WEIGHT LOSS SUPPLEMENT USE BY GYM CLIENTELE

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WEIGHT LOSS SUPPLEMENT USE BY GYM CLIENTELE

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A Thesis

Submitted to

the Graduate Faculty of

Auburn University

in Partial Fulfillment of the

Requirements for the

Degree of

Master of Science

Auburn, Alabama
August 4, 2007

WEIGHT LOSS SUPPLEMENT USE BY GYM CLIENTELE

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VITA

Brenda Denise White was born and raised in Selma, Alabama. She attended Texas Woman's University where she received her Bachelor of Science degree in Dietetics in May, 1997. In September 1998 she entered the dietetic internship at Brooke Army Medical Center, Fort Sam Houston, Texas and became a registered dietitian in November 1999. Brenda worked as a clinical and outpatient dietitian and food service manager for three years at Womack Army Medical Center, Fort Bragg, NC, and for three years at The United States Army Aeromedical Center, Fort Rucker, AL. In May 2005, Brenda completed a Master of Science degree in Human Resource Management from Troy State University at Dothan. Brenda began the graduate program in the Department of Nutrition and Food Science at Auburn University in May, 2005.

THESIS ABSTRACT

WEIGHT LOSS SUPPLEMENT USE BY GYM CLIENTELE

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Master of Sciences, August 4, 2007
(B.S., Texas Woman's University, 1997)

89 Typed Pages

Directed by Sareen S. Gropper

Obesity remains a major public health problem in the United States. Although practical means, such as a decreasing energy intake, increasing exercise, and modifying behavior, may be used to combat this growing problem, billions are spent yearly on weight loss products. The objective of this study was to examine the use of weight loss supplements among gym clientele. Clientele (n=227) from 14 gyms in central and eastern Alabama and central, western Georgia completed an anonymous supplement use questionnaire which asked about the use of weight loss and multivitamin/mineral supplements, alcohol and smoking, and health problems. Use of weight loss supplements among the surveyed gym clientele was 16.3%. Use of weight loss supplements did not significantly differ between women (16.2%) and men (16.5%), or between individuals $\leq$49 years (16.4%) versus those $\geq$50 years (16.2%). Weight loss supplement use also did not significantly differ by race, or between smokers and non-smokers, or beverage alcohol users versus non-alcohol users. There was no difference in weight loss

supplement use among study participants based on frequency of gym attendance. Sixty-one percent of study participants were classified as overweight or obese based on body mass index (BMI); however, weight loss supplement use did not significantly differ between those with a BMI $\leq$ 24.9 kg/m^2 (14.3%) versus those with a BMI $\geq$ 25.0 kg/m^2 (18.0%). Multivitamin/mineral supplement use by study participants was 59.5%, with individuals $\leq$49 years using these supplements (55.8%) significantly less than those $\geq$50 years (78.4%). Weight loss supplement use by study participants reporting health problems was significantly higher (27.8%) than those who did not report any health problems (13.4%). Weight loss supplements containing ephedra, yohimbe, bitter orange, or a combination of these were more commonly used (70.3%) than those containing other active ingredients (29.7%). Six study participants (16.2%) used two or more weight loss supplements. Adverse side effects were reported by 16.2% of participants using weight loss supplements. In conclusion, while use of weight loss supplements was not as prevalent as use of multivitamin/minerals by gym clientele, about 1 in every 6 persons who went to a gym reported weight loss supplement use. Further, the significantly greater weight loss supplement use by gym clients with reported existing health problems is particularly troublesome and may put them at higher risk of adverse side effects. Additional efforts by gyms to provide accurate educational information on weight loss supplements to its membership may be warranted. Health care professionals also need to inquire about the use of such supplements with patients and provide education as needed.

ACKNOWLEDGMENTS

The author would first like to thank God for his numerous blessings throughout preparation and defense of her thesis. The author would also like to thank specifically, her major professor/advisor, Dr. Sareen Gropper, a true gem, for her never ending support, guidance, sincerity, and immeasurable insight. Genuine gratitude is also expressed to her committee members, Dr. B. Douglas White and Dr. Kevin Huggins, for their support and time. In addition, the author would like to thank Dr. Steven Shumate for his thorough technical assistance with statistical analysis. A special thank you is extended to the gym managers and fitness directors in the southeast region who provided use of their facilities. The author extends a great deal of appreciation and gratitude to her mother, Estelle F. Gales, for always offering encouragement and seeing her strengths. Finally, the author thanks her family, specifically her niece Tyesha Mitchell, for being uniquely significant, and friends, specifically Leon Johnson, for always offering support, advice, and volunteering to listen to the numerous practice presentations in lieu of her thesis defense and Michael Elston for providing optimism and simplicity at a time when it was truly needed.

Style manual of journal used: Journal of Food Science

Computer software used: Microsoft Word 2000 and 2007, Microsoft Excel 2000, SPSS Version 12.0.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION

Obesity is a major public health problem in the United States. The National Health and Nutrition Examination Survey (NHANES) for 2003-2004 for the United States reported that 66% of adults (>20 years of age) were overweight (body mass index [BMI] 25 to 29.9 kg/m^2) or obese (BMI $\geq$30 kg/m^2) (Ogden and others 2006)**.** These findings represent an increased prevalence from the previous NHANES III data. As the prevalence of obesity increases, so does the prevalence of obesity-related chronic diseases, such as heart disease, type 2 diabetes, hypertension, and cancer, among others.

Weight loss treatments are typically aimed at decreasing energy intake and increasing energy expenditure. Practical methods to reduce energy intake and increase energy expenditure include behavior modification, dietary energy restriction, and increase physical activity or exercise. However, many consumers do not embrace these lifestyle changes. Rapid, quick-fix methods, such as the use of weight loss supplements or prescription weight loss medications are often preferred or used as an adjunct with other methods (Blanck and others 2001; Morrison and others 2004; Saper and others 2004; Wilborn and others 2005).

Several surveys have examined supplement use in various population groups. The most often consumed supplements are those that contain vitamins and minerals. Studies to date suggest that multivitamin/mineral supplements, when taken in

recommended amounts, may be useful. However, consumption of weight loss supplements may not be. A report by the Federal Trade Commission in 2002 noted fraudulent reporting of claims of weight loss supplements is rampant, and 50% of manufacturers make claims, which are most likely, spurious. Thus, the reported benefits of weight loss supplements should be weighed with the possible adverse effects (FTC 2002).

In 2004, there were about 50, one-ingredient dietary weight loss supplements and numerous combination-ingredient weight loss supplements available for consumer use (Lenz and Hamilton 2004). The most common ingredients in these supplements included ephedra (especially prior to 2004), bitter orange, and yohimbe. Yet, use of products containing these ingredients has been associated with adverse side effects including rapid heart beat, elevations in blood pressure, and jitteriness, nervousness, and anxiousness, among others.

Americans typically report that they are trying to lose weight or want to build muscle mass, increase strength, or prevent disease. The local gym provides an environment enabling clients to expend energy and to enhance strength and cardiovascular fitness as well as to build muscle. However, it is unclear to what extent people who frequent gyms are also using other approaches to achieve "better health." Many clients who frequent gyms are extremely focused on meeting goals of weight loss, muscle mass attainment, body fat loss, among others, and may use multiple and what could be considered as "extreme" methods to achieve their goals. Further, the use of weight loss supplements in older individuals or those with existing health problems who may be more prone to the adverse effects associated with use of weight loss supplements

may be dangerous. The purpose of this study was to examine the use of weight loss supplements among gym clientele.

CHAPTER 2

LITERATURE REVIEW

Obesity is a major public health problem in the United States. The National Health and Nutrition Examination Survey (NHANES) for 2003-2004 for the United States reported that 66% of adults (>20 years of age) were overweight (body mass index [BMI] 25 to 29.9 kg/m^2) or obese (BMI $\geq$30 kg/m^2) (Ogden and others 2006)**.** These findings represent an increased prevalence from the previous NHANES III data. As the prevalence of obesity increases, so does the prevalence of obesity-related chronic diseases, such as heart disease, type 2 diabetes, hypertension, and cancer, among others. As the prevalence of chronic diseases increases, so do health care costs. In 2002, healthcare costs related to obesity reached $92.6 billion (Finkelstein and others 2003). If the obesity epidemic is not controlled, it is estimated that health care cost may increase by 25% by 2030 (NANA 2003).

Weight loss treatments are typically aimed at decreasing energy intake and increasing energy expenditure. Practical methods to reduce energy intake and increase energy expenditure include behavior modification, dietary energy restriction, and increased exercise or physical activity. However, many consumers do not embrace these lifestyle changes. Rapid, quick-fix methods, such as the use of weight loss supplements or prescription weight loss medications are often preferred (Blanck and others 2001; Saper and others 2004; Wilborn and others 2005).

In 2004, there were about 50 one-ingredient dietary weight loss supplements and numerous combination-ingredient weight loss supplements available for consumer use (Lenz and Hamilton 2004). One of the most common ingredients in these supplements prior to 2004 was ephedra (Blanck and others 2001; Corum 2004). In fact, in 1999, the American Herbal Products Association reported 12 to 17 million Americans used weight-loss products which contained ephedra (Rubin and Rubin 2005). In 2001, approximately 7.5% of dietary supplements sold were ephedra-based, and, in 2002, ephedra sales averaged about $1.25 billion (Hardy 2005).

Ephedra remained a popular weight loss supplement for decades despite reports of adverse health effects. By 2001, over 1,300 adverse reports and 88 deaths had been reported due to ephedra (CU 2004). Yet, ephedra continued to be the weight loss supplement of choice for many Americans until it was banned by the Food and Drug Administration (FDA) in April, 2004 (Porter 2004; Woolf and others 2005). The ban included ephedra as well as its' alkaloids - ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine, and norephedrine (FDA 2004; Rados 2004).

Following the ban on ephedra, manufacturers began searching for ephedra substitutes that provided weight loss benefits without adverse health effects. Thus far, bitter orange and yohimbe appear to be the primary ephedra alternatives. Table 2.1 provides a list of a few of the many weight loss supplements on the market which contain bitter orange and/or yohimbe. As noted in Table 2.1, these substances are generally listed as the first, second, or third ingredient, or as part of a proprietary blend in dietary weight loss products.

Table 2.1. Popular yohimbe and bitter orange-containing supplements promoting weight loss.

Products	First Ingredient/Amount per serving if given	Second Ingredient/Amount per serving if given	Third Ingredient/Amount per serving if given
The Burn for Men	Synephrine HCL 20 mg (Bitter Orange Alkaloid)	Yohimbine HCL 4 mg	Evodiamine 12 mg
The Burn for Women	Synephrine HCL 20 mg (Bitter Orange Alkaloid)	Yohimbine HCL 3 mg	Evodiamine 10 mg
Thermo Hydroxadrine	Octopamine HCL (Bitter Orange Alkaloid)	Tyramine	N-Methyl-Tyramine
Tight ⟶ ⟶	Synephrine (Bitter Orange Alkaloid) 96% of 375 mg blend		
Thermo-Cuts Extreme	Guarana Extract 375 mg	Green Tea Extract 250 mg	Citrus aurantium Extract 180 mg
Magma 9	Citrus Aurantium 400 mg	Caffeine Anhydrous 250 mg	Octopamine 150 mg
NYX Care Y3	Yohimbine HCL	Thyroid Support Complex: 150 mcg	Potassium Iodide
Lipo 6	Synephrine HCL 20mg (Bitter Orange Alkaloid)	Guggulsterones Z&E 1:1 20 mg	Yohimbe HCL 3mg
N Cinerate	Yohimbe listed as part of proprietary blend.		
H.E.A.T Stack	Yohimbe listed as part of proprietary blend. Alpha-Y Rauwolfia Serpentina extract; (27% α- yohimbine)		
Beta 3	Octopalean 500mg (Bitter Orange Alkaloid)	Microcrystalline Cellulose	Kosher Gelatin
Yohimbe Fuel	Yohimbe Bark Extract 400 mg		
Shred X	Yohimbe	Kola Nut Berries Extract	Guarana Seed Extract
Jet Fuel	(Listed as part of Jet Fuel proprietary blend (1207 mg), Synephrine HCL (Bitter Orange Alkaloid), Yohimbine Hal, Octopamine (Bitter Orange alkaloid)		

In addition to yohimbe and bitter orange, other weight loss supplements on the market contain one or more active ingredients which function as stimulants in the body. Dexatrim, for example, contains caffeine, green tea leaf extracts, and eleuthero root

extracts. Lean System 7 contains synephrine (bitter orange) as well as Coleus Forskohlii, an aspirin/anticoagulant-like herb. Ripped Fuel contains both synephrine (bitter orange) and yohimbe, as well as, guarana. Hot Rox contains a "Hot Rox" formula which includes A7-E™ Super-Thermogenic Gel™ 50/700, yohimbe, guarana, and B vitamins. Stacker 3 contains Kola nut, White Willow Bark, caffeine, and guarana. Bitter orange, guarana, and green tea are also found in Xenadrine NRG.

This review of literature will address specifically the prevalence of use of weight loss supplements and the effectiveness, purported mechanisms, and adverse health effects by which some common dietary weight loss supplements, including ephedra, yohimbe, and bitter orange, are thought to promote weight loss. In addition, other common ingredients such as caffeine are also briefly discussed since they are sometimes used in combination to promote weight loss. However, because some of these compounds are thought to stimulate weight loss through the actions of epinephrine and/or norepinephrine, and/or through direct effects on adrenoreceptors, a brief review of epinephrine and norepinephrine's synthesis and actions is provided.

Prevalence of Supplement Use

Supplement use is prevalent among Americans and supplements are thought by many Americans to be helpful. The Council for Responsible Nutrition (CRN 2006) reported in 2004 that >75% of Americans believe supplements are safe and effective. In 2006, an Ipsos-Public Affairs telephone survey found that 69% of Americans believe supplements are safe and effective (Ward and Blumenthal 2005). However, given some of the reports by the Federal Trade Commission which showed significant fraudulent

claims on various weight loss products, perhaps Americans need to be more concerned (FTC 2006)

Several surveys have examined the use of different types of supplements including multivitamin and minerals, herbal, food-type dietary, and weight loss supplements. A few of the more recent studies are presented hereafter.

The National Health Institute Survey (NHIS) (2003) reported 21% of 135 million American adults consumed some form of non-vitamin/mineral supplement. Chronic or highest supplement users were women (some with menopause) with various ailments such as gastrointestinal problems and headaches, while those with serious diseases such as cardiac disease and diabetes were categorized as low supplement users (Croomie 2006).

Radimer and others (2003) evaluated the 1999-2000 National Health and Nutrition Examination Survey (NHANES) data pertaining to the use of supplements such as non-multivitamins/mineral supplements, multivitamin/mineral, and individual vitamin/mineral supplements. Supplements were used significantly more often by the following: women versus men, the elderly (60 years or older) versus the young (20-39 years), Whites versus Blacks and Mexican Americans, exercisers versus non-exercisers, nonsmokers versus smokers, and beer drinkers versus non-beer drinkers. The most commonly used supplement (35%) was multivitamin/mineral supplements.

Kimmons and others (2006) evaluated the use of multivitamins among adults, 2,239 women and 1,532 men, age 18 years or older. The results indicated 63.7% of the women and 52.9% of the men consumed multivitamins at least once if not more per week. Women, age ≥ 35 years, were more likely to use a multivitamin supplement

versus those 18 to 34 years. Both non-Hispanic White women and women in general were more likely to consume a multivitamin supplement versus non-Hispanic black women and men, respectively. Multivitamin supplements were used more often by normal-weight women versus obese women.

Nachtigal and others (2005) evaluated the use of supplements (including vitamins, minerals, herbs and weight loss products) over a 10-year period in 15,655 men and women, over 40 years of age. Weight loss was also assessed in a subgroup of subjects. The subjects completed a 24-page questionnaire on health, height, weight, dietary intake, physical activity, and supplement use. Whites (92.6% men/92.5% women) were found to consume supplements more often than Hispanics (0.9% men/1.4% women), African Americans (1.4% men/1.1% women), Native Americans/Native Alaskans (1.7% men/1.6% women), and Asians or Pacific Islanders (2.5% men/2.8% women). Women with some college education (42.1%) were more likely than men (36.1%) to consume dietary supplements. Women (57.4%) were more likely to smoke then men (44.9%). Long-term users of supplements such as multivitamins (58.6%), vitamin B_6 (60.2%), vitamin B_{12} (60.2%) and chromium (58%) showed less weight gain versus those who did not take these supplements long-term. Subjects considered overweight or obese based on body mass index showed less weight gain over the 10-year period with use of ≥5 multivitamin pills per week, ≥35 mg/day of vitamin B_6, ≥35 μg per day of vitamin B_{12}, and ≥150 μg per day of chromium versus normal weight subjects who consumed lesser amounts of these supplements.

Fogel and Kholodenko (2005) evaluated weight loss supplement use among college students. Questionnaires were completed by 50 students (47% White, 13% Black, 8% Hispanic, and 8% Asian American) with an average age of 22 years. About 50% (n=25) of the students were found to be using weight loss supplements although 60% reported themselves as normal weight. Newberry and others (2001) also reported 27 out of 272 (10%) college students assessed took some form of weight loss supplement despite having a normal body mass index.

Marinac and others (2007) evaluated the use of 90 herbal and dietary supplements in a group of 267 older adults, age 57 to 93 years who lived in Kansas City, Missouri. A 35-item survey was administered personally to each subject. The researchers found that 21% of adults took at least one supplement. Most participants indicated that the supplements were used mainly to maintain wellness and/or a general state of health. Garlic and glucosamine were the supplements that were most commonly used by these subjects.

Deuster and others (2003) evaluated various factors which may influence the overall health of one of the military's elite fighting forces, the U.S. Army Rangers. Some of these factors included use of dietary supplements, food, alcohol, and tobacco. This study consisted of 38 male Rangers, age 18 to 40 years, with average body fat <20%. All subjects were required to complete two questionnaires, the Block-National Cancer Institute Health Habits and History Questionnaire (HHHQ) and the Symptoms Checklist Questionnaire. Caffeinated beverages intake ranged from 3 to 8 cups per day and sports drink intake range from 2.8 to 3.2 cups per day. Alcohol was consumed by 76% of the Rangers, and 53% smoked or used some form of tobacco (i.e. snuff or chewing). Only 3

of the 38 smoked cigarettes. Supplements were used by 81.5% of the Rangers for strength, increased muscle mass, and weight loss. Thirteen percent consumed ephedrine or creatine-containing products. The authors concluded that there was a need for health education in this elite group of men.

Blanck and others (2007) evaluated the use of weight loss supplements among other methods (i.e. decreased energy intake, fad diets, meal substitutes and/or exercise) to enhance weight loss as part of the National Physical Activity and Weight Loss Survey. The survey was administered via telephone by the University of South Carolina Prevention Research Center over a 4-month timeframe. They interviewed 9,403 (5,348 women and 4,055 men) adults, age 18 to >55 years, in the United States. Weight loss supplements were used most often by women versus men (11.3% and 6% respectively); however, men (15%) used weight loss supplements longer than women (7.7%). Weight loss supplements also were used for a longer timeframe by those 55 years or older (25%) versus those age 35 to 54 years (9.2%) versus those age 18 to 34 years (8%). Supplement use was greatest in non-Hispanic Whites (15%) versus Hispanics (12%). Of the 9,403 adults evaluated, 6,634 (71%) used other weight loss methods in addition to weight loss supplements. Thirty-six percent of supplement users also exercised and decreased energy intake versus 29% of nonusers. Seventy-four percent used weight loss products with known stimulants (i.e. ephedra, bitter orange, caffeine, green tea, etc.). Fifty-five percent used weight loss products with ephedra.

Perkin and others (2002) evaluated the use of dietary supplements other than multivitamin/mineral supplements in 1,000 college students (607 women, 385 men, 8 gender unreported) with a median age 26 years. The subjects were attending college in

Florida and of various ethnicities, including African-American, Asian American, White, and Hispanic American. The survey consisted of 15 questions which requested information on smoking, health status, supplement use, and reasons for supplement use, among others. The researchers found that 26.3% of the subjects used dietary supplements. Nearly 35% said they had no knowledge or had never thought about using supplements. The top three reasons for dietary supplement use were to increase power (61%), to lose weight (38%), and to decrease body fat (36%). The researchers also found that more women versus men used dietary supplement to lose weight and for long-term health maintenance, and more men versus women used dietary supplement to increase muscle mass. Seventy-six percent of supplement users were undergraduates, 18% were smokers, and 73% exercised >3 times per month. Whites (78.7%) were more likely to use supplements the other ethnicities. Supplements such as protein powder, Ginseng, and St. John's Wort were among the supplements used most often.

Kanayama and others (2001) assessed the prevalence of use of non-prescription drugs (such as ephedrine, androstenedione, and anabolic steroids) and food-type supplements (including creatine and protein) through an anonymous questionnaire. The questionnaire used common name brands of the supplements for easy recognition (i.e. Diet Fuel, Ripped Fuel, Stacker products, etc.). The questionnaires were given to 511 patrons (334 men and 177 women) in five gyms in the Boston, Massachusetts area over a 3-year timeframe. The results indicated in men that the use of ephedrine (26%) was higher than the use of androstenedione (18%) and anabolic steroids (5%). Similarly, women used ephedrine (13%) more often than androstenedione (5%), and none used anabolic steroids. Protein and creatine use was higher in men, 61% and 47%

respectively, than the other supplements. Similarly, protein and creatine use was higher in women, 34% and 7% respectively, than the other supplements. From these percentages, it was estimated that during a 3-year timeframe, 1.8 million men and 240,000 women used ephedrine products nationally in gyms.

Morrison and others (2004) assessed the use of dietary supplements via a questionnaire in 222 adults (182 men, 40 women), age 18 to 55 years, who were members of one gym in Long Island, New York. The majority of supplement users were white males. Younger adults (30 years or younger) consumed more supplements versus older adults (> 30 years). About 85% of subjects used at least one supplement. The supplements most often used included multivitamins/minerals (45%), protein powders (42%), vitamin C (35%), and ephedra (13%). The primary reasons for supplement use given by the subjects were to increase muscle mass (49%), increase body strength (22%), and become better at endurance or resistance type exercises (24%). Bodybuilders were more likely to use protein, ephedra, and creatine supplements versus the other subjects.

Tseng and others (2003) examined the use of ephedrine, pseudoephedrine, phenylpropanolamine, and methylephedrine, common ingredients in cold medications and banned by the International Olympic Committee, in athletes. All four substances were found in the urine of athletes during several national sport competitions (including bodybuilding) in Taiwan. Urine samples collected from 1,803 athletes from 1991 to 2001 showed the presence of ephedrine (28% of samples), pseudoephedrine (44% of samples), phenylpropanolamine (17% of samples), and methylephedrine (11% of samples).

In summary, supplement use is prevalent with about 20% to 80% of Americans (adults) using supplements depending on the group surveyed. Further, supplement use is

common among all age groups and races, but perhaps higher in non-Hispanic Whites. Women appear to be more likely to use supplements than men. Use of weight loss supplements or products containing stimulants such as bitter orange and yohimbine also appears to be fairly common with the ban of ephedrine; however, ephedrine (found in cold medications) is still being used. Because many of the supplements used by Americans contain compounds which either stimulate or mimic the actions of norepinephrine and/or epinephrine, the next section of the literature review will briefly cover the synthesis and actions of epinephrine and norepinephrine.

Epinephrine and Norepinephrine

Synthesis

Epinephrine and norepinephrine as well as dopamine and L-dopa are synthesized in the body from the amino acid tyrosine and comprise a group of compounds known as the catecholamines. Both epinephrine and norepinephrine are similar in structure; epinephrine has an additional methyl group and norepinephrine an additional hydrogen ion.

Epinephrine is made and stored (about 80 to 85% of stored catecholamines) primarily in the adrenal gland; norepinephrine is made and stored (about 15 to 20% of stored catecholamines) in the adrenal gland, in various regions of the central nervous system and in nerve endings. Secretion from the adrenal medulla occurs in response to various stimuli (such as hunger, exercise, fright, mediations, etc.), and is mediated by nerve impulses which cause acetylcholine release from preganglionic neurons that

innervate the adrenal medulla. Epinephrine and norepinephrine function as hormones in the blood and as neurotransmitters in the brain and nervous system.

Mechanisms of Action

Epinephrine and norepinephrine circulate in the blood and bind to catecholamine adeno- or adrenergic receptors on target tissues. There are three main types of catecholamine receptors, $\alpha_{1,}$ α_2, and β receptors, on target cell plasma membranes. For each adrenoreceptor, there are three subtypes - α_{1A}, α_{1B}, $\alpha_{1C,}$ and α_{2A}, α_{2B}, $\alpha_{2C,}$ and $\beta_{1,}$ $\beta_{2,}$ and β_3 (LaFontan and others 1995; Strosberg 1993). The chemical structure of the adrenoreceptors is similar, and each is coupled to a specific guanine nucleotide binding protein (G protein). The catecholamines appear to have preferences for specific adrenoreceptors. For example norepinephrine prefers α_2 adrenoreceptors followed by the βs, whereas epinephrine appears to prefer the β adrenoreceptors, primarily $\beta_{3,}$ then $\beta_{2,}$ then β_1 (Lafontan and others 1995; Lafontan and others 1997). All adrenoreceptors are located on the same cells, but in varying amounts depending on the cell location. The α_1 receptors, including subtypes A, B, and C, are found in blood vessels, smooth muscle (especially the gastrointestinal tract), and the central and peripheral nervous systems. The α_2 adrenoreceptors including subtypes A, B, and C are found throughout the body, especially in presynaptic membranes and nerve endings of adjacent cells, and in the central nervous system. $Beta_1$ receptors are found in the central nervous system, as well as the heart and kidneys. $Beta_2$ are found throughout the body, but especially in the heart and lungs. $Beta_3$ is found mostly (~75%) in adipose tissue (Revelli and others 1993). Stimulation of beta receptors increases cAMP and lipolysis; however, the lipolytic effects

are thought to be the greatest with stimulation of the β_3 receptors. Studies evaluating differences in locations of adrenoreceptors indicate there are more β adrenoreceptors in the abdominal area of both men and women, and there are more α adrenoreceptors in the gluteus/thigh areas of women (Blaak 2001).

The main target cells of epinephrine and norepinephrine include the liver, adipocytes, skeletal muscle, and selected pancreatic cells. Generally, norepinephrine and epinephrine increase cardiac output and blood pressure. They also promote the degradation of glycogen in muscle and liver cells, stimulate the synthesis of glucose in the liver, and stimulate lipolysis in adipose tissue. In addition, norepinephrine is associated with thermogenesis. These latter two effects are particularly desirable for promoting weight loss.

Lipolysis is stimulated when norepinephrine binds to adrenoreceptors at nerve endings. This binding of norepinephrine stimulates the release of epinephrine from the adrenal medulla. Epinephrine then circulates in the blood and binds to adrenoreceptors on adipose tissue cell membranes, and activates a specific G protein, Gi_1. Gi_1 protein appears to activate adenyl cyclase, the enzyme responsible cAMP production. The increase in cAMP activates protein kinase A which then phosphorylates various proteins to initiate the lipolytic process (LaFontan and others 1995). Lipolysis diminishes as levels of cAMP decrease.

In addition to activating lipolysis, norepinephrine also activates in brown adipose tissue and to some degree in skeletal muscle a process known as thermogenesis (Inokuma and others 2005). In target tissues, the binding of norepinephrine stimulates GTP

hydrolysis to form GDP which then activates uncoupling protein 1 (UCP), also called thermogenin, which is found in the mitochondrial membrane. Thermogenin causes changes in the transport of protons into the mitochondria resulting in increased heat production from NADH and $FADH_2$ via the electron transport (respiratory) chain (Argyropoulos and Harper 2002; Thomas 2003).

Ephedra

Overview

The herb Ma Huang, also referred to as ephedra, has been used in medicine for thousands of years in China, Pakistan, and India. There are over 40 species of ephedra found throughout the world; it is the stem of the plant that is primarily used as a decongestant and bronchodilator (Porter 2004; Powers 2001; White and others 1997; Woolf and others 2005). The active ingredient in the plant is ephedrine, which was isolated in the late 1880s. Over time several other active alkaloids (referred to as ephedrine derivatives hereafter in this thesis) were identified in various ephedra species. These ephedrine alkaloid derivatives include methylephedrine, norpseudoephedrine, norephedrine, psuedoephedrine, and methylpsuedoephedrine. In 1924, a synthetic form of ephedrine was developed and introduced to the United States. It was used as a primary ingredient in cold and asthma medications, but also was later used in supplements promoting weight loss.

Ephedrine alkaloids in dietary supplements are normally from the whole herb or herb extract. Of 20 dietary supplements analyzed in 2000, the total alkaloid content ranged from 0.0 to 18.5 mg per dosage unit. The ephedrine and psuedoephedrine contents were 1.1-15.3 mg and 0.2-9.5 mg, respectively. Another similar study found

that the alkaloid contents of various products varied 44 to 260% (Gurley and others 1998; Gurley and others 1998; Gurley and others 2000).

Synthetic ephedrine is completely (100%) absorbed within an hour when given orally. It has a half-life in plasma of about 3 to 11 hours; natural ephedra's half-life is thought to be similar or slightly longer than that of the synthetic ephedrine (Dolley 1991; Gurley and others 1998; White and others 1997).

The botanical ephedra is regulated by the Dietary Supplement and Education Act (DSHEA), while the synthetic ephedrine and its derivatives are regulated by the Food, Drug, and Cosmetic Act (FD&C Act) which is overseen by the Food and Drug Administration (Rados 2004). Sales of over-the-counter cold and allergy products containing psuedoephedrine, the ephedra alkaloid, have been limited as of September 2006 by the Food and Drug Administration due to its use in amphetamine type drugs. Many cold and allergy products now contain phenylephrine. The maximum daily dose allowed by Food and Drug Administration is 60 mg (or 10 mg/serving) in these over-the-counter products (Hatton and others 2007). Some drug companies are requesting that the Food and Drug Administration increase the amount to 25 mg per serving because 10 mg/serving is not very effective. Over-the-counter products with phenylephrine and other ephedra alkaloids are currently being using as "energy booster" and weight loss aids. In some of these weight loss products, ephedrine is combined with caffeine © and/or aspirin (A). In fact, the combination of ephedrine, caffeine, and aspirin is commonly referred to as ECA or "the Stack". Studies have typically used a 1:10:10 or 1:10:15 ratio of The Stack. While the exact doses vary, most supplements provide about

25 mg ephedrine, 200 mg caffeine and 325 mg aspirin per dose (Aggarwal 2006; Shekelle and others 2003; Yehya 2001).

Mechanisms of Actions

Generally, ephedrine alkaloid derivatives have varied mechanisms of actions. Each alkaloid derivative, to some degree, has some effect on the cardiovascular as well as the respiratory system. Since ephedrine is the most active alkaloid, it is associated with most of the effects of ephedra (CRN 2000). The actions of ephedrine and its derivatives mimic those of the catecholamines epinephrine and norepinephrine, as well as those of amphetamines (Rados 2004; Wooltorton and Sibbald 2002). In fact, epinephrine and ephedrine are similar structurally (as shown here).

Figure 2.1. Ephedrine and Epinephrine

Ephedrine and its derivatives stimulate the sympathetic nervous system indirectly by stimulating the release of norepinephrine and epinephrine from storage sites in vesicles in axon terminals within the sympathetic nervous system. Ephedrine directly affects the sympathetic nervous system by binding directly to $\beta_{1,}$ β_2 and β_3 adrenoreceptors, which are found primarily on adipose tissue; this has led to some of it marketing claims as a "fat burner" and "thermogenic". Some studies, however, have not found that ephedrine binds to β_3 adrenoreceptors (Shannon and others 1999). The ephedrine-induced increase in norepinephrine results in the activation of lipolysis in adipose and muscle via the cAMP-

mediated cascade of reactions. The ephedrine-induced stimulation of epinephrine release results in epinephrine direct actions on other adrenoreceptors including α_1, α_2, β_1, and β_2, which are found on blood vessels and other tissues throughout the body. These interactions promote constriction of blood vessels which leads to increases in systolic and diastolic blood pressure, increased heart rate, palpitations, and nervousness, among other effects. Ephedrine also increases bronchodilation (Persky and others 2004; Powers 2001).

Adverse Effects

According to the Toxic Exposure Surveillance System data base from 1993 to 2002, adverse effects with ephedra use far outnumbered those associated with the use of other dietary and weight loss supplements (i.e. Kava kava, St John's Wort, Yohimbe, etc.). Approximately 1,953 "minor" and 42 "major" adverse effects were reported for ephedra as a sole ingredient. However, when ephedra was present with other ingredients (aspirin, guarana, St. John's Wort), the number of "minor" adverse effects increased to 7,835 and the number of "major" adverse effects increased to 131 including two reported deaths. Calls, noted as exposures to ephedra-containing products from 1993 to 2002, increased from 55 to 8,189 during this same time frame (Woolf and others 2005).

Haller and Benowitz (2000) evaluated 140 adverse reports from the Food and Drug Administration from June 1997 to March 1999. Cardiovascular effects (such as arrhythmias, palpitations, myocardial infarctions, stroke, etc.) accounted for 47% of reported adverse effects and nervous system problems accounted for 18% of adverse effects. Elevations in blood pressure appeared to be the most reported, followed by palpitations, stroke and seizures (Woolf and others 2005; Wooltorton and Sibbald 2002). There were 10 reported deaths and 13 reports of permanent disability (Haller and others

2000). Ephedrine is also known to cross the blood brain barrier and thus affect brain function (FDA 2003).

The adverse effects of ephedrine alkaloids may be amplified if it is consumed with other substances. For example, caffeine, illegal stimulants (phenobarbital/meth, street drugs, etc.) monoamine oxidase inhibitors, and beta blockers may intensify the effects of ephedrine on α and β adrenoreceptors. Moreover, preexisiting conditions, such as kidney problems, heart conditions [coronary thrombosis, congestive heart failure, myocardial infarctions, etc.], and diabetes may place individuals at higher risk for some adverse events when ephedrine is combined with other stimulants (Dolley 1991; Hoffman and Lefkowitz 1996).

Studies which have examined the effectiveness of ephedrine on weight loss and metabolism also have reported side effects. Some of these side effects include: dry mouth, heart burn, and insomnia (Boozer and others 2001). Use of combinations of ephedrine, caffeine, and/or aspirin is associated with jitteriness, dizziness, xerostomia, insomnia, tachycardia, arrhythmias, increased blood pressure, constipation, and headaches (Daly and others 1993; Vukovich and others 2005). Adverse reactions associated with long term use have not been sufficiently evaluated (Shekelle and others 2003; Yehya 2001).

Although ephedra has been banned in the United States, attempts are ongoing by manufacturers, such as Utah Nutraceutical Corporation, to bring it back into consumer hands. Utah Nutraceutical Corporation's current attempts are in appeal (FDA 2007).

Effectiveness of Ephedrine on Weight Loss and/or Metabolic Rate

Ephedrine's history as a weight loss drug began in 1972 in Denmark. After an ephedrine/caffeine/phenobarbital mixture was given to asthma patients by a Danish

general practitioner (Dr. Eriksen), patients reported decreased appetite and weight loss. A new pill known as “the Elsinore” pill was promptly prescribed as a weight loss agent by physicians for patients. In fact, a local pharmaceutical company reported producing 1 million tablets weekly. Consequently, by 1977, over 70,000 patients were taking the tablets for weight loss (Malchow-Moller and others 1981; Manninen 2006).

Malchow-Moller and others (1981) evaluated the effectiveness of “the Elsinore pill” without the phenobarbitol. The researchers compared the pill to diethylpropion (a common weight-loss ingredient) and a placebo. Subjects included 132 obese adults, age 18 to 60 years, who were 20 to 80% overweight. Forty-nine subjects received the Elsinore pill, which contained 50 mg ephedrine sodium and 50 mg caffeine sodium benzoate; 50 subjects received the diethylpropion, which contained 12.5 mg, and 33 subjects received the placebo. All of the subjects received 2 tablets (3 times per day) prior to each meal and consumed 1200 kcal per day. Weight loss was significantly greater in the group receiving “the Elsinore pill” and diethylpropion when compared to the placebo (median weight loss of 8.1 kg, 8.4 kg, and 4.1 kg for “the Elsinore pill,” diethylpropion, and the placebo respectively).

The following paragraphs describe the results of several studies evaluating the effects of ephedrine alone or in combination with other ingredients on weight loss and/or metabolic rate. The results of eight studies are presented.

Shannon and others (1999) evaluated the effects of ephedrine on energy expenditure in 10 adults. The subjects consisted of 6 men and 4 women, aged 25 to 35 years, with a BMI 22 to 27 kg/m^2. Subjects received, during alternating periods in a cross

over design, a placebo or ephedrine (50 mg) three times per day. Energy expenditure was significantly greater (3.6%) with ephedrine than with the placebo.

Pasquali and others (1992) evaluated the effects of 6 weeks of administration of ephedrine on energy expenditure, weight loss, and nitrogen excretion in 10 subjects, age 20 to 36 years with a BMI 31 to 40 kg/m^2. Five subjects were randomly assigned to receive ephedrine and five were randomly assigned to receive the placebo. All subjects consumed a calorie-restricted diet (1965 kJ). Each subject randomly received 50 mg of ephedrine hydrochloride three times per day or the placebo. Weight loss did not significantly differ between the two groups. The metabolic rate decreased in both the ephedrine and placebo group during the restricted diet; however, after consumption of ephedrine but not the placebo, metabolic rate increased significantly. In addition, the researchers found that less nitrogen was excreted in urine in the ephedrine group versus the placebo group suggesting ephedrine may have a protein sparing effect in these obese subjects.

Vukovich and others (2005) evaluated the efficacy of Ma huang (20 meq ephedra alkaloids) and caffeine (150 mg) versus a placebo on metabolic rate for a three-hour timeframe in eight subjects (4 males/4 females), age 22 to 25 years, mean body fat 15.7$\pm$ 1.2% for males and 27.6 $\pm$ 3.5% for females. Subjects fasted 12 hour and abstained from caffeine for at least 48 hours prior to assessments of metabolic rate. Metabolic rate was significant higher 30 minutes following ingestion of the ephedra/caffeine combination (10.7$\pm$ 2.5%) versus after consumption of the placebo (4.5 $\pm$2.5%).

Boozer and others (2002) evaluated the efficacy of an ephedra/caffeine combination on weight loss over a six month period. The subjects consisted of 30 men

and 137 women, aged 34 to 58 years, BMI 27 to 35 kg/m^2. Subjects were randomly divided into a placebo group (n=83) or the ephedrine/caffeine group (n=84). The ephedrine/caffeine group received two tablets, each containing 15 mg ephedrine alkaloid and 32 mg caffeine, three times per day 30 minutes prior to meals. Weight loss was significantly greater in the ephedrine/caffeine group (-5.3 ± 5.0 kg) versus the placebo group (–2.6 ± 3.2 kg). Body fat loss also was significantly greater in the ephedrine/caffeine group (-4.3 ± 3.3 kg) versus the placebo group (–2.7 ± 2.8 kg).

Daly and others (1993) evaluated the efficacy of an ECA combination on weight loss. This eight week study included 24 adults, age 22 to 37 years, mean BMI 37 kg/m^2. Subjects were divided into a placebo group (n=13) or an ECA group (n=11). The ECA group received 75-150 mg ephedrine/150 mg caffeine/330 mg aspirin per capsule. One capsule was taken prior to each meal, three times per day. The placebo group received a placebo which was taken before each meal, three times per day. The subjects consumed three meals per day and were allowed to consume their usual intake. After eight weeks, mean weight loss in the ECA group (4.85 lb) was significant greater than in the placebo group (1.54 lb). After another eight weeks and subjects switched from the ECA to the placebo and vice versa, mean weight loss in the ECA group (3.2 lb) again was significantly greater than in the placebo group (1.3 lb).

Pasquali and others (1987) evaluated the effects of ephedrine in 10 women (BMI 27 to 41 kg/m^2) on an energy restricted diet in a two-month, cross-over study. The women were randomly assigned to receive a 1000 to 1400 kcal/day diet and either 150 mg/day ephedrine hydrochloride tablets (50 mg prior to each meal) or a placebo. Weight loss in

subjects receiving the ephedrine (5.3 ± 1.34 lb) was significantly greater than those receiving the placebo (1.41 ± 1.1 lb).

In a 6-month study by Astrup and others (1992), the effects of ephedrine (20 mg) and caffeine (200 mg) versus ephedrine (20 mg) versus caffeine (200 mg) versus placebo on weight loss were examined in obese subjects. The study included 180 obese subjects (BMI >30 kg/m^2), age 20 to 65 years. The subjects were divided into four groups and received an energy restricted (4.2 MJ/day) diet, and prior to each meal either ephedrine and caffeine (EAC), solely ephedrine (E), solely caffeine ©, or a placebo (P). Weight loss in those receiving EAC was significant greater than those receiving the placebo (16.6 ± 6.8 kg versus 13.2 ± 6.6 kg, respectively).

Molnar and others (2000) evaluated weight loss in 32 boys and girls, age 14 to 18 years, receiving 500 less kcal/day and either two or three tablets of 10 mg ephedrine and 100 mg caffeine (EC) or a placebo based on weight over 20 weeks. Weight loss was significantly higher in the EC group. The adolescent consuming EC lost an average of 17.4 pounds whereas those taking the placebo lost an average of 1.1 pounds.

In summary, these studies suggest that ephedrine modestly increases metabolic rate and promotes weight loss.

Yohimbe

Overview

Yohimbe is the bark of one of the tallest evergreen trees, Pausinystalia yohimbe or Corynanthe yohimbe. It is also referred to as *P yohimbe*, and may appear on labels as yohimbe bark, yohimbine hydrochloride, johimbe, Actibine, Aphrodyne, Yocon, or

Yohimex. Yohimbe has been used in western Africa (the Congo, Nigeria, etc.) for centuries as an additive to folk and herbal medicine, as an aphrodisiac, as an hallucinogenic [smoked], warrior stimulant and pain-reliever. It augments the activity of monoamine oxidase inhibitors when combined with aged meat (sausage), aged cheese and fermented brews/red wine. In addition it is purported to improve libido, act as an antioxidant, prevent myocardial infarctions and plaque buildup in arteries, improve fatigue, and promote weight loss. It is also used in veterinary medicine to wake animals from the sedative, xylazine. Manufacturers currently advertise yohimbe as an anabolic steroid substitute, weight loss aid, and "Viagra" alternative/aphrodisiac (Blackmore 2002; Sahelian 2004).

Yohimbine is considered unsafe and has been banned by Commission E (Germany regulatory agency). In the United States, as with ephedra and bitter orange, it is currently regulated as a dietary supplement by DSHEA and as a drug (yohimbine hydrochloride) via the Food Drug and Cosmetic Act. Yohimbine hydrochloride, as a drug, has been approved by the FDA for impotence only in men. It is prescribed by physicians at doses of 5.4 mg**,** three times per day. It is normally available in tablet and capsule forms. Dosages of yohimbine hydrochloride in research are generally ≤ 30 mg. Although in Germany doses of 100 mg/day were used prior to its ban. Yohimbine can be administered orally, intravenously, dermally or via inhalation (ACS 2005; Temple and Smith 1992).

Yohimbine is one of 32 alkaloids found within the yohimbe bark. Two other main alkaloids include rauwolscine, followed by corynanthine. Each alkaloid has

different pharmacological effects, potency levels, and adrenoreceptor selectivity as discussed further under mechanism of action.

The alkaloid content and amount of yohimbe in dietary supplements vary greatly. The yohimbe extract/alkaloid content in several dietary supplements ranged from <0.1 to 489 ppm as compared to the 7089 ppm normally found in genuine yohimbe bark (Betz and others 1995). Yohimbe bark contains 6% or less of total P yohimbe alkaloids; only 10 to 15% of this is actually yohimbine. The amount of yohimbine in 20 commercial aphrodisiac products ranged from 1.32 to 23.16 mg per tablet (Zanolari and others 2003).

The efficacy and side effects associated with yohimbine are strongly associated with the source consumed (bark, liquid, powder extract), absorption, distribution, clearance, and excretion of yohimbine (http://www.raysahelian.com/yohimbe.html). Owens and others (1987) evaluated the absorption and clearance of yohimbine from plasma in eight men, age 21 to 36 years, consuming 10 mg yohimbine hydrochloride. Yohimbine was rapidly absorbed and had a half-life of 0.6 hours. After 24 hours, little yohimbine or yohimbine metabolites was found in the urine (0.35% of 10 mg yohimbine hydrochloride). Hedner and others (1992) also evaluated the plasma clearance and urinary excretion of intravenously administered yohimbine from 13 males, mean age 30 years. Yohimbine was administered over a 2-minute timeframe via catheter at 0.25 mg/kg of body weight. Yohimbine had a plasma half-life of 0.3 to 0.8 hours in 12 subjects, and was excreted virtually unchanged. Excretion, however, was biphasic with initial excretion occurring at 36 minutes in 9 subjects and 13 hours in three subjects. Guthrie and others (1990) also evaluated the clearance, distribution, and bioavailability of yohimbine hydrochloride in seven males, mean age 28 years. In this cross-over study, the subjects

randomly received either 10 mg yohimbine hydrochloride orally or intravenously. The trials were separated by one week. The absorption and rate of clearance were similar to the findings of Owens and others (1987). Intravenous distribution took about 6 minutes; oral distribution was about 9 minutes. Oral bioavailability varied more among subjects (7 to 87%); this variance was likely the result of differences in intestinal absorption and hepatic clearance. Le Corre and others (2004) found variable metabolism of yohimbine in 172 adults (87 women, 85 men). Seventeen subjects did not metabolize yohimbine as suggested by <1 μg/L 11-hydroxy-yohimbine in the plasma. In the other 155 subjects, metabolism from yohimbine to 11-hydroxy-yohimbine varied 1000-fold within a 15-minute timeframe.

Mechanisms of Action

Yohimbine and rauwolscine appear to act on α_1 and α_2 adrenoreceptors as antagonists. Of interest, however, yohimbine has a higher affinity for α_2 rather than the α_1 adrenoreceptors, and rauwolscine has more of an affinity for the α_2 adrenoreceptors with no affinity for α_1 adrenoreceptors. Corynanthine, in contrast, is basically a selective α_1 adrenoreceptor antagonist. Yohimbine's metabolites include 11-hydroxy-yohimbine and 10-hydroxy-yohimbine. 11-hydroxyyohimbine is the most prevalent of the two, and it has a longer half-life than yohimbine. Although it will bind to α_2 adrenoreceptors, it has a weaker affinity for these adrenoreceptors (LeVerge and others 1992). Yohimbine can cross the blood brain barrier, whereas 11-hydroxyyohimbine does not readily cross (Hedner and others 1992; Hubbard and others 1988).

Yohimbine stimulates both the parasympathetic and sympathetic nervous systems via its' effects on α_2 adrenoceptor. As an α_2 adrenoreceptor antagonist, yohimbine blocks the inhibitory activity of the α_2 adrenoreceptors. It has a very high affinity for receptors on tissues such as the eyes, genitals, and adipose tissue (IMAG 2000).

Yohimbine's chemical formula is $C_{21}H_{26}N_2O_3$. The other yohimbe alkaloids are structured similarly. They all have a 5-carbon center (as shown below), which affects interactions with various adrenoreceptors and their effectiveness as antagonists.

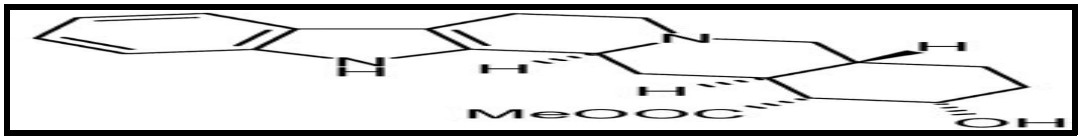

Figure 2.2. Yohimbine

When α_2 adrenoreceptors are activated, norepinephrine is not released and reuptake of norepinephrine is dominant. Therefore, yohimbine's blockage of these α_2 adrenoceptors increases release of norepinephrine and decreases uptake of norepinephrine. Numerous studies indicate yohimbine-induced norepinephrine release increases lipolysis and increases plasma nonesterified fatty acids, as well as glycerol (Berlan and others 1991; Goldberg and Robertson 1983).

Adverse Effects

Consumer Reports (2004) lists yohimbe in their likely hazardous section of "Dangerous Supplements Still at Large." They recommend yohimbe, as well as, 11 other dietary supplements be avoided. The report indicates yohimbe is associated with increased blood pressure, myocardial infarctions, respiratory abnormalities, and death. Yohimbe also has been linked with hepatic damage, shakiness, elevations in heart rate, and altered emotions such as anxiety, irritability, and restlessness, among others (Cameron and others 2000; Clark and others 1997; Goldberg and Robertson 1983; Price and others 1984).

Effectiveness of Yohimbine on Weight Loss and/or Metabolic Rate

Only a few studies have examined the effects of yohimbine on metabolic rate and/or weight or fat loss. These studies are presented hereafter.

Kucio and others (1991) evaluated the efficacy of yohimbine and a reduced calorie diet versus a placebo and a reduced calorie diet on weight loss and energy expenditure. This 42-day study included 20 women, age 26 to 35 years, with a BMI 37 to 45 kg/m^2. Weight and energy expenditure were measured initially and on days 21 and 42. For 21 days, the subjects were required to consume a 1,000 kcal diet. From day 22 to day 42, the subjects were randomly assigned to receive either 5 mg yohimbine or placebo (4 times per day) 1½ hours before each meal (3 total) and one prior to bed. Weight loss was significantly greater during the last 21 days in the yohimbine/reduced-calorie diet group (3.35 kg) versus the placebo/reduced-calorie diet group (2.21 kg). Resting energy expenditure measured prior to consumption of the meal was lower in the yohimbine

group versus the placebo group (day 22 vs. day 42); however, after consumption of the meal, energy expenditure increased.

Ostojic (2006) evaluated the efficacy of yohimbine on weight loss and body composition. This 21-day placebo-controlled study included 20 male soccer players, age 20 to 28 years. All subjects were evaluated prior to and after supplementation. Subjects were randomly assigned to receive 10 mg, two times per day of yohimbine HCL or a placebo. No significant difference was found in muscle mass in the placebo group versus the yohimbine group after 21 days. However, there was a significant decrease in body fat in the yohimbine group pre versus post (9.3% ± 1.1 vs. 7.1% ± 2.2, respectively). In addition, body fat loss was significantly lower in the yohimbine group versus the placebo group post (7.1% ± 2.2 vs. 9.2% ± 1.9).

Zahorska-Markiewicz and others (1986) evaluated the weight loss and metabolic effects of yohimbine versus a placebo in 21 overweight women, age 20 to 42 years. The women consumed a restricted caloric intake of 400 calories per day and received either yohimbine hydrochloride (15 mg) or a placebo for four weeks. Weight loss was significantly greater in those receiving the yohimbine versus placebo. Metabolic rate also was significantly increased following consumption of the yohimbine.

In a six week cross-over design study, 20 women age 19 to 30 years with a BMI >30 kg/m^2 consumed a low-energy diet (1000 kcal/day) and either a placebo or yohimbine (5 mg capsule yohimbine 4 times a day) weeks. Prior to the study and at the end of three weeks of treatment, weight loss and metabolic rate were measured. Mean weight loss was significantly greater in subjects receiving yohimbine versus the placebo**.** There was only

a slight increase in metabolic rate; however it was not significant (Berlan and others 1991).

In summary, these few studies suggest that yohimbine appears to promote body weight and fat loss in individuals (Berlan 1991; Kucio and others 1991; Ostojic and others 2006; Zahorska-Markiewic and others 1986); however, additional studies are needed.

Bitter Orange

Overview

Citrus aurantium, also known as the Seville orange, sour orange, or bitter orange, has been around for a number of centuries and, as the name implies, it is derived from oranges. Bitter orange was thought to be first cultivated possibly in Southeast Asia, and then later introduced to Europe and the United States. It is currently available in various forms (i.e. oil, fruit, peel, and juice). Bitter orange's vivid orange/red color, coarse outer layer, and sour/tart pulp distinguishes it from the sweet orange. It is, however, the modern sweeter orange (i.e. Valencia, naval, etc.), which is eaten most often by consumers for its taste, nutritional constituents, and antioxidant properties (Blumenthal 2004; English 2002; Jellin and others 2002). Yet, bitter orange has been used extensively in traditional Asian medicine as a digestive aide for gastrointestinal tract problems as well as in western medicine as a cold aide (i.e. expectorant), digestive aid (i.e. laxative; abdominal spasms, etc), and to raise blood pressure.

The flower, peel, extracts from dried fruit, and oils extracted from the peel of bitter orange are used in foods, beverages, fragrances, and natural medicine. For example, it is commonly used in foods such as jams, preserves and syrups to supply the sharp/tart taste. It is also used in drinks such as liqueurs, soft drinks, flavored waters, etc. The oils are

frequently added to perfumes to supply their unique fragrances. Extracts from the flower are used to make tea. The amounts added to products vary. For example, ≤ 5% is usually added to juices (NTP 2004).

Active ingredients in bitter orange include five biogenic amine alkaloids. These alkaloids are synephrine, octopamine, N-methyltyramine, tyramine, and hordenine. The two alkaloids of relevance for this literature review are synephrine and octopamine because they are considered the most active alkaloids and typically found in the highest concentrations in bitter orange (Allison and others 2005; Avula and others 2005). For example, levels of synephrine in Citrus aurantium species range from about 0.02 to 0.17% (Avula and others 2005). Generally, fresh fruit contains about 0.020% bitter orange alkaloids, dried fruit contains 0.352% bitter orange alkaloids, and dried extract contains 3.003 to 3.079% bitter orange alkaloids (Avula and others 2005). Brackett (2006) reported that extracts of Citrus aurantium may contain as much as 4% to 90% synephrine.

Bitter orange is thought to contain three positional isomers (i.e. meta/para/ortho) with two chiral forms (i.e. d/l) for each alkaloid. However studies to date have not confirmed the presence or lack of the ortho isomer in bitter orange products. One product Ultra Thermogenic Fuel that has been analyzed was found to contain both para and meta isomers of synephrine (Allison and others 2005). However, dietary supplements do not list on the label whether they contain para and/or meta (or ortho) isomers or if the alkaloids are in the d or l chiral forms. Given that selected isomers of bitter orange have been linked with adverse effects and that some isomers may be more active than others, such information would be valuable. One study reported that the d form of octopamine is more potent then its' l form (and also may be associated with adverse cardiovascular effects)

(Allison and others 2005; Blumenthal 2005; Fugh-Bergman and Meyers 2004; NTP 2004; Penzak and others 2001). Dried extracts of bitter orange were found to contain 3% of d and l isomers of synephrine and supplements contained from 0.3 to 0.99% of d and l isomers of synephrine (Pellati and others 2002). Dietary supplements normally list on the label the amount of bitter orange in milligrams (mg) /100 grams (g) and synephrine or octopamine as a percent of the (mg/100g). For example, MetaSlim contains 150 mg bitter orange extract (standardized to 6% synephrine) per capsule (Blumenthal 2005; NTP 2004). Dietary weight loss products contain various levels of bitter orange's extracts, ranging from 100 to >200 mg extracts per dose. The extracts themselves may supply as little as 10 mg to 40+ mg bitter orange alkaloids (i.e. octopamine and/or synephrine) per serving. Octopamine can also be listed on labels as norphen, p-Norsynephrine, or norsynephrine. Furthermore, synephrine may be listed in the ingredients of dietary weight loss products as oxedrine, p-Oxedrine, and (±)-Synephrine (NTP 2004).

Dosages of citrus aurantium of 1 mg/kg are considered to be safe and effective for weight loss for the average adult consumer (Jones 2001). Some weight loss products such as Nutres Lipo 6 recommend for "max weight loss" a maximum dose of 120 mg per day. Synephrine has been used in clinical trials at 300 mg per day. A dosage of 1,000 mg per day has been suggested as the adult lethal dose for m-synephrine. Bitter orange is considered a "performance enhancer," and has been banned by the National Collegiate Athletic Association (NTP 2004).

Synephrine appears to be quickly absorbed, although 80% is typically excreted in urine. Plasma concentrations peak at 1 to 2 hours following ingestion and the half-life of synephrine is about 2 to 3 hours (Martindale 2004).

Mechanisms of Action

Both synephrine and octopamine, the two main active alkaloids in bitter orange, can be synthesized, but typically only in trace amounts, in the body (Zucchi and others 2006). The concentration of trace amines in humans is very low (i.e. 0.1 to 10 nM) (Fugh-Berman and Meyers 2004). Octopamine is synthesized from tyramine via the enzyme dopamine beta-hydroxylase; synephrine is then made from octopamine via the enzyme phenylethanolamine N-methyl transferase.

Octopamine and synephrine are similar in structure to norepinephrine and epinephrine, respectively, and are found in similar locations in the body (Williams and other 1987). As shown below, synephrine is similar in structure to epinephrine as well as to ephedrine, and octopamine is similar in structure to its analog norepinephrine.

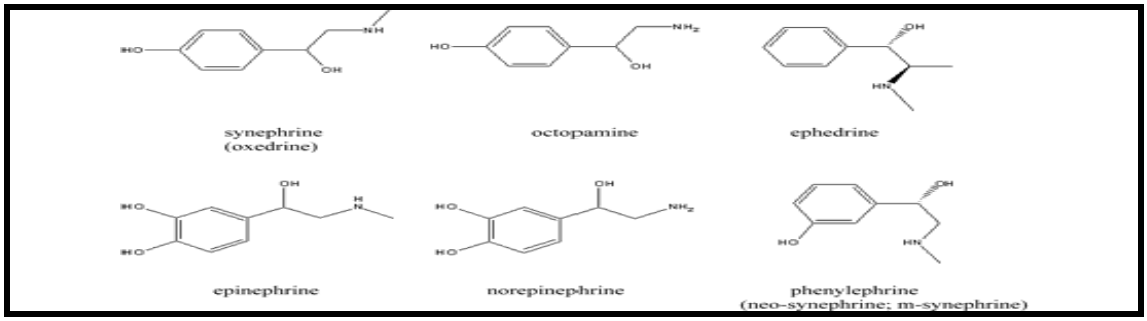

Figure 2.3. Synephrine, Octopamine, Ephedrine, Epinephrine, Norepinephrine and Phenylephrine.

The differences in the structures of these alkaloids and their phenol analogs are very minuscule however significant because the presence or absence and position of the hydroxyl (OH) and methyl (CH_3) groups greatly affects their mechanism of action and effects on the body. The OH group of p-synephrine or p-octopamine is always located on the benzene ring at the #4 carbon, whereas with m-synephrine or m-octopamine it is located on the benzene ring at the #3 carbon. These differences change the

stereochemistry and can influence the activity of these biogenic amines (Bouchard and other 2005). Their phenol analogs epinephrine and norepinephrine have methyl (CH_3) groups attached. The presence of the methyl group is believed to increase lipophilicity (English 2002; Galitzky and others 1993; Wenke 1967).

Like epinephrine and norepinephrine, both octopamine and synephrine appear to have neurotransmitter properties. Yet both octopamine and synephrine (para) are significantly less potent (active) than norepinephrine and epinephrine on both α and β adrenoreceptors.

Synephrine appears to affect all of the α adrenoreceptors and the β_3 adrenoreceptors, but has no affect on β_1 or β_2 adrenoreceptors. Octopamine appears to have a strong affinity specifically for β_3 adrenoreceptor, and not the α adrenoreceptors (Carpene and others 1999;Yen and others 1998). Galitzky and others (1993) reported that octopamine solely interacted with β_3 adrenoreceptors in humans. Whether octopamine (para) has a greater or lesser effect on β_3 receptors versus synephrine (para) is controversial (NTP 2004).

Both octopamine and synephrine appear to decrease cAMP production (Bouchard and others 2005; Fugh-Berman and others 2004). Octopamine has been shown to stimulate lipolysis via β_3 adrenoreceptors in white adipocytes from various mammals (Fontana and others 2000). Fontana and others (2000) analyzed the adrenergic properties of octopamine and tyramine in various mammals. Octopamine also decreased glucose transport into adipose cells of rats and showed a very weak response to α_2

adrenoreceptors in human fat cells. They concluded that tyramine has no activity, and octopamine had a stronger affinity for the β_3 adrenoreceptors.

Carpene and others (1999) examined the lipolytic effects of octopamine, synephrine, dopamine, tyramine, epinine, β-phenylethylamine, and phenylethylamine on β_3 adrenoreceptors in white fat cells of rat, hamster, dog, guinea pigs, and humans. Dopamine, tyramine, and β-phenylethylamine were not effective in activating lipolysis. However, synephrine, epinine, and phenylethylamine moderately activated lipolysis in all species studied. Octopamine fully activated lipolysis in the rat, hamster, and dog, but only moderately activated lipolysis in the guinea pigs and humans. Yet, when β_3 adrenoreceptor human cells were transposed inside the Chinese hamster ovary cells, octopamine was more receptive/had more of an affinity to these cells (Carpene and others 1999).

Visentin and others (2001) found that octopamine, although less potent than norepinephrine blocked-insulin stimulated uptake of glucose into cells by its direct agonistic effects on β_3 adrenoreceptors and promoted lipolysis.

Adverse Effects

Bitter orange is believed to have fewer adverse effects than ephedra, although, within a six-year timeframe (1998 to 2004), Health Canada documented 16 reports of adverse events associated with use of bitter orange dietary supplements (CARN 2007). These adverse events were cardiovascular-oriented and included increased heart rate, myocardial infarction and ventricular fibrillation, among others. All of these cases consisted of consumers using bitter orange with no other stimulant (i.e. ephedra/caffeine),

or a combination of bitter orange and caffeine, or bitter orange, caffeine, and ephedra/ephedrine. Two of these 16 patients died; both patients had taken products containing bitter orange, ephedra/ephedrine, and caffeine (Blumenthal 2005; English 2002; Jordan and others 2004).

The effects of both synephrine and octopamine can be exacerbated if combined with other substances including aspirin and caffeine. In some cases, caffeine is added as kola nut or guarana, both of which naturally contain caffeine. As with ephedra, when synephrine or octopamine are combined with other stimulants (i.e. caffeine/guarana, etc), the effects are elevated. Several reports have noted major adverse effects associated with the use of bitter orange or bitter orange combinations. These side effects include increased blood pressure and heart rate (Bui and others 2006; Haller and others 2005). Several other ill effects have been associated with the use of products containing bitter orange. For example, Gange and others (2006) reported that use of CortiSlim, a dietary product which contains bitter orange, was associated with angina in a 57 year old overweight male. Nykamp (2004) found that the over-the-counter product Edita's Skinny Pill, containing 300 mg bitter orange and other weight loss ingredients, was associated with a myocardial infarction in a 55 year old white female with no previous history of heart disease or heart-related problems. Nykamp (2004) also reported that heart arrhythmias in a 57 year old female (also taking 50 mcg thyroxine for hypothyroidism) was associated with the use of an herbal extract containing 500 mg bitter orange (6% synephrine extract). Other reported single cases of adverse effects associated with bitter orange include exercise-associated syncope in a 22-year old female patient, and a stroke in a 38 year old male (Bouchard and others 2005). Further, use of octopamine and other amines has been linked with cluster

headaches and migraines in susceptible individuals (Allison and others 2005). Other researchers have found that the quantity of the alkaloids in bitter orange extracts may exacerbate conditions such as cardiovascular disease and hypertension (Blumenthal 2005; NTP 2004).

Effectiveness of Bitter Orange Products on Weight Loss and/or Metabolic Rate

Seifert and others (2001) evaluated the efficacy of bitter orange on metabolic rate. This cross-over study included 23 subjects (14 women/9 men), ages 18 to 32 years, BMI 22 to 29 kg/m^2. All subjects were advised not to exercise before each trial. Day 1 consisted of consumption of three Citrus Aurantium capsules versus a placebo and Day 2 consisted of consumption of four Citrus Aurantium capsules versus placebo. The subjects randomly received either Citrus Aurantium capsules or the placebo. Resting metabolic rate significantly increased 8% from 1.18 kcal/min on day 1 to 1.28 kcal/min on day 2 in the bitter orange group whereas no significant change was found in the placebo group 1.26 kcal/min on day one versus 1.24 kcal/min on Day 2.

Hedrei and Gougeon (1997) evaluated the effects of Citrus Aurantium containing octopamine and synephrine on energy expenditure in seven adults. The subjects were required to fast overnight (12 hours) for each day of this 3-day study. Subjects receive a 392 calorie nutrient-dense meal, a meal plus 5 capsules or five capsules alone. Metabolic rate increased significantly (14.9%) following ingestion of both the meal and Citrus Aurantium versus ingestion of only the meal (13.5%). The RQ increased with the Citrus Aurantium capsules only and with the Citrus Aurantium capsules combined with the nutrient-dense meal Energy expenditure after consuming the capsules and the meal was significantly increased (0.88 ± 0.11 kj/min to 1.89 ± 0.09 kj/min. There was also a

significant increase in energy expenditure with ingestion of only the CA capsules (0.56 ± 0.16 kj/min to 0.91 ± 0.02 kj/min).

Xenadrine, a common weight loss supplement, was evaluated to determine its' effects on resting energy expenditure and body fat. The supplement's ingredients include bitter orange, guarana, and Ma huang. This 44-day study consisted of 20 healthy subjects, 15 women and 5 men. The subjects were randomly assigned to receive a placebo (n=8) or Xenadrine (n=12). No significant differences were found between the two groups for body fat or resting metabolic rate. However, subjects in the Xenadrine group lost significantly more body fat than those in the placebo group when comparing body fat lost pre and post study (Armstrong and others 2001).

Colker and others (1999) evaluated the effects of Citrus Aurantium, caffeine, and St. John's Wort on body composition in a 6-week study including 20 subjects, ages 38 to 60 years. Nine subjects were assigned to group A and received 975 mg bitter orange with 6% synephrine, 528 mg caffeine, and 900 mg St. John's Wort; seven subjects were assigned to group B and received a placebo of maltodextrin, and four were assigned to group C and received no supplementation. Weight loss was significantly greater in group A as compared to the other two groups. Body fat loss in group A also was significantly higher as compared to the other two groups.

Greenway and others (2006) evaluated the weight loss efficacy of citrus aurantium (9 mg synephrine). Eight subjects (7 women/1 man, age 18 to 60 years) who were overweight or obese (BMI 25 to 40 kg/m^2) were randomly assigned to receive either the supplement (18 mg synephrine) or a placebo two times per day. After two months, the supplement group gained significantly more weight (1.13 ± 0.27 kg/m^2) than the placebo

group (0.09 ± 0.28 kg). However, the subjects receiving the supplement had significantly greater increases in metabolic rate versus the placebo group (144.5 ± 31.7 kcal/24 hours versus 23.8 ± 56.7 kcal/24 hours).

In summary, the few studies which have examined the effectiveness of bitter orange in promoting weight loss or increasing metabolic rate show positive effects; however, additional studies are warranted (Colker and others 1999; Greenway and others 2006; Hedrei and Gougeon 1997; Seifert and others 2001).

Other Common Weight Loss Supplement Ingredients

Manufacturers of weight loss supplements often combined substances such as Kola nut, guarana, yerba mate, green tea, black tea and caffeine, which are known to increase metabolism, to maximize effects (Andrews and other 2006; Kanfer and others 1993; Roseland and others 2006; Schweitzer and others 2006; Upton 1991). These products contain common xanthines such as caffeine, theobromine, and/or theophylline. Caffeine may be listed as guaranine or guarana, mateine or yerba mate, theine or tea (green/black) when found in these products (SD 2007). The caffeine content of dietary weight loss supplements often contains 200^{+}mg. This 200 mg amount is equivalent to about two cups of brewed coffee or strong tea. Schweitzer and others (2006) examined the caffeine content of 63 dietary supplements and found that 52% had >200 mg of caffeine per suggested serving. Guarana and Kola nut are common xanthine alkaloids which naturally contain large amounts of caffeine. Thus, these substances are often added to products for the caffeine content (Andrews and other 2006; Roseland and others 2006; USDA 2006).

Caffeine, theobromine, and theophylline are well known for their ability to decrease fatigue and increase wakefulness. Caffeine is also found in numerous supplements on the market which promote weight loss. Some of these products include: CortiSlim, Hydroxycut Harcore, Lipo 6, Hot Rox, Xenadrine EFX, Zantrex, and Ripped Fuel.

Caffeine, a methylxanthine, is added to weight loss promoting products for a couple of reasons. First, caffeine inhibits phosphodiesterase which then prolongs the actions of cAMP. Second, caffeine prohibits cellular re-uptake of norepinephrine and thus prolongs norepinephrine's lipolytic effects. Third, caffeine blocks specific adenosine receptors (adenosine$_1$ and adenosine $_{2A}$) located throughout the body and, when blocked, a decrease in the metabolic rate is prevented. These properties make caffeine a valuable complement to other weight loss substances such as ephedrine. However, caffeine, especially in high doses, can cause side effects. Some of the more common adverse effects of caffeine include nervousness or jitteriness, decrease in concentration, gastrointestinal distress (i.e. increase in stomach acid), headaches, irritation, body aches, and depression. However, side effects appear to be most common with overconsumption or intake of > 400 mg per day. Death has also been reported with doses greater than the lethal dose (LD_{50}) based on weight (150 to 200 mg/kg of body weight) (Juliano 2004). Kerrigan and other (2005) reported two cases of caffeine overdose due to intake of caffeine pills.

Aspirin is also sometimes used, especially in ephedra-based weight loss products, because it inhibits prostaglandin activity by acetylating a serine residue on the enzyme

cyclooxygenase, a key enzyme in prostaglandin production. Since some prostaglandins inhibit lipolysis, aspirin counters the effects to sustain lipolysis.

Justification

Given the hazards associated with weight loss supplements and the desire for quick-fix methods to lose weight by some population groups, the purpose of this study was to examine the use of weight loss supplements by gym clientele. The results of this survey will provide information on the need for and types of nutrition education that may be posted in gyms so clients may lose weight appropriately.

Research Hypotheses

1. Women will be more likely to use weight loss supplements than men.
2. Younger clients will be more likely to use weight loss supplements versus older clients.
3. Participants who are overweight or obese will be more likely to use weight loss supplements than those who are underweight or normal weight.
4. Whites will be more likely to use weight loss supplements than other ethnicities.
5. Weight loss supplement use will be lower among individuals with health problems than those without health problems.
6. Supplement use will be higher among participants who go to the gym more frequently than those who go to the gym less frequently.
7. Smokers will be more likely to use weight loss supplements than non-smokers.
8. Subjects who drink alcohol will more likely use weight loss supplements than those who do not drink.
9. Those who take multivitamin/mineral supplements will be more likely to use

weight loss supplements than those who do not use multivitamin/mineral supplements.

10. Weight loss supplement use will be higher among participants who use meal replacement bars or liquid meals than those who do not.
11. Older clients will more likely use multivitamin/mineral supplements than younger clients.
12. Multivitamin/mineral use will be higher in those reporting health problems than those not reporting health problems.

CHAPTER 3

WEIGHT LOSS SUPPLEMENT USE BY GYM CLIENTELE

ABSTRACT

Obesity remains a major public health problem in the United States. Although practical means, such as a decreasing energy intake, increasing exercise, and modifying behavior, may be used to combat this growing problem, billions are spent yearly on weight loss products. The objective of this study was to examine the use of weight loss supplements by gym clientele. Clientele (n=227) from 14 gyms in central and eastern Alabama and central, western Georgia completed an anonymous supplement use questionnaire which asked about the use of supplements (weight loss and multivitamin/mineral), alcohol and smoking, and health problems. Use of weight loss supplements among the surveyed gym clientele was 16.3%. Use of weight loss supplements did not significantly differ between women (16.2%) and men (16.5%), or between individuals $\leq$49 years (16.4%) versus those $\geq$50 years (16.2%). Weight loss supplement use also did not significantly differ by race, or between smokers and non-smokers, or beverage alcohol users versus non-alcohol users. There was no difference in weight loss supplement use among study participants based on frequency of gym attendance. Sixty-one percent of study participants were classified as overweight or obese based on body mass index (BMI); however, weight loss supplement use did not significantly differ between those with a BMI $\leq$ 24.9 kg/m^2 (14.3%) versus those with a

BMI $\geq$ 25.0 kg/m^2 (18.0%). Multivitamin/mineral supplement use among study participants was 59.5%, with individuals $\leq$49 years using these supplements (55.8%) significantly less than those $\geq$50 years (78.4%). Weight loss supplement use by study participants reporting health problems was significantly higher (27.8%) than those who did not report any health problems (13.4%). Weight loss supplements containing ephedra, yohimbe, bitter orange, or a combination of these were more commonly used (70.3%) than those containing other active ingredients (29.7%). Six study participants (16.2%) used two or more weight loss supplements. Adverse side effects were reported by 16.2% of participants using weight loss supplements and were not confided to any one supplement or ingredient. In conclusion, while use of weight loss supplements was not as prevalent as use of multivitamin/minerals by gym clientele, about 1 in every 6 persons reported weight loss supplement use. Further, the significantly greater weight loss supplement use by gym clients with reported existing health problems is particularly troublesome and may put them at higher risk of adverse side effects. Additional efforts by gyms to provide accurate educational information on weight loss supplements to its membership may be warranted. Health care professionals also need to inquire about the use of such supplements with patients and provide education as needed.

INTRODUCTION

Obesity is a major public health problem in the United States. The National Health and Nutrition Examination Survey (NHANES) for 2003-2004 for the United States reported that 66% of adults (>20 years of age) were overweight (body mass index [BMI] 25 to 29.9 kg/m^2) or obese (BMI $\geq$30 kg/m^2) (Ogden and others 2006). These findings represent an increased prevalence from the previous NHANES III data. As the prevalence

of obesity increases, so does the prevalence of obesity-related chronic diseases, such as heart disease, type 2 diabetes, hypertension, and cancer, among others.

Weight loss treatments are typically aimed at decreasing energy intake and increasing energy expenditure. Practical methods to reduce energy intake and increase energy expenditure include modifying behavior, restricting dietary energy, and increasing physical activity. However, many consumers do not embrace these lifestyle changes. Rapid, quick-fix methods, such as the use of weight loss supplements or prescription weight loss medications are often preferred or used as an adjunct with other methods (Blanck 2001; Morrison and others 2004; Saper 2004; Wilborn and others 2005).

Several surveys have examined dietary supplement use in various population groups. The most often consumed supplements are those that contain vitamins and minerals. Studies to date suggest that multivitamin/mineral supplements, when taken in recommended amounts, may be useful. However, consumption of weight loss supplements may not be. A report by Federal Trade Commission in 2002 noted fraudulent reporting of claims of weight loss supplements is rampant, and 50% of manufacturers make claims which are most likely spurious. Thus, the reported benefits of weight loss supplements should be weighed with the possible adverse effects (FTC 2002).

In 2004, there were about 50, one-ingredient dietary weight loss supplements and numerous combination-ingredient weight loss supplements available for consumer use (Lenz and Hamilton 2004). The most common ingredients in these supplements included ephedra (especially prior to 2004), bitter orange, and yohimbe. Yet, use of products containing these ingredients has been associated with adverse side effects including rapid

heart beat, elevations in blood pressure, and jitteriness, nervousness, and anxiousness, among others.

Americans typically report that they are trying to lose weight or want to build muscle mass, increase strength, or prevent disease. The local gym provides an environment enabling clients to expend energy and to enhance strength and cardiovascular fitness as well as to build muscle. However, it is unclear to what extent people who frequent gyms are also using other approaches to achieve "better health." Many clients who frequent gyms are extremely focused on meeting goals of weight loss, muscle mass attainment, body fat loss, among others, and may use multiple, and what could be considered as "extreme", methods to achieve their goals. Further, the use of weight loss supplements in older individuals or those with existing health problems who may be more prone to the adverse effects associated with use of weight loss supplements may be dangerous. Only two studies have examined supplement use in people who go to the gym (Kanayama and others 2001; Morrison and others 2004). These studies, however, were done in the northeastern United States and focused on all supplements and the reasons for using the supplements. The purpose of this study was to examine the use of weight loss supplements by gym clientele in central and eastern Alabama and central, western Georgia.

SUBJECTS AND METHODS

Subjects

Adults, 19 years and older who go to a gym for exercise were recruited from 15

gyms located in central and eastern Alabama and western, central Georgia. The gyms include: in Auburn, AL - AC Fitness, Gold's Gym, and World's Gym, in Montgomery, AL – World's Gym, in Selma, AL - Vaughn Fitness and Wellness Center, Bodybuilder's Inc. and Fitness Express, in Phenix City, AL – Curves and Fitness Plus, in Columbus, GA - two Gold's Gyms and North Columbus Athletic Club, and in Fort Benning, GA - Audie Murphy Fitness Center, Fort Benning Officer's Club, and Briant Well Fitness Center. The study was approved by Auburn University Institutional Review Board for the Use of Human Subjects in Research

Methods

Permission to administer surveys during May and June 2007 was obtained from gym managers. The permission letter also stated any restraints on data collection such as who was allowed to pass out the survey and how the surveys could be collected.

The 23 question, 2-page anonymous survey was developed to determine the use of weight loss supplements and products consumed by gym clientele. Brand names of supplements and products were listed in the survey to facilitate recognition by clientele. Surveys were read for clarity by several people before administration. In addition, health risk behaviors (i.e. use of alcohol or tobacco) as well as adverse effects experienced with the use of these supplements/products were examined. Other information that was requested included subjects' weight and height, reason for going to the gym, forms of exercise utilized (i.e. weight training, pilates, kick boxing, aerobic/toning circuit training, elliptical, walking, and running, gym frequency), and diagnosed health problems. Investigators calculated body mass index (BMI) from the self-reported height and weight

data, and used this information to classify individuals as underweight, normal weight, overweight, or obese based on Centers for Disease Control definitions.

An information sheet (explaining the study's purpose, risks, benefits, and the telephone number/e-mail address of the investigator) along with the survey, an envelope, and a pencil attached to a clipboard were given to adults who agreed to participate. These materials were passed out by the investigator at: Gold's Gym in Auburn and Columbus (Airport Freeway only), Vaughn Fitness Center, Briant Wells Fitness Center, Audie Murphy Fitness Center, Fort Benning Officer's Club Fitness Center, and Fitness Plus. In addition, surveys, information sheets, envelopes, and slotted boxes were left at these locations for clients to fill out if they wanted to participate. Participants completed the survey, and either directly placed the survey into the slotted box or placed the survey in the envelope which was then placed into the slotted box. The investigator collected surveys from each location every two to three days.

Surveys, information sheets on a clipboard (with a pencil), and envelopes were passed out by the fitness instructors or managers at: Gold's Gym in Columbus (Miller Road), Curves in Phenix City, World's Gym in Auburn and in Montgomery, AL Vaughn Wellness and Fitness Center, Bodybuilder's Inc. and Fitness Express. Participants completed the survey, and then placed it directly into the slotted box or placed it in the envelope which was then placed in the slotted box. Curves, both World's Gym and Bodybuilder's Inc. did not permit the slotted boxes. At these facilities, participants, upon completing the survey, placed it in an envelope and gave it to gym personnel. The investigator collected surveys from each location every two to three days.

Statistical Analysis

Analysis of data was performed using the software SPSS for Windows (SPSS Inc., version 12.0, Chicago, IL). Chi square analysis was used to compare weight loss supplement use and the following: gender, age, ethnicity, body mass index, gym frequency, multivitamin/mineral use, smoking, alcohol use, health problems, meal replacement use, and the primary reason for gym use**.** A p value of <0.05 was used to determined statistical analysis.

RESULTS

Participating subjects included 227 adults from 13 gyms in central and eastern Alabama and western, central Georgia. The number of surveys completed at gyms are: in Auburn, AL - Gold's Gym (n=19), and World's Gym (n=12), in Montgomery, AL – World's Gym (n=20), in Selma, AL - Vaughn Fitness and Wellness Center (n=11), Bodybuilder's Inc. and Fitness Express (n=6 and n=5), in Phenix City, AL – Curves (n=12) and Fitness Plus (n=12), in Columbus, GA - two Gold's Gyms (n=22 and n=10) and North Columbus Athletic Club (n=33), and in Fort Benning, GA - Audie Murphy Fitness Center (n=16), Fort Benning Officer's Club (n=18), and Briant Well Fitness Center (n=41). These gyms ranged from dedicated weight lifting and body building facilities to upscale clubs that were targeting professionals and/or families. Data were collected over a 2 ½ week period in May and June 2007.

Characteristics of the study population are shown in Table 3.1. As noted in Table 3.1, there were fairly equal numbers of male and female participants. Sixty-one percent of participants were classified as overweight or obese based on BMI. The study participants were primarily non-Hispanic Whites (55.8%) and African American (33.5%),

and were 21 to 39 years of age (52.5%). Most clients (46.5%) visited the gym 2 to 4 times per week. Of the 27 subjects (11.9%) who smoked, most smoked 1 to 5 cigarettes per day. Alcohol use was reported by 132 subjects (58.1%), with most reporting consumption at <1 serving per week.

Table 3.2 reports the characteristics of the users of weight loss supplements by clientele frequenting gyms in central and eastern Alabama and western, central Georgia. Of the 227 study participants, 16.3% used weight loss supplements. There were no significant differences in weight loss supplement use among study participants based on gender, age, ethnicity, frequency of gym attendance, smoking or alcohol use/nonuse, and meal replacement use/nonuse. The more commonly used meal replacement products were protein bars (38.1%) followed in descending order by Slimfast products (19.0%), Weight Watchers products (16.7%), and South Beach products (7.1%). Weight loss supplement use by study participants reporting health problems was significantly higher (27.8%) than those who did not report health problems (13.4%). The most commonly reported health problems included: hypertension (32.7%), hyperlipidemia and heart disease (25.0%), and diabetes (19.2%). Weight loss supplements containing ephedra, yohimbe, bitter orange, or a combination of these were more commonly used (70.3%) than those containing other active ingredients (29.7%). Six study participants (16.2%) used two or more weight loss supplements. Adverse side effects were reported by 16.2% of participants using weight loss supplements and were not confined to any one supplement or ingredient. Of the 15 subjects with health problems and taking weight loss supplements (26.7%) reported side effects.

Multivitamin/mineral supplement use among gym clientele was 59.5%, with individuals ≥50 years using these supplements (78.4%) significantly ($p = 0.010$) more than those ≤49 years (55.8%). Most multivitamin/mineral supplement users (40.5%) reported taking a supplement once a day. No significant differences were found in multivitamin/mineral use in those reporting health problems (65.5%) and those reporting no health problems (57.9%).

DISCUSSION

Dietary supplement use is prevalent in the United States, with over 50% of Americans taking at least one supplement (Kimmons and others 2006; Radimer and others. The most commonly used supplement is one that provides multivitamins/ minerals. Similar to the findings of national studies (Kimmons and others 2006; Radimer and others 2004), the present study found that 59.5% of study participants attending gyms consumed a multivitamin/mineral at least once per day, and multivitamin/mineral use was more prevalent (78.4%) in those ≥50 years of age.

Among those who want to lose body weight or body fat, another group of supplements - those promoting weight loss - is often preferred. In 2004, there were about 50 one-ingredient dietary weight loss supplements and numerous combination-ingredient weight loss supplements available for consumer use (Lenz and Hamilton 2004). The prevalence of use of weight loss supplements among adults ranges from about 7.0% to 15.2% in the general population (Blanck and others 2001; Blanck and others 2007), and was not estimated in two recent studies examining supplement use among gym clientele in the Long Island, NY and Boston, MA areas (Kanayama and others 2001; Morrison and others 2004). The finding of 16.3% use of weight loss supplements among gym clientele

in the present study is slightly higher than the 15.0% reported for a larger cross sectional population by Blanck and others (2007). These findings suggest that gym clientele may be a population that is more likely to use weight loss supplements than others.

Findings from larger population studies generally report that more women use weight loss supplements as well as other dietary supplements than men, and those that used supplements tended to be younger (18 – 34 years) and obese versus older and non-obese (Blanck and others 2001; Blanck and others 2007; Kimmons and others 2006; Radimer and others 2004). These findings are in contrast to the present study which found that among gym clientele, women and men were equally likely to use weight loss supplements. However, similar to findings of others (Blanck and others 2007), use of weight loss supplements did not significantly differ by race in the present study.

Of the 227 study participants, 61% of gym clientele were overweight or obese. However, no significant difference in weight loss supplement use was found between those classified as overweight or obese versus those classified as under- or normal weight. These findings are in contrast to those of Blanck and others (2007) which reported that the odds of weight loss supplement use increased with BMI in the general population. It is not surprising, however, for weight loss supplements to be used by gym clientele with a normal BMI. Many gym members are working out at gyms to tone and build muscle mass and lose body fat for competitions. Such clients may use one or more products to aid in attaining their goals.

The significantly higher weight loss supplement usage by subjects reporting health problems (27.8%) versus those subjects who did not report any health problems (13.4%) is worrisome. Over 70% of the products used by study participants contained

ephedra, yohimbe, bitter orange, or a combination, and other products used contained caffeine, guarana, and green tea extracts among other ingredients. Other studies also have found that weight loss supplements used by consumers often contained bitter orange, yohimbe, ephedra, and/or caffeine (Blanck and others 2007; Morrison and others 2004; Perkin and others 2002). Side effects associated with the use of many of these products are known to increase blood pressure and heart rate, among other actions. For those with pre-existing hypertension or heart problems (as in over 50% of study participants), these side effects may be even more dangerous.

CONCLUSIONS

In conclusion, while use of weight loss supplements was not as prevalent as the use of multivitamin/minerals by gym clientele, about 1 in every 6 persons reported weight loss supplement use. Further, the significantly greater weight loss supplement use by gym clients with reported existing health problems is particularly troublesome and may put them at higher risk of worsening health problems. Additional efforts by gyms to provide accurate educational information on weight loss supplements to its membership may be warranted. In addition, health care professionals also need to inquire about the use of such supplements with patients and provide education as needed.

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Table 3.1 Demographic Characteristics of Gym Clientele

Characteristic	n	%
Gender		
Females	112	49.3
Males	115	50.7
Age Group (years)		
19-20	26	11.5
21-29	68	30.0
30-39	51	22.5
40-49	45	19.8
50-59	24	10.6
≥60	13	5.7
Race		
Black/African American	76	33.5
White	129	56.8
Hispanic	11	4.8
Asian	3	1.3
Other	8	3.6
Body Mass Index (kg/m^2)		
≤ 24.9	85	39.0
≥ 25.0	133	61.0
Reported Health Problems		
Yes	55	24.2
No	164	72.2
No Response	8	3.5
Gym Frequency		
Daily	43	18.9
2-4 Times/Week	105	46.3
4-6 Times/Week	69	30.4
No Response	10	4.4
Smoke		
Yes	27	11.9
No	196	86.3
No Response	4	1.8
Alcohol		
Yes	132	58.1
No	95	41.9
MultiVitamin/Mineral Use		
Yes	135	59.5
No	92	40.5
Weight Loss Supplement Use		
Yes	37	16.3
No	189	83.3
No Response	1	0.4
Meal Replacement Use		
Yes	42	18.5
No	185	81.5

Table 3.2 Characteristics of Users of Weight Loss Supplements

Characteristic	n	%	Chi-Square	p-Value
Gender				
Females	18	16.2	0.004	0.951
Male	19	16.5		
Age Group (years)				
≤ 49	31	16.4	0.001	0.978
≥ 50	6	16.2		
Body Mass Index (kg/m^2)				
≤ 24.9	12	14.3	0.526	0.468
≥ 25.0	24	18.0		
Race				
Black/African American	16	21.1	3.163	0.675
White	18	14.1		
Other	2	25.0		
Reported Health Problems				
Yes	15	27.8	5.947	0.015
No	22	13.4		
Gym Frequency				
Daily	12	27.3	4.796	0.091
2-4 Times/Week	16	15.2		
4-6 Times/Week	8	11.9		
Smoke				
Yes	4	14.8	0.076	0.783
No	33	16.9		
Alcohol				
Yes	17	13.0	2.623	0.105
No	20	21.1		
MultiVitamin/Mineral Use				
Yes	23	17.0	0.108	0.742
No	14	15.4		
Meal Replacement Use				
Yes	10	23.8	2.084	0.149
No	27	14.7		

CHAPTER 4

SUMMARY OF FINDINGS

Consumption of weight loss supplements did not differ by gender. There was almost an equal number of male and female subjects who used weight loss supplements. This finding does not support research hypothesis one which stated that women will be more likely to use weight loss supplements than men.

Consumption of weight loss supplements did not differ by age. This finding does support research hypothesis two which stated that younger clients will be more likely to use weight loss supplements than older clients.

Consumption of weight loss supplements did not differ by BMI classification. This finding does not support research hypothesis three which stated that clients who are overweight or obese will be more likely to use weight loss supplements than those underweight or normal weight.

Consumption of weight loss supplements did not differ with ethnicity. This finding does not support research hypothesis four which stated non-Hispanic Whites will be more likely to use weight loss supplements than other ethnicities.

Consumption of weight loss supplements was not lower among clients with health problems. This finding does not support research hypothesis five which stated that weight loss supplement use will be lower in those clients with health problems than those without health problems.

Consumption of weight loss supplements was not higher among clients who go the gym more frequently. This finding does not support research hypothesis six which stated supplement use will be higher among participants who go to the gym more frequently than those who go to the gym less frequently.

Consumption of weight loss supplements did not differ between smokers and nonsmokers. This finding does not support research hypothesis seven which stated smokers will be more likely to use weight loss supplements than non-smokers.

Consumption of weight loss supplements did not differ between drinkers of alcohol and non-alcohol drinkers. This finding does not support research hypothesis eight which stated subjects who drink alcohol will more likely use weight loss supplements than those who do not drink.

Consumption of weight loss supplements did not differ by those subjects who took multivitamin/mineral supplements than those who did not. This finding does not support research hypothesis nine which stated subjects who take multivitamin/mineral supplements will be more likely to use weight loss supplements than those who do not use multivitamin/mineral supplements.

Consumption of weight loss supplements did not differ by those subjects who used meal replacement bars or liquid meals. This finding does not support research hypothesis ten which stated subjects who use meal replacement bars or liquid meals will be more likely to use weight loss supplements than those who do not use meal replacement bars or liquid meals.

Consumption of multivitamin/mineral supplements were used more often by older clients versus younger clients. This finding does support research hypothesis eleven

which stated older clients will more likely use multivitamin/mineral supplements than younger clients.

Consumption of multivitamin/mineral supplements did not differ by clients reporting health problems versus those with reporting no health problems. This finding does not support research hypothesis twelve which stated multivitamin/mineral use will be higher in those reporting health problems than those not reporting health problems.

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APPENDIX: QUESTIONNAIRE

A questionnaire on "The prevalence and use of dietary supplements by adults with gym memberships". Your participation would be appreciated

1. Gender: ☐ Female ☐ Male

2. Age (years): ☐19-20 ☐ 21-29 ☐ 30-39 ☐ 40-49 ☐ 50-59 ☐ >60

3. What is your ethnicity? ☐ Black/African American ☐ White/NonHispanic ☐ Hispanic ☐ Asian ☐ Other

4. What is your <u>primary</u> reason for going to the gym?

☐ Toning ☐ Muscle Building ☐ Losing Weight ☐ Decrease Risk of Disease

We would appreciate your answers to all questions. However, if you do not wish to answer some questions your participation is still appreciated.

5. What is your weight? _____ **What is your height?** _____

6. What forms of exercise do you do? (Check all that apply)

☐ Weight Training ☐ Pilates ☐ Kick boxing ☐ Aerobic/Toning Circuit Training

☐ Elliptical ☐ Walking ☐ Running ☐ Other _____

7. How often do you go to the gym? ☐ Daily ☐ 2-4 Times per week ☐ 4-6 Times per week

8. Do you currently smoke?

☐ No ☐ Yes

9. If you smoke, how much per day?

☐ 1-5 per day ☐ 6-10 per day ☐ 11-15 per day ☐ 16 to 1 pack per day

10. Do you currently take a multivitamin / mineral supplement? ☐ No ☐ Yes

11. If so, please indicate how often:

☐ Once a day ☐ More than once a day ☐ Twice a week ☐ 3 Times a week

☐ 4 Times a week ☐ > 5 Times a week ☐ Once every 2-3 weeks ☐ Once a month

12. Do you currently take any weight loss supplement? ☐ Yes ☐ No

13. For any supplement taken, check the supplement and how often it is taken.

	Once A day	More than once a day	Twice a week	3 times a week	4 times a week	>5 times a week	Once every 2-3 weeks
Xenadrine	☐	☐	☐	☐	☐	☐	☐
Hot Rox	☐	☐	☐	☐	☐	☐	☐
Hydroxycut (Any Form)	☐	☐	☐	☐	☐	☐	☐
Stacker 3	☐	☐	☐	☐	☐	☐	☐
Lipo 6	☐	☐	☐	☐	☐	☐	☐
CortiSlim	☐	☐	☐	☐	☐	☐	☐
Ripped Fuel	☐	☐	☐	☐	☐	☐	☐
Lean System 7	☐	☐	☐	☐	☐	☐	☐
Zantrex (Any Form)	☐	☐	☐	☐	☐	☐	☐
Acutrim	☐	☐	☐	☐	☐	☐	☐
Dexatrim	☐	☐	☐	☐	☐	☐	☐

Common Herbs	Once A day	More than once a day	Twice a week	3 times a week	4 times a week	>5 times a week	Once every 2-3 weeks
Hoodia Gordonii	☐	☐	☐	☐	☐	☐	☐
Green Tea	☐	☐	☐	☐	☐	☐	☐
Black Tea	☐	☐	☐	☐	☐	☐	☐
Bitter Orange / Synephrine	☐	☐	☐	☐	☐	☐	☐
Yohimbe / Yohimbine	☐	☐	☐	☐	☐	☐	☐
Ephedra / MaHuang	☐	☐	☐	☐	☐	☐	☐

14. For any supplement listed as taken in question 13, please list the supplement name and, if known, the amount taken:

_____

15. If you take any weight loss supplements not listed in question 13, please list the supplement and amount taken (if known) below:

16. Do you drink alcoholic beverages?

☐ No ☐ Yes

17. If so, how much do you drink (1 serving = 5 ounces wine, 1 ½ ounces liquor, or 12 ounces beer)?

☐ < 1 serving per week ☐ 1-2 servings per week ☐ 3-5 servings per week ☐ > 6 servings per week

18. If you take any supplements, have you noticed any side effects?

☐ No ☐ Yes

19. If yes, please describe below:

20. Are you using any other dietary weight loss products such as meal replacement bars or liquid meals?

☐ No ☐ Yes

21. If yes check all that apply:

SlimFast ☐ **Weight Watchers** ☐ **Jenny Craig** ☐ **Sweet Success** ☐

NutriSystem ☐ **SouthBeach Diet** ☐ **MediFast** ☐ **Jillian Michaels** ☐

Other ☐ (Please List) _____

22. Have you been diagnosed by a physician with any health problems?

☐ No ☐ Yes

23. If yes, please list them below:

THANK YOU FOR YOUR PARTICIPATION!