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Safety of Ephedra and related anorexic medications

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Background: The increasing incidence of obesity, anorexia and bulimia has resulted in an increased interest in anorexic medications that can modify human eating behaviors. History and medical research is replete with consequences of addressing behavioral disorders with pharmacologic approaches to intervention in the absence of cognitive therapies such as self-efficacy counseling, which we and others have shown to be extremely effective at modifying behaviors previously thought to be resistant to such treatment. This paper looks at some of the ramifications of using anorexic medications, including Ephedra, in modern society's efforts to address weight-related health problems. *Methods*: A review of the medical literature about Ephedra and related anorexic medications was undertaken as they are linked to eating disorders. The findings included limited evidence of clinical benefit from such medications with concerns over side effects such as cardiovascular, gastrointestinal, CNS and other potential problems. We provide information about current recommendations for using these medications along with concerns for their use. *Conclusion*: This paper is a review of Ephedra and similar anorexic medications and nonprescription substances used in the treatment of obesity and other eating disorders along with some of the potential and proven consequences of such treatment.

Keywords: anorexia, anorexic medications, bulimia, Ephedra, globesity, obesity, phen-fen, weight loss

Expert Opin. Drug Saf. (2008) 7(6):1-11

The discussion of pharmaceuticals such as Ephedra, Fenfluramine, Phentermine, Olestra and so on would not be of significant interest today if it were not for the pandemic of obesity occurring worldwide producing a market for prescription and nonprescription medications and dietary supplements [1] amounting to more than US$19 billion/year. According to the World Health Organization (WHO) statistics of 2005, there are more than 1.6 billion overweight or obese people worldwide. Whereas changes in physical activity and increased caloric consumption accounts for most if not all of this change, the current focus of the pharmaceutical industry has been on developing medications designed to reduce appetite and/or absorption of ingested food.

As shown in **Figure 1**, industrialized countries lead the way in this obesity epidemic with an average of two-thirds of the populations of most of these countries being either overweight or obese using body mass index (BMI) criteria. **Figure 2** shows a significant increase in the incidence of obesity in the US over the past 10 – 15 years. Sadly enough, whereas obesity threatens the lives of two-thirds of the people in industrialized countries, worldwide (including industrialized nations) the other end of the spectrum of malnutrition, anorexia, bulimia and purging threatens another three million Americans and 1 – 3% of the world's population according to US health statistics and WHO data. Thus, like obesity, anorexia and bulimia have led to a search for medications that will influence our abnormal eating behaviors. This obsession with eating and appearance in addition to the

10.1517/14740330802510915 ISSN 1474-0338

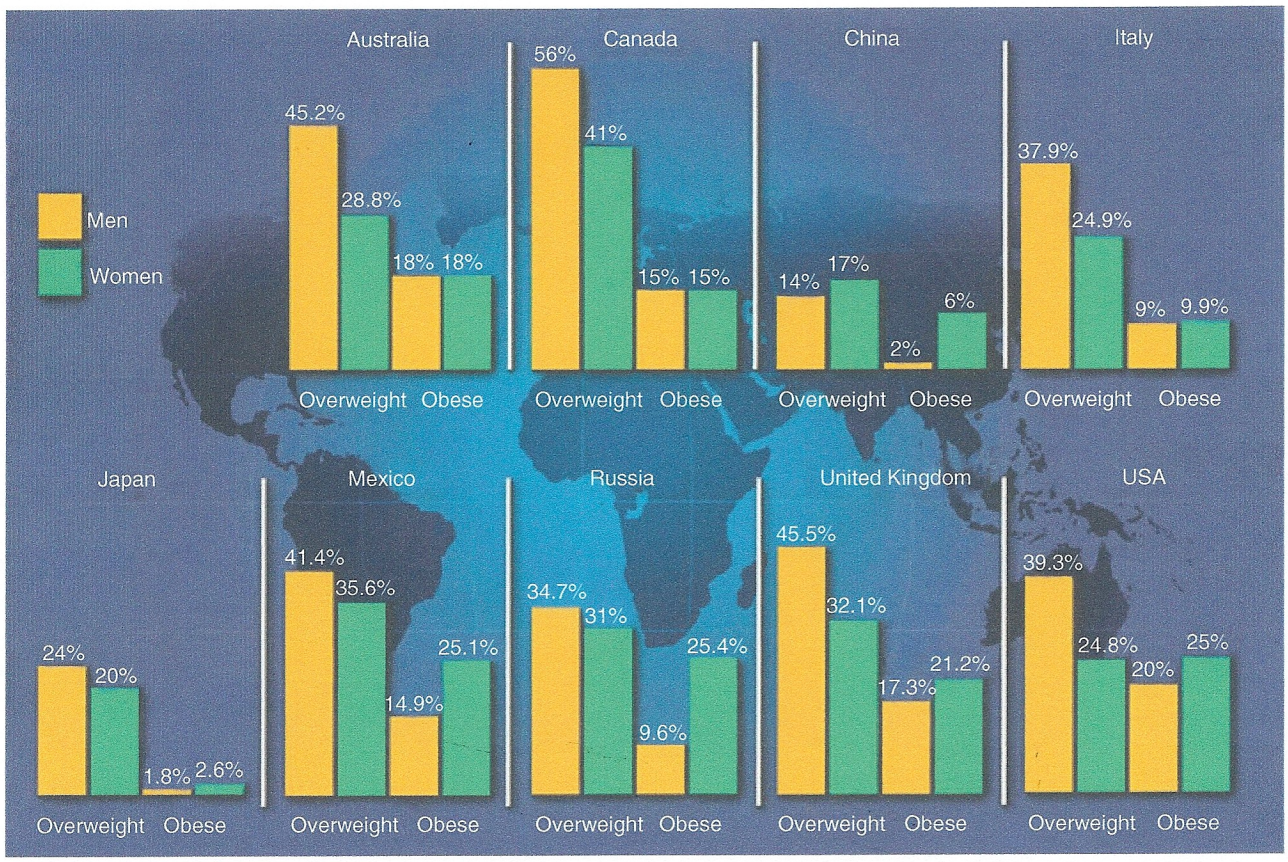

Figure 1. The epidemic of obesity worldwide. The bar graph shows the incidence of overweight and obese men and women in various regions of the world.

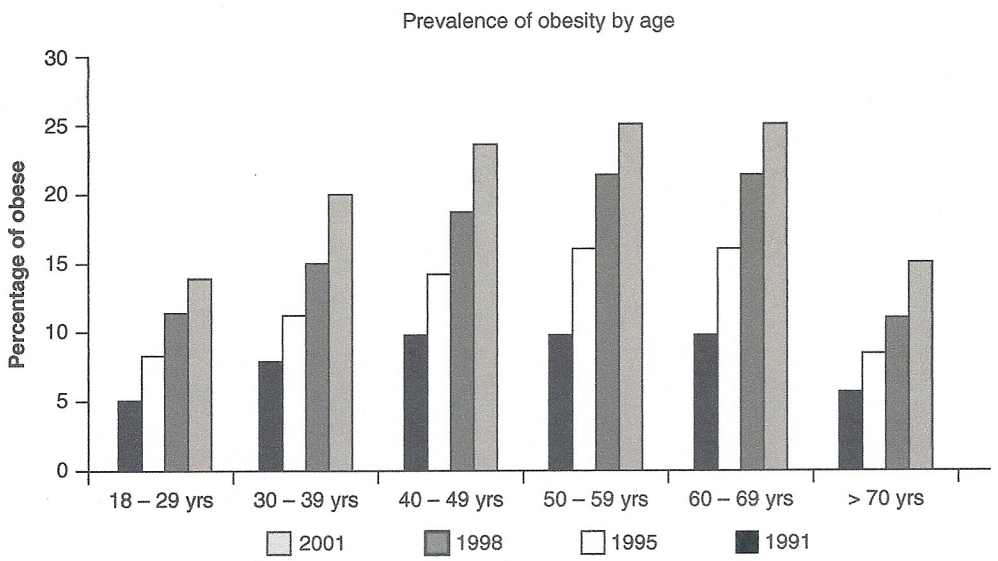

Figure 2. Obesity trends in the US. The incidence of obesity from 1991 to 2001 shows an increasing incidence of obesity across all age ranges.

Figure 3. Modern medicine derived from nature. A petri plate reveals the growth of the mold penicillium that inhibited the growth of bacterial colonies leading to the discovery of penicillin by Sir Alexander Fleming. The second image shows an example of foxglove.

now obvious economic costs of subsequent related health-care issues (e.g., heart disease, hypertension, diabetes mellitus, certain types of cancer etc.) has resulted in the coining of a relatively new term by the WHO, 'globesity'. This review will not only focus on Ephedra and other anorexic medications (along with their properties) of great public interest at present, but will also, it is hoped, alert the reader to the possible risk to individuals taking these medications.

1. The history of Ephedra

Most prescription and nonprescription medications have their origin in nature awaiting our discovery and use. For example, Sir Alexander Fleming discovered penicillin in 1928 after looking at petri plates (**Figure 3**) in his laboratory at St. Mary's Hospital in London. According to history, the petri plates were to be cleaned by a graduate student that summer but the student had failed to do so. Dr Fleming reviewed the petri plates before discarding them and his discovery lead to the modern era of antibiotics. Similarly, the medication *Digitalis purpurea* was found in the common garden plant foxglove (**Figure 3**). It was not long ago that physicians/clinicians stood at the bedside of their patients and ground the leaves of the foxglove to provide them with this crude form of the medicine.

As most people know, too much of something may kill you, whereas just the right amount might save your life. Such is the case with the herbal compound Ephedra, which contains six active ingredients: ephedrine, pseudoephedrine, *N*-methylephedrine, *N*-methylpseudoephedrine, norephedrine and norpseudophedrine. These active ingredients can now be made synthetically in a laboratory, so they no longer need to be extracted from Ephedra plants. Joint firs make up the genus Ephedra of the family Ephedraceae. The joint fir species best known for its medicinal use is *Ephedra sinica*. The Arizona joint fir is classified as *Ephedra fasciculata*, and the California joint fir is classified as *Ephedra californica*. The plant from which Ephedra is derived is found mostly in dry regions throughout the world (**Figure 4**), including the Himalayan [2] mountains of Asia and the Andes of Argentina, Europe, northern Africa and the southwestern [3] US, and can grow from sea level to a height of 5,000 meters. It has been marketed to the general public under numerous names including Ma Huang, Mexican tea, Mao, Mormon tea [4], yellow horse and many others. The plant shown in **Figure 4** is densely branched with pollen and seeds [5] that when further processed become an amber color solution.

Ephedra and its various components have been used for more than 5,000 years in Chinese medicine for the treatment of asthma, fever and rhinorrhea. It was one of 365 herbs found in the text by Shen Nong on Chinese herbalism in the first century AD. It was not until 1924 that physicians in the US became aware of its use as a bronchodilator and nasal decongestant. In the US it was once thought to be useful for the treatment of venereal disease [3], although there is no proof that it was ever effective. There are numerous active ingredients in Ephedra, which vary depending on the area where the plant is grown. Some of these active ingredients include cyclopropyl rings, tryptophan derivatives and ephedrine. As the result of these active ingredients, Ephedra has been used for weight loss [6], asthma [7], nasal allergies [8], the treatment of low blood pressure [9], as an energy enhancer for athletic performance and even for sexual arousal [10] in women. Failure to take into account the risk versus benefit ratio can lead to the inappropriate use of such medications. During the Second World War, Luftwaffe pilots were instructed to take more and more stimulants to enhance their fighter performance. They eventually exceeded their bodies' ability to handle the effects of these amfetamines and found they were suddenly unable to perform adequately over the skies of London, with historic consequences.

When the sudden death of Baltimore Orioles pitcher Steve Bechler in February 2003 was associated with his use of an Ephedra-containing dietary supplement, the US FDA, for

Figure 4. The transition from plant to pharmaceutical. Ephedra plants have grown wildly on Huffaker Lookout High Desert Preserve (Reno, Nevada, US) since the time of the dinosaurs. Both the stem and seed components are shown here.

the first time since the passage of the Dietary Supplement Health and Education Act of 1994, stopped the sale of a dietary supplement [11]. Although this raised the issue of public awareness, it is an unfortunate reflection of society that it required the death of someone well known before action was taken whereas numerous other individuals whose names are unknown except to their family members and friends had already been adversely affected. Later, as shown in 2007 [12,13], both Ephedra associated with high-protein high-fat dieting (Figure 5) and the use of Fenfluramine Phentermine combination are clearly associated with worsening of coronary blood flow and/or progression of heart disease. Ephedra has even been used in the production of methamfetamine, deemed by many to be the most dangerous addictive street drug of our time. This ban on the sale of Ephedra by the US FDA (Table 1), however, affected only dietary supplements and has not affected the advertising of Ephedra or the sale of traditional Chinese herbal remedies, herbal teas and conventional foods or drugs that contain chemically synthesized ephedrine. Because ephedrine remains available worldwide and because of the potential health effects related to its use, it is appropriate for us to look at Ephedrine (the remnant of Ephedra) and related anorexic drugs in further detail.

2. Ephedrine, the remnant of Ephedra

2.1 Mechanism of action

Ephedra contains the alkaloids ephedrine $C_{10}H_{15}NO$, either derived from Asian gymnosperms (genus *Ephedra* [14,15]) or synthesized as pseudoephedrine, that are routinely isolated and used in over-the-counter (OTC) products as decongestants. Ephedrine acts like epinephrine (adrenaline) with resultant stimulation of both alpha and beta adrenergic receptors [8], resulting in bronchodilation, vasoconstriction and tachycardia. The onset of action for the formulation ephedrinum hydrochloridum is 15 – 60 min. The duration of action is 3 – 6 h when taken orally. It is partially metabolized in the liver by oxidative deamination, demethylation, aromatic hydroxylation and conjugation; but, it is primarily excreted in the urine within 24 h with 60 – 77% of the drug unchanged on excretion. The actual amount excreted in an unchanged form is dependent on urine pH. As urinary pH becomes more acidic, more of the ephedrinum hydrochloridum is excreted unchanged. Cautious interpretation of urine drug screens must be applied as Ephedra itself may cause a false-positive test for amfetamines when using enzyme multiplied (EMIT) immunoassay. Ephedrinum not only crosses the placenta yielding potential fetal effects, but it also crosses the blood–brain barrier accounting for its neurological effects. It is excreted in breast milk and therefore should never be used in pregnant or nursing women. Because of its potential to cause insomnia it should not be taken within 4 – 6 h of bedtime as it may inhibit sleep.

2.2 Dosing and route of administration of Ephedrine

Correct dosing of ephedrine for medical treatment of asthma, acute bronchospasm, rhinorrhea, idiopathic orthostatic hypotension and hypotension resulting from anesthesia can be accomplished using p.o., i.v., i.m. or s.c. routes or nasal spray (for nasal compression) preparations. Each form of the ephedrine comes as a sulfate compound and the following recommended doses are as per the Physicians Desk Reference. Recommended dosing of Ephedra alkaloids should not

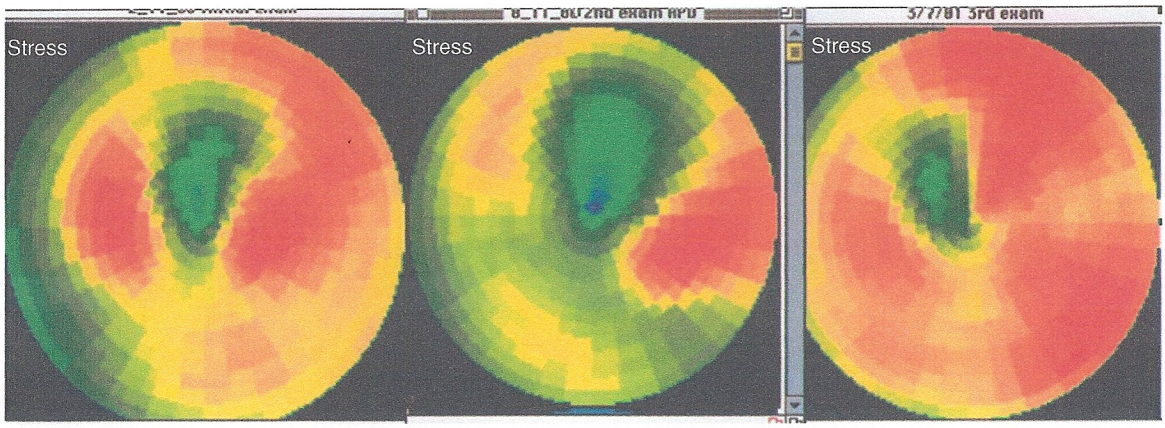

Figure 5. Evidence of deleterious effects of Ephedra and low-carbohydrate dieting on coronary artery blood flow. The first image shows the results of myocardial perfusion imaging (MPI), published in 2007, in a patient with heart disease. Blood flow is qualitatively demonstrated using color images. The first study was performed on 11 February 2000. The region of green in the center of the field demonstrates disease in the left anterior descending artery. The second study completed on 11 August 2000 reveals worsening of coronary artery disease as shown by a larger region of green and the presence of blue in the center of the image. A third and final study performed on 7 March 2001 shows significant improvement in coronary blood flow after the low-carbohydrate, high-fat diet and Ephedra are stopped.

Table 1. The sequence of actions by the US FDA on Ephedra.

Time	FDA activity
July 1993	First public warning about possible safety issues
October 1995	Special Working Group on Food Products Containing Ephedrine Alkaloids concluded there was sufficient evidence to suggest adverse effects associated with use
August 1996	Food Advisory Committee discusses safety of ephedrine; unable to reach consensus
June 1997	FDA published a proposed dosing rule including duration limits and product labeling
July 1999	US General Accounting Office (GAO) released Dietary Supplement Uncertainties in the Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids. This time concluding too little evidence to support dosage and duration limits
April 2000	FDA withdrew much of its proposed rule
August 2000	Office of Women's Health of the US Department of Health and Human Services (HHS) convened a public meeting to discuss safety
September 2000	Office of Women's Health recommended that further research be done
June 2002	US Department of HHS commissioned the RAND Corporation to evaluate safety and efficacy of Ephedra
February 2003	RAND Corporation released Ephedrine and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects White paper published presenting the evidence on ephedrine's safety and effectiveness
March 2003	Proposed rules to establish manufacturing and labeling standards for all dietary supplements
December 2003	Plan to prohibit sales of dietary supplements containing ephedrine
February 2004	Final Ruling Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated because They Present an Unreasonable Risk in the Federal Register

exceed 8 mg total per dose, with no more than 24 mg per 24-h period. For weight loss, the recommended dose of ephedrine is 12.5 – 25 mg/day p.o. taken 2 – 3 times. The dose should not exceed 8 mg every 6 h and should not be given for more than 7 days.

Adult dosing

p.o.: 25 – 50 mg every 3 – 4 h

i.v.: 5 – 25 mg given 'slowly', may be repeated for desired effect every 5 – 10 min. Not to exceed 150 mg/day

i.m.: 25 mg

Nasal: 2 – 3 sprays per nostril every 4 h as needed

Pediatric dosing

p.o. or s.c.: 3 mg/kg/day or 25 – 100 mg/m^2/day divided into doses given every 4 – 6 h

i.v. (slowly)/i.m.: 0.2 – 0.3 mg/kg/dose, which may be given every 4 – 6 h

Nasal: (6 – 12 years of age) 1 – 2) sprays per nostril every 4 h as needed

2.3 Solution compatibility

Ephedrine sulfate remains stable in dextran, normal saline (NS), 5% dextrose in lactated ringers (D5LR) and equivalent solutions of saline, dextrose (up to 10%) and lactated ringers. In addition to the doses noted earlier, ephedrine can also be found as a hydrochloride compound with similar dosing.

2.4 Medication compatibility with Y-site tubing

Propofol, Milrinone lactate, Etomidate, Chloramphenicol, Lidocaine, Metaraminol, Nafcillin and Penicillin G.

2.5 Medication incompatible

Thiopental, Hydrocortisone, Pentobarbital, Phenobarbital. Whereas these medications are incompatible owing to drug–drug interactions as outlined in the Physicians Desk Reference, it is fair to note that the concomitant use of stimulant medications such as methylphenidate, dextroamfetamine and noradrenergic antidepressants such as venlafaxine or duloxetine may result in cardiovascular complications.

2.6 Significant adverse effects

The use of Ephedra has been associated with dysrhythmias including sinus tachycardia, atrial fibrillation, angina, hypertension, hypotension and palpitations. Individuals have noted anxiety, apprehension, insomnia, agitation, irritability, headaches, hyperactivity, restlessness and dizziness. The long-term use of ephedrine may result in symptoms of paranoid schizophrenia and suicidal tendencies. Gastrointestinal irritability including anorexia, nausea, vomiting and xerostomia may occur. Painful urination may occur along with tremors, weakness, dyspnea and diaphoresis.

2.7 Contraindications to the use of ephedrine

Individuals known to be sensitive to ephedrine or other sympathomimetic amines should avoid its use along with those individuals who have cardiac dysrhythmias, acute-closure glaucoma, anorexia or bulimia. Individuals with schizophrenia and bipolar disorder would be advised to avoid using ephedrine; also, those using other sympathomimetic agents should avoid Ephedra. As noted earlier, pregnant women and those lactating should not take ephedrine owing to its crossing of the placenta and its excretion in breast milk.

People who have atherosclerotic coronary artery disease (ASCAD), dysrhythmias (atrial fibrillation, atrial flutter, sinus tachycardia, reentrant dysrhythmias, ventricular ectopy or tachycardia, pre-excitation syndromes etc.) and hypertension may have worsening of their underlying disease as the result of taking ephedrine medications. Patients taking cardiac glycoside medications or those undergoing general anesthesia may have an associated increase in beta adrenergic stimulation. Diabetes mellitus may be worsened with ephedrine as can problems with urinary flow particularly in men with prostatic hypertrophy and/or urinary stricture. Seizure activity can be increased in those individuals prone to such activity. People with thyrotoxicosis or hyperthyroidism should avoid this medicine. Patients who are taking monoamine oxidase inhibitors (MAOI) and/or atropine-containing compounds may have associated hypertensive problems. Concomitant use of ephedrine with other sympathomimetic medications has additive sympathomimetic increases in heart rate and blood pressure and should be avoided. This is also true of patients taking theophylline, particularly when multifocal atrial tachycardia (MAT) may develop. The ability of ephedrine to readily cross the blood–brain barrier may result in confusion particularly in elderly individuals. The simultaneous use of alcohol and many nutraceuticals (e.g., yohimbe) may result in further CNS stimulation. Other problems include addiction, gastric ulcers and depression.

2.8 Treatment of ephedrine overdose/toxicity

There is no specific antidote for the ingestion of ephedrine. Most of the treatment is supportive. The vasopressor effect of ephedrine may be diminished by treatment with alpha- and beta-adrenergic antagonists; however, like cocaine overdosing, the simultaneous use of beta-blocking agents alone may precipitate a myocardial infarction. When diastolic blood pressures (e.g., > 110 mm of Hg) are significantly elevated, intravenous nitroprusside may be required. Close monitoring of blood pressure and heart rate with this treatment is indicated. Associated agitation and hyperactivity may require haloperidol (2 – 5 mg i.m. for adults) when patients are unresponsive to reductions in sensory input. Intravenous diazepam and/or phenytoin may be required if seizures occur. For individuals experiencing hyperthermia treatment may included both external cooling and in more severe cases muscle paralysis with pancuronium.

3. Ephedra alternatives in the world of weight loss

The prevalence of obesity and the frustration experienced by most individuals trying to lose weight have led to a variety of OTCs being sold for weight loss. As noted earlier, the industry for such medications is staggering. We will now look at only a few of the alternatives used by people attempting to lose weight along with pertinent information. It is important to establish that none of the prescription medications or any of the OTC remedies should be used while nursing or during pregnancy.

3.1 Green tea

The consumption of green tea has been associated with several potential benefits. Green tea typically contains less caffeine per cup than coffee and it is known to have antioxidants that may be beneficial. Essentially, tea should not be thought of as having caffeine but rather another methylxanthine known as theophylline. Although both caffeine and theophylline are methylxanthines, like nonsteroidal anti-inflammatories, simply belonging to the same drug class, for example, phosphodiesterase inhibitors, does not mean they will have identical effects on a milligram-to-milligram basis. At present, there seems to be no evidence that green (or any color for that matter) tea aids weight loss; however, there is also no evidence to suggest that tea has a detrimental effect.

3.2 Thermogenic approach to weight loss

Hypothyroidism, a hypothermic condition, has long been associated with obesity, elevated lipid levels and presumably coronary artery disease [16]. In the mid-1960s – 1970s research into reducing lipids by giving thyroid hormone to euthyroid individuals demonstrated an increase in cardiovascular complications including dysrhythmias and heart attacks. Others have tried adding iodine to their diet to increase their thyroid levels with similar concerns. This lesson into giving supraphysiologic levels of a compound/substance to the human body has frequently been associated with adverse clinical consequences. Nonetheless, advocates of taking supplements with EPA-rich fish oil, sesamin, hydroxycitrate, pantethine, L-carnitine, pyruvate, aloe vera, aspartate, chromium, coenzyme Q10, green tea polyphenols, aloe vera, DHEA derivatives, cilostazol, diazoxide and fibric acid drugs have supported the taking of these substances that might produce weight loss by means of the assumption that they increase body and/or liver metabolism (namely hepatothermic). These same individuals would frequently argue against the ingestion of such substances if they required a prescription, but seem to have no problem consuming such supplements (made by the same pharmaceutical companies) as long as they do not require a prescription. Such substances along with several herbal supplements are well known for causing liver disease. Close monitoring of liver function is indicated when taking these substances, something the general public cannot do without the assistance of a clinician or physician. Nearly all the OTC dietary aids used at present contain some combination of these ingredients; yet, because they do not require a prescription the general public and some health-care providers seem to deem them harmless. There is no evidence that any of these ingredients can produce weight loss but ample evidence that they may be harmful.

3.3 Chromium

Chromium is a common ingredient in numerous dietary supplements. Some research suggests [17] that 'high' doses of this element may lower plasma insulin, leptin and triglycerides concentrations. However, at a reasonable dose, chromium does not have a significant effect on body mass and animal studies have suggested that it may actually damage the genetic materials in cells [18] and result in sterility.

3.4 Compounds that affect dietary absorption of carbohydrates and fats

In February 2007, the US FDA approved olestra as an OTC agent for weight loss including its addition in food substances (e.g., potato chips). This medicine works by reducing the amount of fat (~ 30%) that can be absorbed in the diet by means of lipase inhibition. However, this may also be associated with a reduction in fat-soluble vitamins (A, K, E and D) needed to maintain one's health. Although its use can result in a fairly modest weight loss in approximately one-third of those [19] who use it, it is associated with significant gastrointestinal bloating and fecal incontinence. Thus, olestra may reduce the amount of dietary fat that can be absorbed from the diet but it does not affect other sources of caloric intake [20]. Similarly, olestra, which is a sucrose polyester with properties of fat that cannot be metabolized by human enzyme systems, also causes small decreases in fat-soluble vitamins [21].

3.5 Sibutramine

Sibutramine works via changing the balance of the brain chemicals 5-hydroxytryptophan (serotonin) and norepinephrine (noradrenaline). Therefore, people already taking serotonin reuptake inhibitors, MAOIs, decongestants or bronchodilators should not take Sibutramine. This change in brain chemistry helps increase metabolism and the 'feeling of fullness'. It may be particularly useful for binge-eaters [22]. Studies indicate that Sibutramine is effective in achieving weight loss during the first 3 months, with slower weight loss thereafter. There are various cardiovascular benefits and risks resulting from changes in serotonin and norepinephrine. Although the drug seems to reduce lipid levels, it has also been shown to increase heart rate and blood pressure. People who have a history of dysrhythmias, hypertension and/or a history of cerebrovascular (strokes) disease should not take this medication.

3.6 Sympathomimetic agents

Sympathomimetic drugs simulate the effect of epinephrine and norepinephrine on the body. They are biological stimulants that increase metabolism, raise glucose and lipid levels, heart rate and blood pressure. They are the equivalent of the human 'fight or flight' response and also the equivalent of the body being placed under 'stress'. The obvious question is whether this is biologically stable over a sustained period of time.

Phentermine is now the most commonly prescribed appetite suppressant in the US and perhaps worldwide. It has been associated with an increase in blood pressure as well as depression, which may already be a problem for the obese individual. An effort to reduce this problem with depression among those taking Phentermine has led to researchers

combining the antidepressant fluoxetine with Phentermine (Phen-Pro) to determine if the fluoxetine can diminish the level of depression. This is the classic situation of treating an idiopathically induced problem by giving another medication instead of stopping the first medication. In the past [13], Fenfluramine has been associated with cardiovascular and possibly neurological effects when combined with Phentermine (Fen-Phen). This seems to be another example of a potentially bad idea.

3.7 Amfetamines

These are the drugs that lead to the initially enhanced performance of the German Luftwaffe followed by its eventual demise. The amfetamines dextroamfetamine, methamfetamine and phenmetrazine are powerful stimulants. These medications were used extensively in the past and were associated with modest weight loss and sometimes significant mood changes. They are highly addictive, produce agitation and insomnia and can be used to synthesize methamfetamine.

3.8 Cannabinoid-1 receptor antagonists

Rimonabant [23] is a cannabinoid-1 receptor (C1R) antagonist. As the C1R receptor promotes weight gain (the classic munchies with marijuana), the blockage of this may promote weight loss. It may also have unforeseen significant effects on the brain as unpublished research we did in the early 1990s demonstrated significant uptake of marijuana in the cerebellum with positron emission tomography (PET) imaging. Blockage of these brain centers may yield problems with cerebellar function. Although Rimonabant is an investigational agent, it seems to be particularly useful in patients with diabetes mellitus [24]. Like all of the medications and supplements noted in the review article, Rimonabant may be found on the Internet and may possibly be purchased without a doctor's recommendation or supervision. Similarly, the twin issues of bioavailability and pharmacokinetics of these drugs must be questioned in the absence of regulation in the US. This drug received approval for use in the EU in 2006 demonstrating that different agencies do not always agree. This does not make one agency right and another wrong, simply different.

3.9 Antiseizure medications

Zonisamide [25] and Topiramate [26] are antiseizure medications that have been studied because of associated weight change in people on medication for epilepsy. Although some antiseizure medications result in weight gain, these agents are thought to be associated with weight loss. Research, however, shows little weight change not associated with caloric restriction. Specific problems include nephrolithiasis with Zonisamide in addition to forgetfulness, nausea, headaches and dizziness. Topiramate is now being investigated for binge-eating [27] and has been shown to have a beneficial effect when combined with cognitive-behavior therapy (CBT).

3.10 Regulating mitochondria

Axokine is a ciliary neurotrophic factor regulator that influences cellular metabolism through mitochondrial transcription factor A and nuclear respiratory factor 1 [28]. The result is to signal the brain to reduce/suppress one's appetite. In research done so far, 46% of the subjects lost at least 10 pounds whereas those who received a placebo showed the same weight loss 5% of the time. So far, a chief problem with antibodies being produced in 73.5% of the individuals, thereby neutralizing the effect of the medication, has resulted in legal problems. This emphasizes the concern of anorexic medications.

4. Expert opinion

During the last half-century, human beings have developed new processes to both produce and preserve food for immediate and long-term consumption. Such abilities would presumably result in increased survival of the species by reducing starvation and providing in times of need. The exact opposite has occurred, however, with recent increases in the incidence of obesity and weight-related (e.g., heart disease, diabetes mellitus, hypertension, certain forms of cancer etc.) diseases and death. Arguments over who is to be blamed for these increased health problems has lead to various discussions implicating the food industry, governments, the pharmaceutical industry and others, with efforts to even blame our ancestors for providing us with 'thrifty genes'.

The increased incidence of obesity in the world along with anorexia, bulimia, binging, purging and other eating disorders over the last several decades has resulted in the coining of the term globesity by the WHO. During this time more and more people have been trying to lose weight through various diets, dietary supplements, medications and surgical procedures that promise weight loss. Prescription and OTC anorexic medications and compounds have been associated with several health problems including valvular heart disease, liver disease and other serious health issues. Dissatisfaction with the medical community and the increase in available information (albeit potentially misinformation) from the Internet are only two of the reasons why people have been looking away from conventional medicine to alternative approaches to help with weight loss. These alternatives include the use of potentially toxic herbal supplements. A review of the literature reveals several health problems associated with the use of some of these supplements, of which Ephedra [29-31] is only one. These potentially serious adverse effects have included dysrhythmias, heart failure, myocardial infarction, changes in blood pressure (both hypotension and hypertension), liver disease, ocular problems and even death.

The pharmaceutical industry has attempted to address some of these issues and continues to invest a significant amount of money into research for the development of new medications designed to focus on newer targets including

leptin [32] and other hormones [33] that may aid in weight loss when manipulated. Despite the potential promise there is little reason to believe that these new medicines will be more successful than their predecessors. Leptin itself acts as a regulator of hunger and like so many other substances found in the human body, has more than one effect. It is now known that leptin is involved with immunologic response and altering leptin levels, whether by medication or by dietary efforts, may improve heart disease by reducing the inflammatory component of the disease. It may, however, also have suppressive effects on the immunologic system opening people to infection and other potential problems. By themselves, anorexic medications used in an effort to promote weight loss have resulted in ocular [34], pulmonary [35,36], hepatic [37] and valvular problems [38-42]. If previous research has demonstrated anything, the combination of certain diets, particularly when added to anorexic medications and/or dietary supplements, can lead to several health problems including heart disease, liver disease, osteoporosis, esophageal rupture, gastrointestinal concerns, liver and kidney damage in addition to neurological problems. Our research [43-68] has confirmed the interaction between heart disease, dietary factors and vitamin and mineral supplements that may promote the inflammatory environment within our bodies leading to this immunologic disease. These findings support the need for caution when addressing the treatment of eating disorders and the importance of a multidisciplinary approach in treating such problems.

Efforts to pharmacologically manipulate the complex chemical processes of our bodies may result in answers to the weight problems of modern society but are more likely to produce devastating problems that we now do not or cannot understand. During my fellowship years in cardiology, we studied the effects of hirudin. Like my predecessor who worked with foxglove leaves, my experience was one of recognizing the balance that exists among biological systems, including *Homo sapiens*. When hirudin is used to reduce thrombotic effects occurring with myocardial infarctions, just the right amount can produce the desired effects. This therapeutic effect, however, was difficult to achieve with hirudin and more often than not my first sign that the patient had been randomized to hirudin were cuts on the face after shaving, a problem the women, fortunately, did not experience. The resultant bleeding problems proved to be more problematic than the thrombosis we were trying to treat. These experiences have led me to believe that greater than expected caution should always be applied when trying to manipulate biological processes. As survival of the species is highly dependent on nutrition, it is likely that the genetic structure of this is both complex and unlikely to be successfully manipulated by such simple creatures as ourselves. Despite the scientific information showing changes in diet and lifestyle impacting weight-related issues, the past 50 years have shown that we are more unlikely to learn from our mistakes and the health consequences resulting from our pharmacologic efforts to manipulate this complex genetic system than we are to learn from them. Perhaps we should not be surprised that many people have lost confidence in the medical and scientific community and have turned towards alternative practitioners and substances that may be even more toxic and certainly less regulated and less studied. How we proceed towards resolving globesity will have a significant impact on the survival of the species and we need to proceed cautiously.

Bibliography

1. Eisenberg DM, Davis, RB, Ettner, SL, et al. Trends in alternative medicine use in the United States, 1990-1997. JAMA 1998;280:1569
2. Price, Robert A. Systematics of the Gnetales: a review of morphological and molecular evidence. Int J Plant Sci 1996;157(6)(Suppl): Biology and Evolution of Gnetales S40-9
3. Caveney, Stanley, David A Charlet, et al. New observations on the secondary chemistry of world Ephedra. Am J Bot 2001;88(7):1199-208
4. Meyer, Susan E. Ephedra. Provo, UT: USDA Forest Service, Rocky Mountain Research Station; 1995
5. Hickman, James C. Ed. The Jepson Manual: higher plants of California. Berkeley and Los Angeles, Ca: University of California Pre; 1993
6. Betz JM, Gay ML, Mossoba MM, et al. Chiral gas chromatographic determination of ephedrine-type alkaloids in dietary supplements containing Ma Huang. J AOAC Int 1997;80:303
7. Redman CM, Druce, HM. Nonprescription bronchodilator use in asthma. Chest 1998;11:657
8. Langwinski R. Central effects of ephedrine. Pol Tyg Lek 1972;27:1205
9. Unger DL. Blood pressure and pulse rate changes in hypertensive asthmatic patients: effects of an ephedrine compound. Ann Allergy 1968;26:637
10. Meston CM, Heiman JR. Ephedrine-activated physiological sexual arousal in women. Arch Gen Psychiatry 1998;55:652
11. Rados C. FDA Consum. Ephedra ban: no shortage of reasons. 2004;38(2):6-7
12. Fleming RM. The effect of Ephedra and high fat dieting – a cause for concern! A case report. Angiology 2007;58:102-5
13. Fleming RM. The Longitudinal effects of Fenfluramine-Phentermine use. Angiology 2007;58:353-9
14. Pickup ME, May CS, Sendagire R, et al. The pharmacokinetics of Ephedrine after oral dosage in asthmatics receiving acute and chronic treatment. Br J Clin Pharmacol 1976;3:123
15. Sten GC. Requirements for pharmacists dispensing Ephedrine products. Am J Health Syst Pharm 1995;52:1630
16. Fleming RM, Harrington GM. What is the relationship between myocardial perfusion imaging and coronary artery disease risk factors and markers of inflammation? Angiology 2008;59 (In press)
17. Bennett R, Adams B, French A, et al. High-dose chromium(III) supplementation

has no effects on body mass and composition while altering plasma hormone and triglycerides concentrations. Biol Trace Elem Res 2006;113(1):53-66

18. Bailey MM, Sturdivant J, Jernigan PL, et al. Comparison of the potential for developmental toxicity of prenatal exposure to two dietary chromium supplements, chromium picolinate and [Cr(3)O(O(2) CCH(2)CH(3))(6)(H(2)O)(3)](+), in mice. Birth Defects Res B Dev Reprod Toxicol 2007;[Epub ahead of print]
19. Rubio MA, Gargallo M, Isabel Millán A, Moreno B. Drugs in the treatment of obesity: sibutramine, orlistat and rimonabant. Public Health Nutr 2007;10(10A):1200-5
20. Fleming RM. Caloric intake, not carbohydrate or fat consumption, determines weight loss. Am J Med 2003;114:78
21. Neuhouser ML, Rock CL, Kristal AR, et al. Olestra is associated with slight reductions in serum carotenoids but does not markedly influence serum fat-soluble vitamin concentrations. Am J Clin Nutr 2006;83:624-31
22. Wilfley DE, Crow SJ, Hudson JI, et al. The Sibutramine Binge Eating Disorder Research Group. Efficacy of sibutramine for the treatment of Binge eating disorder: a randomized multicenter placebo-controlled double-blind study. Am J Psychiatry 2007;[Epub ahead of print]
23. Scheen AJ. Cannabinoid-1 receptor antagonists in type-2 diabetes. Best Pract Res Clin Endocrinol Metab 2007;21(4):535-53
24. Despres JP, Golay A, Sjostrom L; Rimonabant in Obesity-Lipids Study Group. Effects of Rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005;353(20):2121-34
25. Ben-Menachem E. Weight issues for people with epilepsy-A review. Epilepsia 2007;48(Suppl 9):42-5
26. Klein KM, Theisen F, Knake S, et al. Topiramate, nutrition and weight change: a prospective study. J Neurol Neurosurg Psychiatry 2007; [Epub ahead of print]
27. Claudino AM, de Oliveira IR, Appolinario JC, et al. Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. J Clin Psychiatry 2007;68(9):1324-32
28. Liu QS, Wang QJ, Du GH, et al. Recombinant human ciliary neurotrophic factor reduces weight partly by regulating nuclear respiratory factor 1 and mitochondrial transcription factor A. Eur J Pharmacol 2007;563(1-3):77-82. Epub 2007 Feb 27
29. Rezkalla SH, Mesa J, Sharma P, et al. Myocardial infarction temporally related to Ephedra–a possible role for the coronary microcirculation. WMJ 2002;101:64-6
30. van der Hooft CS, Stricker BH. Ephedrine and Ephedra in weight loss products and other preparations. Ned Tijdschr Geneeskd 2002;146:1335-6
31. Ernst E. Cardiovascular adverse effects of herbal medicines: a systematic review of the recent literature
32. Bernachon-Agache F, Bernachon E, Coussieu C, et al. Leptin and old person's nutrition. J Nutr Health Aging 2005;9:327-9
33. Berk ES, Kovera AJ, Boozier CN, et al. Adiponectin levels during low- and high-fat eucaloric diets in lean and obese women. Obes Res 2005;13:1566-71
34. Rouher R, Cantat A. Anorectic drugs and retinal venous complications. Ann Oculaist 1962;195:667-8
35. Takahashi T, Wagenvoort CA. Density of muscularized arteries in the lung: its role in congenital heart disease and its clinical significance. Arch Pathol Lab Med 1983;107:23-8
36. Gertsch M, Stucki P. Weitgenhend reversibele primar vaskulare pulmonale hypertonie bei einem patienten mit menocil-einnahme. Z Kreislaufforsch 1970;59:902
37. Stuart KL, Bras G. Veno-occlusive disease of the liver. Q J Med 1957;26:291. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with Fenfluramine-phentermine. N Engl J Med 1997;337:581-8
38. Khan MA, Herzog CA, St Peter JV, et al. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. N Engl J Med 1998;339:713-8
39. Jick H, Vasilakis C, Weinrauch LA, et al. A population based study on appetite suppressant drugs and the risk of cardiac valve regurgitation. N Engl J Med 1998;339:719-24
40. Weissman NJ. Appetite suppressant valvulopathy: a review of current data. CVR & R 1999;146-55
41. Burger AJ, Sherman HB, Charlamb MJ, et al. Low prevalence of valvular heart disease in 226 phentermine-fenfluramine protocol subjects prospectively followed for up to 30 months. JACC 1999;34:1153-62
42. Fleming RM. Defining and treating heart failure. In: Chang JB editor, Textbook of angiology. Springer-Verlag, New York, NY; 1999. p. 1407-18
43. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet 1990;336:129-33
44. Fleming RM, Rater D, Ketcham K. Reducing cholesterol and triglycerides in the elderly patient by diet alone. The council on arteriosclerosis for the 66th Scientific Sessions of the AHA; 1993;127
45. Fleming RM, Rater D. Dietary changes without medications can equally reduce cholesterol in both the young and older patient. The council on arteriosclerosis for the 66th Scientific Sessions of the AHA; 1993;128
46. Fleming RM, Rater D, Ketcham K. Studying the effect of medications on cholesterol and triglycerides in subjects not receiving dietary counseling. The council on arteriosclerosis for the 66th Scientific Sessions of the AHA; 1993;128
47. Fleming RM, Ketcham K. Dietary reinforcement is an integral component of cholesterol reduction. The council on arteriosclerosis for the 66th Scientific Sessions of the AHA; 1993;128
48. Fleming RM, Fleming DM, Gaede R. Hyperlipidemic elderly patients: comparing diet and drug therapy. The council on arteriosclerosis for the 67th Scientific Sessions of the AHA; 1994;101
49. Fleming RM, Fleming DM, Gaede R. Treatment of hyperlipidemic patients: diet versus drug therapy. The council on arteriosclerosis for the 67th Scientific Sessions of the AHA; 1994;101
50. Fleming RM, Ketcham K, Fleming D, Gaede R. Controlling hypercholesterolemia by diet and drug therapy in the elderly. 1st Annual Scientific Session on Cardiovascular Disease in the Elderly; 1995
51. Fleming RM. Reducing cholesterol and triglyceride levels in both the young and elderly patient by dietary changes, with and without hyperlipidemic medications.

17th World Congress of the International Union of Angiology; Westminster, London, SWI, The Royal Society of Medicine; 1995

52. Fleming RM, Ketchum K, Fleming DM, Gaede R. Investigating differences in cholesterol and triglyceride levels as influenced by diet and hyperlipidemic medications. 42nd Annual World Assembly of the American College of Angiology; Maui, HI; 1995
53. Fleming RM, Ketchum K, Fleming DM, Gaede R. Treating hyperlipidemia in the elderly. Angiology 1995;46:1075-83
54. Fleming RM, Ketchum K, Fleming DM, Gaede R. Effect of dietary counseling on hypercholesterolemia lost unless periodic counseling continues. The 69th Scientific Sessions of the AHA; 1996
55. Fleming RM, Ketchum K, Fleming DM, Gaede R. Assessing the independent effect of dietary counseling and hypolipidemic medications on serum lipids. Angiology 1996;47:831-40
56. Fleming RM, Ketchum K, Fleming DM, Gaede R. Intensive dietary counseling a necessary adjunct to significantly increase the effectiveness of hypolipidemic medications. 5th World Congress on Heart Failure-Mechanisms and Management. Washington, DC; 1997
57. Fleming RM. Assessing PET myocardial perfusion and viability in 32 patients undergoing risk factor modification. XVI World Congress of the International Society of Heart Research; Rhodes, Greece; 1998
58. Fleming RM. The importance of FDG in the assessment of risk factor modification outcomes. XVI World Congress of the International Society of Heart Research; Rhodes, Greece; 1998
59. Fleming RM. Determining the outcomes of risk factor modification using positron emission tomography (PET) imaging. International College of Angiology. 40th Annual World Congress; Lisbon, Portugal; 1998
60. Fleming RM, Boyd L, Forster M. Unified Theory approach reduces heart disease and recovers viable myocardium. 42nd Annual World Congress International College of Angiology; San Diego, CA; 2000
61. Lipsenthal L, Ornish D, Fleming RM. Diets to reduce weight and CV risk: hype or hope? Lower fat is better. 73rd AHA Scientific Sessions; 2000
62. Fleming RM. The effect of low-fat, moderate fat and high fat diets on weight loss and cardiovascular disease risk factors. The Asian-Pacific Scientific Forum. 42nd Annual Conference on Cardiovascular Disease Epidemiology and Prevention; Honolulu; HI; 2002
63. Fleming RM. The effect of dieting on weight loss and cardiovascular disease. 49th Annually Congress of the American College of Angiology; Maui, HI; 2002
64. Fleming RM. The clinical importance of risk factor modification: looking at both myocardial viability (MV) and myocardial perfusion imaging (MPI). Intern J Angiol 2000;9:55-69
65. Fleming RM, Boyd L, Forster M. Reversing heart disease in the new millennium-the Fleming Unified Theory. Angiology 2000;51:617-29
66. Fleming RM. The effect of high protein diets on coronary blood flow. Angiology 2000;51:817-26
67. Fleming RM. The effect of high, moderate and low fat diets on weight loss and cardiovascular disease risk factors. Prev Cardiol 2002;110-118.
68. Fleming RM. Caloric intake, not carbohydrate or fat consumption, determines weight loss. Am J Med 2003;114:78

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