of hospitalization for PPH (cHOSP)	$514	$488 - 540	CMAC*
Probability of heart-lung transplant (pTRANS)	100%	50 - 100 %	Expert opinion
Cost of heart-lung transplant (cTRANS)	$500,000	$475,000 - 525,000	CMAC*
Efficacy: achievable weight loss (kg)			20, 41-51
• Dexfenfluramine	8.18 kg	5.1 - 10.8 kg	
• Fenfluramine/phentermine	12.15 kg	7.8 - 15.7 kg	
• Fluoxetine	7.93 kg	7 kg gained to 26.6 kg lost	
• Diet and exercise alone	4 kg	5.6 kg gained to 7.7 kg lost	
Dropout rate (Dr)			20, 41-51
• Dexfenfluramine	7.25%	0 - 7.8%	
• Fenfluramine/phentermine	4.38%	0 - 14%	
• Fluoxetine	16.03%	13 - 17.8%	
• Diet and exercise alone	4.10%	0 - 8.3%	
Cost to recruit replacement enlisted member (RC)	$6200	$5890 - $6510	Navy Recruiting Command
Cost to train replacement enlisted member (TC)	$29,353	$10,048 - $60,111	56
Probability of paying separation pay to discharged member (pSep Pay)	20%	10 - 30%	Dept. of the Army, Deputy Chief of Staff for Personnel
Amount of separation pay (Sep Pay)	$3855	$3470 - $4240	DOD
Hourly wage (Hr)	$13.94	$12.55 - $15.33	DOD
Compliance with treatment regimen (Comp)			52-55
• QD (Fluoxetine)	80%	73 - 87%	
• BID (Dexfenfluramine)	78%	70 - 85%	
• TID (Fenfluramine & phentermine)	62%	52 - 77%	

* CMAC = CHAMPUS Maximum Allowable Charge

Equation

Average cost effectiveness of drug A = C/E_A

$$C/E_A = \frac{\sum \text{Treatment costs} + \sum \text{Side effect costs} + \sum \text{Treatment failure costs} + \sum \text{Opportunity costs}}{\text{Effectiveness}_A}$$

$[IV + (2 \times Diet) + (6 \times FU) + (4 \times Disp) + DC_A +$	Treatment costs
$pPPH \times [(pHosp \times cHosp) + (2 \times FU) + (pTrans \times cTrans)] +$	Side effect costs
$[\left(1 - \frac{Eff}{Wt}\right) \times (TC + RC + (pSep\ Pay \times Sep\ Pay) +$	Treatment failure cost
$(18 \times Hr)]]$	Opportunity cost (lost work time)
$[Kg_A \times Comp \times (1 - Dr_A)]$	Effectiveness

Key to abbreviations:
IV = Initial visit cost
Diet = Dietary consult cost
FU = Short follow-up visit cost
Disp = Prescription dispensing cost
DC_A = Drug acquisition cost for drug A
pPPH = Probability of developing primary pulmonary hypertension (PPH) during year of treatment
pHosp = Probability of hospitalization for PPH in 1 year
cHosp = Cost of hospitalization for PPH
pTrans = Probability of heart-lung transplant for PPH in 1 year
cTrans = Cost of heart-lung transplant
Kg_A = Achievable weight loss (in kg) at 6 months to 1 year on $treatment_A$
Hr = Hourly wage
Eff = Effectiveness (denominator of equation)
Wt = Amount of weight (in kg) needed to lose to meet weight standard
TC = Cost to train a replacement enlisted member
RC = Cost to recruit a replacement enlisted member
pSep Pay = Probability of paying separation pay to discharged member
Sep Pay = Amount of separation pay
Comp = Compliance with dosing regimen
Dr_A = Dropout rate for drug A

Sensitivity Analysis & Results

The model was tested for robustness to the variables and assumptions using multivariate and univariate sensitivity analyses. A Monte Carlo simulation was used for the multivariate sensitivity analysis. During this simulation, all variables were randomly varied throughout the ranges listed in Table 7 over 1000 trials.

The model was most sensitive to changes in the produced changes in the absolute values, but did not change the relative order of the therapies. The multivariate analysis produced the same results, demonstrating the robustness of the model to changes in the variables. Results of the Monte Carlo simulation of the *average* cost-effectiveness are presented in Table 8 and Figure 4.

These results are stratified by the amount of weight the active-duty member needs to lose to meet the weight standard. As the amount of needed weight loss increases, treatment becomes less cost-effective. The reason for this is the probability of treatment failure, with its concomitant costs. As the probability of achieving the desired weight loss decreases, the cost of treatment failure increases. The rate of increase is fairly flat up to the point of mean achievable weight loss for each treatment regimen, and becomes quite steep after that point.

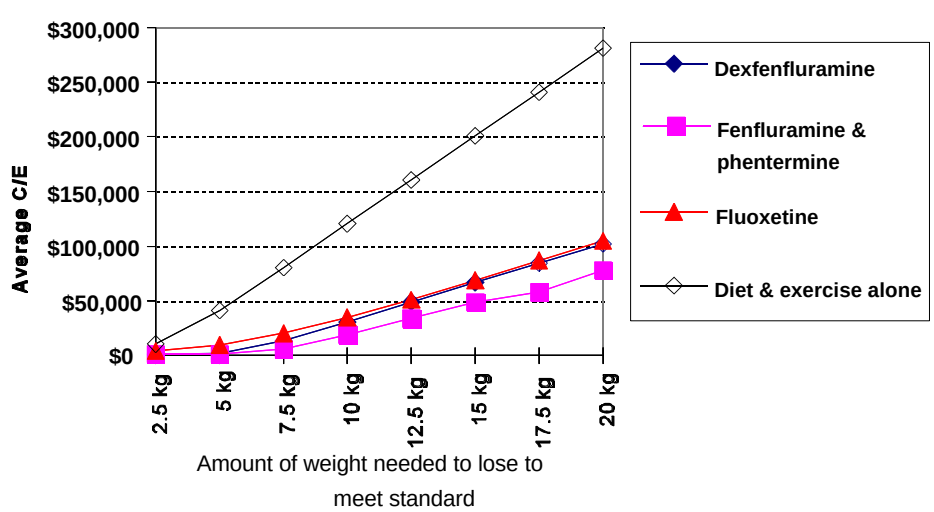

Figure 4: Active-duty average C/E versus needed weight loss

Table 8: Results of Monte Carlo Analysis for Active-Duty Members

Amount of weight needed to lose to meet standard	Fenfluramine & phentermine combination (95% confidence interval)	Dexfenfluramine (95% confidence interval)	Fluoxetine (95% confidence interval)	Diet & exercise alone (95% confidence interval)
2.5 kg (5.5 lbs)	$1033 ($1032-$1034)	$1089 ($1088-$1090)	$3897 ($2590-$5204)	$10,468 ($8549-$12,388)
5 kg (11 lbs)	$1144 ($1098-$1188)	$1747 ($1627-$1866)	$9785 ($6855-$12,715)	$40,928 ($36,506-$45,349)
7.5 kg (16.5 lbs)	$5995 ($5556-$6434)	$13,214 ($12,628-$13,800)	$20,237 ($15,641-$24,834)	$80,261 ($73,521-$87,002)
10 kg (22 lbs)	$18,924 (($18,141-$19,707)	$30,927 ($30,036-$31,819)	$34,592 ($28,344-$40,839)	$120,443 ($111,409-$129,477)
12.5 kg (27.5 lbs)	$33,724 ($32,671-$34,776)	$48,730 ($47,517-$49,942)	$51,152 ($43,279-$59,024)	$160,625 ($149,293-$171,956)
15 kg (33 lbs)	$48,525 ($47,190-$49,860)	$66,532 ($64,989-$68,075)	$68,797 ($59,319-$78,275)	$200,806 ($187,176-$214,437)
17.5 kg (38.5 lbs)	$63,327 ($61,703-$64,951)	$84,335 ($82,457-$86,212)	$86,892 ($75,818-$97,966)	$240,988 ($225,058-$256,918)
20 kg (44 lbs)	$78,128 ($76,212-$80,044)	$102,137 ($99,923-$104,352)	$105,060 ($92,391-$117,729)	$281,170 ($262,940-$299,400)

Due to amount of achievable weight loss, the fenfluramine and phentermine resin combination is always the most cost-effective treatment regimen. Conversely, a regimen of diet and exercise alone is the least cost-effective treatment regimen.

Limitations

The major limitation of this analysis is whether the data obtained from clinical trials in obese civilians is applicable to obese active-duty service members. Unfortunately, complete demographic data on obese service members are not available to compare with the study populations. In addition, clinical studies using pharmacologic agents in comparison to diet and exercise alone have not been performed in the active duty population. The question of personal motivation to meet the weight standard cannot be quantified from a population perspective, and must be taken into account when deciding how to treat the patient's obesity. This model looks at the cost of treatment over one year, with the cost of replacing the active duty member as the treatment failure cost. Additional costs of treatment failure are the future costs of treating cardiovascular disease, diabetes, and other chronic conditions attributable to obesity. Unfortunately, the precise interplay among these factors is unknown, and therefore they are not included in this model. If these factors were known, they would increase the cost of failure, resulting in enhanced cost-effectiveness of pharmacologic treatment.

Obesity is a chronic disease and is best portrayed by a multi-year model. Unfortunately, data for the treatment regimens used in this analysis do not extend beyond a year's time. What is known is that if drug treatment is stopped, the weight is regained.

In addition, the opportunity cost (lost work) incurred by the unit that lost the obese service member, and is awaiting a replacement, is not known and could not be included in the model.

An additional question remains, with respect to active duty members: at what degree of obesity is it more cost efficient to discharge the service

member versus treating his/her obesity? This is a complex personnel question, beyond the scope of this analysis.

Conclusions

When the decision is made to treat the active-duty member for obesity, the most cost-effective treatment regimen is the combination of fenfluramine and phentermine resin added to a structured diet and exercise program. A program of diet and exercise alone is the least cost-effective alternative in the active duty population. The actual treatment regimen must be patient specific, taking into consideration both the benefits and adverse effects of the various treatment regimens.

Summary

For the purposes of these analyses, the non-active duty and active duty populations were considered separately.

For the *non-active duty population*, the efficacy measure used in the analysis was the percent of initial body weight lost. The most cost-effective treatment regimen for the non-active duty beneficiaries is diet and exercise alone. At an incremental cost of $67.96 per % of initial body weight lost, dexfenfluramine (Redux™) is the next most cost-effective regimen.

In the *active duty population*, the efficacy measure was the achievable weight loss with the treatment regimen (in kg), stratified by the amount of weight loss needed to meet the height/weight standard. For active-duty members, the most cost-effective treatment regimen is the combination of fen-fluramine and phentermine resin. Due to the cost of treatment failure, diet and exercise alone is the *least* cost-effective treatment for active duty members.

Appetite suppressants afford a modest increase in the amount of weight loss that is sustained over time. Unfortunately, these medications are not without risk, and the risks are not yet fully known. In addition to PPH, neurological side effects of the medications may obviate use in certain active duty populations or inhibit performance. Response to the medications is variable and patient specific.

The future of pharmacotherapy in the treatment of obesity lies in the ability to sustain weight loss over time, not to enhance the amount of weight lost. Diet and exercise remain the mainstay of weight control.

Due to the lack of actual use data in an active duty population, absence of long-term toxicity data, and limitations regarding future costs of diseases attributable to obesity, no agents are recommended for addition to the Tri-Service Formulary. Clinical studies using pharmacologic agents in comparison to diet and exercise in an active duty population would aid in further evaluation of these agents.

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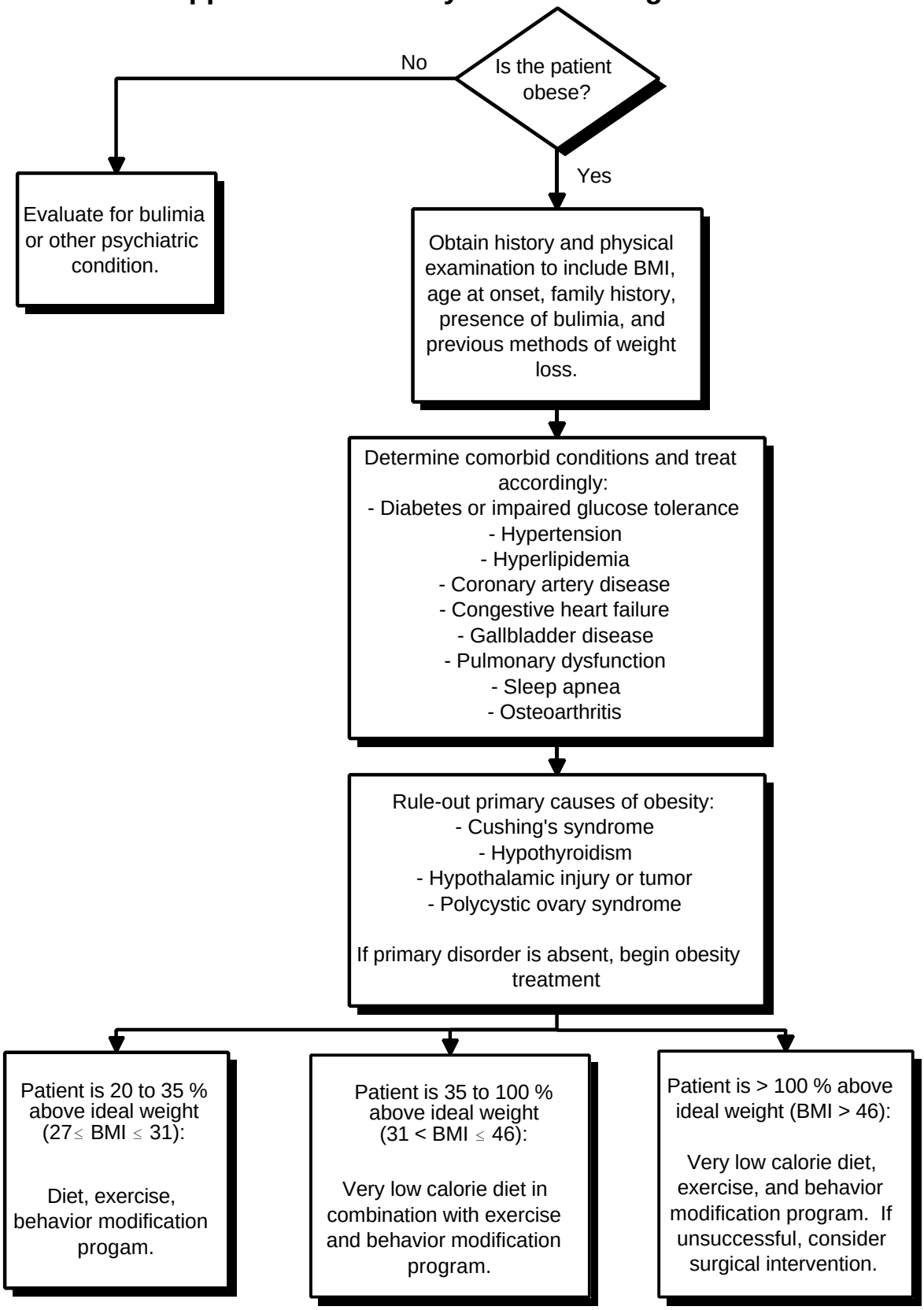
Appendix A: Obesity Treatment Algorithm



Phamacologic treatment may be considered at any level of obesity as adjunctive therapy if BMI ≥ 30 (or ≥ 27 for females or 28 for males with comorbid conditions). If no results are noted after 1 month of treatment, and patient has been compliant with the medication, discontinue use. Safety of anorexiant use beyond 1 year has not been determined.

Adapted from: Agras WS. Obesity. In: Rubenstein E, Federman DD, editors. Scientific American Medicine 1996;9(III):5.