

TOXALERT

Newsletter of the MARYLAND POISON CENTER

**Saving
lives**

**Saving
dollars**

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TOXICITY OF DIET DRUGS **Wendy Klein-Schwartz, Pharm.D., M.P.H.**

Fenfluramine and dexfenfluramine were withdrawn from the market in 1997 after being implicated in the development of valvular heart disease.

Obesity is a significant public health problem in the U.S. It is estimated that 33% of the adult population is overweight, with 14% classified as severely overweight. A complex, multi-factorial disease, obesity is linked to many comorbidities including coronary heart disease, stroke, hypertension, diabetes mellitus, gout and others. Nonpharmacologic treatments usually include diet, behavior modification and physical activity. Americans spend over \$33 billion dollars a year on weight-reducing products.

Appetite suppressant drugs are indicated for individuals at risk for obesity related comorbidities and should be part of a comprehensive weight loss plan. Amphetamine and dexamphetamine were the first appetite suppressant drugs on the market but are no longer used because their marked central stimulant and euphoriant properties led to high abuse potential. The prescription noradrenergic drugs currently approved for the management of obesity are chemically and pharmacologically related to the amphetamines and include benzphetamine, phendimetrazine, diethylpropion, mazindol and phentermine. In therapeutic doses, these drugs increase alertness and sense of well-being, but can also result in irritability, nervousness, insomnia, hypertension and tachycardia. With an overdose, these drugs can produce agitation, hyperactivity, confusion, tremor, hyperreflexia, delirium, convulsions and coma. Cardiac toxicity includes arrhythmias, hypertension, and circulatory collapse. Other manifestations of toxicity include my-

driasis, diaphoresis, fever, and rhabdomyolysis which can progress to acute renal failure. In addition to providing supportive care and GI decontamination with activated charcoal, benzodiazepines should be administered for CNS toxicity, lidocaine for ventricular arrhythmias and nitroprusside or phentolamine for marked hypertension. Initial management of tachyarrhythmias includes administration of oxygen and benzodiazepines to sedate the patient. Pharmacologic intervention with esmolol or labetalol may be required but can worsen hypertension from unopposed alpha adrenergic activity. Fever is treated with external cooling including tepid sponge bath and fan. Controlling associated agitation, psychosis and seizures will also help lower body temperature.

Serotonergic drugs such as fenfluramine, dexfenfluramine and fluoxetine have also been used to suppress appetite. Fenfluramine and the noradrenergic drug phentermine were commonly prescribed together in the combination known as 'Fen-Phen'. Fenfluramine and dexfenfluramine were very popular diet drugs until September 1997 when they were withdrawn from the market because of their implication in the development of valvular heart disease. Of 113 cases of valvular heart disease in individuals on either fenfluramine or dexfenfluramine reported to the FDA, 98% were women with a median age of 44 years and the majority had been on the combination 'Fen-Phen'. Surveys found a prevalence of valvular heart

Diet Drugs (continued)

disease of 32.8% in individuals using these diet drugs, with aortic regurgitation more common than mitral regurgitation.

Fluoxetine (Prozac[®]), a serotonin reuptake inhibitor used in the treatment of depression, was noted to cause weight loss in clinical trials. Although not approved for the management of obesity, its popularity has increased now that fenfluramine and dexfenfluramine are no longer available. Prescribed alone or in combination with phentermine (known as 'Pro-Phen'), fluoxetine's side effects include drowsiness, insomnia, nausea, diarrhea and dry mouth. Overdoses of fluoxetine are usually not as serious as overdoses with cyclic antidepressants. Agitation, dizziness, tremor, drowsiness, seizures, nausea, vomiting, tachycardia and hypotension are common toxic effects. Fluoxetine can also cause serotonin syndrome, the severe manifestations of which include delirium, hallucinations, mania, seizures, coma, clonus, myoclonus, muscle rigidity, hyperthermia, hypertension or hypotension and tachycardia. Serotonin syndrome can occur with serotonergic agents by themselves but is much more commonly the result of an interaction between two drugs with serotonergic properties. Management includes discontinuing the causative agents and providing symptomatic care (including external cooling, paralytic agents, ventilation, anticonvulsants, antihypertensives, benzodiazepines). Serotonin antagonists such as cyproheptadine and methysergide have been used in a few cases.

Sibutramine (Meridia[®]), the newest prescription diet drug on the market, is structurally related to amphetamine. Taken once daily, sibutramine inhibits the re-uptake of norepinephrine, serotonin and possibly dopamine; it should not be taken concomitantly with MAO inhibitors or SSRIs. Common side effects include insomnia, tachycardia, hypertension and dry mouth. Orlistat (Xenical[®]) has not yet been approved by the FDA but is expected to be approved in 1999. A lipase inhibitor, orlistat decreases dietary fat absorption and

fecal incontinence. There are also concerns about a possible association with breast cancer. Phenylpropanolamine, a nonprescription diet drug, can cause nervousness, insomnia, dizziness, diaphoresis, anxiety, headache and hypertension. There are case reports of serious adverse effects associated with phenylpropanolamine including marked hypertension, stroke, intracerebral hemorrhage, seizures, cardiac arrhythmias and acute interstitial nephritis. The doses associated with these severe adverse effects are highly variable, although usually higher than the recommended dosage.

A weight loss combination that is marketed as a natural herbal alternative and is sometimes called 'Herbal Fen-Phen' contains ephedra (*Ma Huang*) and St. John's Wort (*Hypericum perforatum*). The main active ingredient in Ma Huang is ephedrine, with pseudoephedrine and norpseudoephedrine present in smaller amounts. Adverse effects range from hypertension, arrhythmias, insomnia, headache, nervousness and tremors to seizures, myocardial infarctions, strokes and death. The active ingredient in St. John's Wort is hypericin. Dry mouth, dizziness, constipation, other GI symptoms and confusion have been reported with its use. Other concerns regard the potency and purity of these products since amounts vary in different parts of the plant and at different times of year and may depend on growth conditions.

There are many products being promoted through the internet, print ads and health food stores for which there is no evidence of efficacy in the management of obesity. Examples include glucomannan tablets which are purported to produce a feeling of fullness, ipecac syrup to purge after meals, chromium picolinate to improve glucose tolerance and promote development of lean body mass, aminophylline creams for topical application to thighs and stomach, yohimbe creams and yohimbine containing tablets to

“Serotonin syndrome” can occur with agents such as Prozac, either by themselves, or more commonly, due to drug interactions.

“Herbal Fen-Phen” is a weight loss alternative that contains ephedra and St. John's Wort.

Diet Drugs (continued)

block alpha-2 adrenergic receptors resulting in thermogenic properties which 'release fat', and the blue-green algae *Spirulina* which claims to be effective not only for appetite suppression, but also for diabetes, hepatitis, anemia, stress, pancreatitis, cataracts, hair loss and many other conditions. Although not efficacious, some of these products have not been associated with serious adverse effects. Other agents, such as ipecac syrup, have well documented toxicity with chronic use. New products are coming on this unregulated market every day. It is important for health professionals to query their patients about products purchased outside the traditional health care system and to be vigilant in detecting previously unobserved and/or unreported adverse effects.

NATIONAL POISON PREVENTION WEEK: March 21-27, 1999

To commemorate Poison Prevention Week, the Maryland Poison Center will host the **Poison Prevention Olympics** on Saturday March 20 from 10am-2pm. This will be an innovative, exciting way for children ages 4-10 to learn about poisons and staying safe. The theme of our Olympics will be **"Everyone's a winner with poison prevention."** For more information, call Mary Hayes at 410-706-7604.

Poison Prevention Week is March 21-27, 1999.

Call 410-706-7604 for materials and ideas to promote poison prevention in your community.



TOXNOTES: Is metformin safe to use in all diabetic patients?

Metformin (Glucophage[®]) is a biguanide hypoglycemic agent used for the treatment of non-insulin dependent diabetes mellitus. The usual dosing is 500-850 mg twice daily. Since its approval by the FDA in 1995, this agent has become very popular as monotherapy and in combination with other hypoglycemic agents.

Recently there has been increasing concern about lactic acidosis associated with metformin use. Metformin concentrations greater than 45 mg/L are associated with developing acidosis. Frequent monitoring of renal function and metformin concentrations are essential given the age of the diabetic population and the nephropathic nature of the disease state. Serum creatinine greater than 1.4 mg/dL is a contraindication to metformin use. The package insert for the drug was recently revised to specify that a creatinine clearance rate assessment be obtained in patients greater than 80 years old, and to indicate that it is contraindicated in all patients with congestive heart failure who require pharmacologic treatment.

P-450 enzyme inhibitors like cimetidine decrease metformin metabolism. Steroids and alcohols increase the risk of lactic acidosis. These agents should be avoided when possible. Other less frequent toxicities at therapeutic doses include hypoglycemia, hyponatremia, megaloblastic anemia, vitamin B12 deficiency (malabsorption), vasculitis, sweating, metallic taste and diarrhea.

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**Maryland Poison Center Expands
Education Programs**

**For poison
prevention
or profes-
sional edu-
cation pro-
grams, call
410-706-
7604**

Mary Hayes, M.S. recently joined the staff of the Maryland Poison Center as Health Educator. Mary comes to the poison center with health education and research experience in a variety of health care settings. She is coordinating and expanding the public education programs of the Maryland Poison Center throughout Maryland. Among the poison prevention materials she has already developed are brochures for the Hispanic community. If you would like a speaker or materials for the general public about poison prevention, please call Mary at 410-706-7604 or Email her at mhayes@mpc.ab.umd.edu.

The Maryland Poison Center also is expanding its professional education program. To schedule a speaker for an inservice, seminar, class, grand rounds, etc. on a variety of topics, contact Lisa Booze, Clinical Coordinator