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Short Communication

The Marketing of Herbal Supplements to an Uninformed Audience: Should the FDA Regulate Pharmaceutical Companies that produce Supplements?

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ABSTRACT

The Food and Drug Administration, the government agency responsible for protecting and promoting the public health in the United States through the regulation and supervision of food and drug products, has no power to regulate the manufacture or efficacy of dietary supplements. Pharmaceutical companies are at liberty to produce and dose supplements without scientific research to back it up. Consumers may well be at risk. This article provides an overview of the use of herbal supplements in the United States and the lack of regulatory control over their production. Of particular interest is the lack of standard dosages of herbal supplements. We hope to stimulate a discussion about the safety of herbal supplements as they are currently produced, the need for regulatory control over the manufacture of these products, the need for standards in dosing and the need for public education about the use of supplements, especially in persons with underlying morbidity. We offer a brief case report as an example.

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In 2002, Harris Interactive Health Care News conducted a telephone survey of 1,010 US citizens and found that 69% of adults polled reported taking some form of food supplement, (vitamin, mineral, anti–aging medicine, etc.) (Harris survey, 2002). Reports on the business of dietary supplement sales are astronomical ranging from $13–23.7 Billion/year (Moore, 2010; Rea, 2010). And the outlook for supplement manufacturers is good. In a society where an aging population relies on medications to add quality to their lives and hopes to stall the effects of aging, the right mix of "all–natural medicine" and catchy advertising equals big business. An internet search of "supplements" produces over ten million hits. Magazines, television and internet websites present a constant stream of dietary supplement advertisements. As the Council for Responsible Nutrition so aptly stated, "Prevention will be Profitable" (Blatman, 2010).

In 1994, The Congress of the United States enacted the Dietary Supplement Health and Education Act (DSHEA). This act mandated that the manufacturers of dietary supplements alone would be responsible for ensuring that their products are safe. It left the Food and Drug Administration (FDA) as mostly observers. The FDA is responsible only for taking action against those manufacturers if they deem a supplement to be unsafe after it marketed (Barret, 2010).

Under the DSHEA "there is no provision under any law or regulation that the FDA enforces that requires a firm to disclose to the FDA or consumers the information they have about the safety or purported benefits of their dietary supplement products (Overview of dietary supplements by FDA 2010). The FDA does provide an avenue for consumers to report adverse events/illness they believe are related to supplement use in the form of an on–line questionnaire which can be filled–out and filed with the FDA.

The American Association of Poison Control Centers has kept statistics on poisonings secondary to ingestion of dietary supplements since 1983, when fourteen thousand adverse events were reported. By the year 2005 the number of incidents had grown to 125,595. The total number of incidents over that span was over 1.6 million with 230 deaths attributed to ingestion of dietary supplements. Dr. Alexander M. Walker, former chairman of the Department of Epidemiology at the Harvard School of Public Health has reported that "less than 1% of serious adverse events caused by dietary supplements are reported to the F.D.A." We may never know for sure how many adverse reactions are actually occurring secondary to supplement use (Hurley, 2007).

A 42 y/o Caucasian male presented to the emergency department with vague complaints of headaches, racing thoughts and hallucinations, epistaxis and new onset widespread ecchymoses of his trunk and extremities. He says "I bruise easy (sic)." The patient states he has had low platelets before, but he has never had a traumatic bruising. He attributes his symptoms to the "male enhancement" supplement Extenze®. The patient states that he has been taking the supplement for

ten days, and that he has noted increased strength and energy since starting it. He reports noticing the bruising on his shoulders within a week of starting the supplement. When it became widespread he stopped the supplement and sought medical attention. He was admitted to the hospital for evaluation and worked–up for thrombocytopenia secondary to cirrhosis and splenomegaly.

The patient's past medical history is significant for alcoholism, cirrhosis, ascites and bipolar disorder. A review of lab results shows a history of thrombocytopenia (blood platelet count ‹ the normal range 150,000–450,000/µL). In eleven blood platelet counts over the past year the patient had an average count of 61,000 with a low of 38,000 ten months earlier. His most recent platelet count was 42,000 thirty seven days before admission. On the day of hospitalization the patient's platelet count was 14,000*, a 66% drop to "critical value."

The patient's hospital stay was mostly unremarkable. The hallucinations stopped and his racing thoughts "slowed." His platelet count rose steadily during his stay. On the day of discharge, approximately 8 days after stopping the Extenze®, the patient's showed no signs of new bruising, his existing bruises were shrinking and fading, his epistaxis had ceased and his platelet count was 50,000.

Impotence or erectile dysfunction (ED) as it is now termed is the inability in some men to shunt and/or entrap blood in the lacunar network of the penis to produce and maintain erection. It is estimated that up to 30 million men in the U.S. are affected by ED. Performance enhancers or aphrodisiacs such as Spanish fly have been available in the U.S. since the 1800s, but the Pure Food and Drug Law of 1906 eliminated most of them as fraudulent. And what has been available since could not be found at the corner drugstore. These supplements were relegated to the back pages of adult magazines. All of this changed in 1998 when Pfizer Incorporated pharmaceutical company received approval from the FDA for its already patented Sildenafil.

Table :–Extenze® Ingredients

Ingredient	Efficacy Established for ED	Established Dose for ED	Hematological Side Effects
Folate	No	No	No
Zinc (Natural Standard, 2010)	No	No	Yes[a]
DHEA	Yes	50 mg/day	No
Pregnenolone	No	No	No
Black Pepper (seed)	No	No	No
Piper Longum (seed)	No	No	No
Ginger (root) (Backon, 1991)	No	No	Yes[b]
Yohimbe Extract (bark) (Berlin, et.al., 1991)	Yes	No	Yes[c]
Tribulus terrestris	No	No	No
Korean Ginseng Extract (Ries and Sahud, M. 1975)	Yes	300 mg/day	Yes[d]
Cnidium monnieri (seed)	No	No	No
Eleutherococcus Extract (root) (Bazaz'ian, et.al., 1987)	No	No	Yes[e]
Xanthroparmelia scarbosa	No	No	No
GABA	No	No	No
Velvet Deer Antler	No	1000 mg/day	No
Horny Goat Weed (leaf) (Natural Standard, 2010)	Yes	No	Yes[f]
Damiana (leaf)	No	No	No
Muira puama Extract (stem)	Yes	1000–2580 mg/day	No
Pumpkin (seed)	No	No	No
Stinging nettle (root) (Baraibar, et.al., 1983)	No	No	Yes[g]
Astragalus (root) (Zhang, et.al., 1997)	No	No	Yes[h]
Licorice Extract (root)	No	No	No
L–Arginine HCl (Natural Standard, 2010)	Yes	No	Yes[i]
Ho Shou Wu Extract (root)	No	No	No
Boron (as chelate)	No	No	No

[a]Sideroblastic anemia, leucopenia, microcytic anemia and neutropenia have been reported in case reports following the ingestion of large amounts of zinc; [b]Ginger may decrease platelet aggregation and prolong bleeding time by inhibition of thromboxane synthase; [c]Agranulocytosis has been reported. May also inhibit platelet aggregation; [d]Agranulocytosis reported in 4 patients. Anecdotal reports of epistaxis and vaginal bleeding; [e]Rats exhibited anticoagulation upon oral administration; [f]Extended use may result in nosebleed; [h]May increase fibrinolysis and increase risk of bleeding; [i]May increase risk of bleeding

Sildenafil, or "Viagra®" as it is best known, is a smooth muscle relaxant and vasodilator originally designed to treat angina. In trial it produced little relief of anginal symptoms. However, one of the side effects of Viagra®, marked penile erection, has helped to create a whole new industry. The marketing of Viagra® together with the DSHEA opened the flood gates for the influx of other male enhancement supplements.

While Sildenafil has been proven effective in treating ED, Extenze® advertisements make extraordinary claims that it will "Increase the size and girth (of the user's penis), increase libido, treat ED, increase (sexual) stamina and endurance, stop

premature ejaculation and more (Extenze® 2010). Dr. Ira Sharlip, American Urological Association spokesperson says "There is no such thing as a penis (growth) pill that works. These are all things that are sold for profit. There's no science or substance behind them" (Enzyte®,2010).

Yohimbine Hydrochloride is an FDA approved prescription medication indicated for the treatment of erectile dysfunction. This regulation of prescription medications by the FDA ensures that patients using prescription Yohimbine Hydrochloride are receiving a quality controlled product, with established safety and efficacy.

Extenze® lists Yohimbe extract as its primary ingredient (see Table 1). The extract originates from the bark of the *Pausinystalia yohimbe* tree and contains yohimbine, an indole alkaloid. The safety of Yohimbe bark extract is questionable at best. Since the quality of herbal supplements is unregulated, patients who use the extract may be receiving varying amounts of the active yohimbine ingredient from dose to dose, or manufacturer to manufacturer. Additionally, reported adverse reactions to yohimbe have been both extensive and display a broad range of severity. Of note, yohimbine, and (theoretically) yohimbe bark extract have been associated with hematological effects including agranulocytosis, inhibition of platelet aggregation, and a potential increased risk of bleeding. In fact, nine (9) of the active ingredients in Extenze® have been associated with hematological symptoms.

CONCLUSION

The pressing issue with the manufacturing of dietary supplements is that here in the U.S. we tend to like things "Supersized." If a little is good, more must be better. But common sense dictates that this is not true. To paraphrase Aristotle, 'All things in moderation'. According to the FDA "there are no rules that limit a serving size or the amount of a nutrient in any form of dietary supplements" (U.S. Department of Health and Human Services 2010). Perhaps it's time there were such rules. We would like to suggest that there is indeed a need to turn a scientific eye toward the area of dietary supplements and there is a need to set standards for the dosing of herbal supplements.

The fact that the DSHEA provides for no Federal oversight of supplement manufacturers but rather leaves it in the hands of the manufacturers themselves is mind boggling. This is the penultimate example of letting the fox guard the chicken coop. And, the fact that these audacious claims have been made in print and on broadcast television leads one to question whether the Federal Trade Commission has any interest in prohibiting "unfair and deceptive acts or practices in commerce," for which the commission was established (Federal Trade Commission, 2010). Also, the late night timing of many ads could cause one to suspect that there is strong psychological basis behind late night ads. "Strong branding supported by direct–to–consumer advertising is an essential element to successful penetration of the *insomnia* market (Market report source, 2010).

Lastly, the responsibility for educating the public will have to fall to medical providers. It is up to us to broach the subject of sexual dysfunction with our patients and to guide them to better health with informed decisions on the use of medications and supplements. As for prospective users of male enhancement supplements, remember, there is benefit in cynicism. If a supplement is making a claim that sounds too good to be true, it probably is! Caveat emptor!

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