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PERMISSION

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Department Nursing

Degree Master of Science

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Abstract

With the growing epidemic of obesity across the United States, adolescents and adults are using dietary supplements for the purpose of weight loss and to build muscle with the common misconception that these supplements are proven safe and effective by the government before they are available to consumers (Pomeranz, Barbosa, Killian, & Austin, 2015). Since supplements with ephedrine are no longer allowed on the market due to serious health risks, manufacturers have reformulated their supplements to include ingredients that have a similar chemical structure and pharmacological properties as ephedrine and have advertised them as "ephedra-free" (Foster, 2013). There is very limited national data available identifying associated risks or adverse events with ephedra-free supplements. This became an area of clinical interest after a 20 year old female college student presented to the family planning office requesting to initiate an oral contraceptive and had reported the occasional use of over-the-counter ephedra-free Xendarine for weight loss. Her body mass index (BMI) indicated she was underweight; she had no previous medical history, an unremarkable family history, and the review of systems and physical examination was negative for any abnormal or pertinent findings. A literature review was conducted to identify what potential health risks have been associated with the use of ephedra-free weight loss products, which included randomized controlled trials and numerous case reports. The research findings will be discussed, as they identify a strong association of serious cardiovascular and neurological health risks with prolonged use of ephedra-free weight loss products.

Potential Health Risks Associated with the Use of OTC Ephedra-Free Weight Loss Products

Background

Significant attention has been placed on the growing epidemic of obesity, which is defined as a body mass index (BMI) of 30 or greater. Across the United States (U.S.), the Center for Disease Control and Prevention (CDC) has estimated a prevalence of obesity of approximately 25% or greater across a majority of the states (Moaaddeb, Tofade, & Bevins, 2011). With the expanding and readily available weight loss or dietary supplements advertised across numerous forms of media and sold over-the-counter (OTC) in various stores and online, more adolescents and adults are purchasing these supplements to assist with their personal weight loss goals and/or to build more muscle. In fact, studies conducted among adults in the U.S. have identified that 17% have used supplements to improve their sports performance, while 20.6% of women and 9.7% of men have used supplements advertised specific for weight loss (Pomeranz, Barbosa, Killian, & Austin, 2015). In addition, a national survey conducted in 2002 revealed that 29.1% of adolescents and young adults between the ages of 14 and 19 years of age reported using any form of dietary supplement within the last 30 days, while 10.7% reported a history of using dietary supplements for weight loss at some point (Pomeranz, Barbosa, Killian, & Austin, 2015). Unfortunately, the growing use of dietary supplements across the U. S. is perpetuated by consumers misconception regarding their safety and efficacy, which is greatly highlighted by a national study identifying that two-thirds of its respondents believed that these supplements were not only safe and effective, but half of those respondents also believed these supplements were proven safe and effective by the federal government before being placed on the market (Pomeranz, Barbosa, Killian, & Austin, 2015).

As a result of Congress passing the Dietary Supplement Health and Education Act (DSHEA) in 1994, the Food and Drug Administration (FDA) is no longer required to regulate or allowed to verify the safety or efficacy of any dietary supplement before it is placed on the market. This has contributed to an industry with a growth of $32 billion a year. The responsibility of verifying the safety of these dietary supplements is placed on the manufacturers and their adherence to good manufacturing practices. These manufacturers are only required to report any serious adverse events that result in hospitalization, disability or death (Pomeranz, Barbosa, Killian, & Austin, 2015). A review of available national surveillance data obtained from 63 emergency departments (ED) from 2004 to 2013 revealed "an estimated 23,000 emergency department visits in the United States every year are attributed to adverse events related to dietary supplements" (Geller et al., 2015, p. 1531), and of those adverse events, weight loss supplements account for 25.5% and involve cardiovascular manifestations of palpitations, tachycardia, and chest pain (Geller et al., 2015). Potentially contributing to the limited national data on associated adverse events, healthcare providers are not always aware that their patients are consuming dietary supplements, nor do consumers associate any symptoms to these supplements, so most adverse events are never reported to the FDA (Geller et al., 2015; & Pomeranz, Barbosa, Killian, & Austin, 2015).

Relative to this clinical topic, a 20 year old female college student presented as a new patient to the family planning office requesting to start an oral contraceptive. She had no past medical history, and family history was negative for any clotting disorders, heart disease, neurological disorders or cancer. Upon review of her current medications, she reported the use of OTC multivitamin, Midol as needed for menstrual cramps, Tylenol as needed for headaches, and ephedra-free Xenadrine occasionally for weight loss as needed. Her body mass index of

17.2 indicated she was underweight, and she denied any associated symptoms or side effects related to this weight loss supplement. Vital signs were all within normal limits and physical examination was negative for any pertinent or abnormal findings. Due to safety concerns and unknown potential health risks regarding dietary supplements, she was instructed to discontinue use of Xenadrine. With the federal government banning ephedrine-containing dietary supplements from the market in April 2004 due to the serious adverse events, this case highlights the need for research to identify any reported adverse events or potential health risks that have been associated with the use of OTC ephedra-free weight loss supplements (Stephensen & Sarlay, 2009). Pertinent research findings will improve clinical awareness, knowledge, and competency regarding the use of these weight loss supplements in order to provide current and appropriate patient education regarding its use, appropriate monitoring should patients choose to continue to use these supplements despite medical advice, and improve reporting of adverse events to the FDA.

Case Report

Presenting as a new patient to the family planning office, L. J. is a 20 year old female requesting to start oral contraceptives to prevent unplanned pregnancies. Upon review, her past medical history is negative for any medical conditions, surgeries, or hospitalizations. Allergies include penicillin, and her current medication list includes the following: over-the-counter (OTC) ephedra-free Xenadrine as needed for weight loss; OTC multivitamin occasionally; OTC Midol for menstrual cramps as needed; and OTC Tylenol as needed for headaches. She is up to date on recommended vaccinations, including the Human Papillomavirus (HPV) vaccine series. Her reported reproductive history includes a menstrual cycle occurring every month and lasting about 5 days in length without any heavy clots, and a last menstrual cycle that occurred on January 19,

2016. She denies any history of pregnancies, any previous screenings or treatments for sexually-transmitted infections (STIs), or any previous use of prescribed contraceptives. She is heterosexual, is currently sexually active with the occasional use of condoms as a barrier method, and reports utilizing the emergency contraceptive Plan B once around this last New Years. Family history includes the following: hyperlipidemia and benign breast mass removed about 1 year ago in her mother; blood clot following surgery in her father; no medical conditions among siblings (brother & sister); and no family history of clotting disorders. Social history includes the following: currently attending college; single; denies any use of tobacco products or exposure to second hand tobacco smoke; reports current alcohol use of about 3 weekends per month with 2-5 mixed drinks each time; and reports regular physical exercise daily.

Measured vital signs were as follows: height of 67 inches; weight of 110 lbs (50 kg); blood pressure of 112/74; heart rate of 82; respiratory rate of 18; temperature of 98.5 F; and BMI of 17.2 (underweight). Review of systems revealed whitish vaginal discharge without odor occasionally, but was otherwise proved negative for any other symptoms. Upon physical examination, patient was alert, oriented x 3, affect stable, pleasant, cooperative, well-developed, well-nourished, and in no acute distress. Examination of eyes revealed the following: pupils were equal, round, and reactive to light (PEERL); extraocular movements were intact (EOMI); and no discharge or erythema were noted. Heart rate and rhythm were regular without murmur, gallop or rub. Lung sounds were clear bilaterally without rales, rhonchi, or wheezing noted and breathing was unlabored. Abdomen was flat, non-distended, and non-tender without any guarding, masses, organomegaly, and bowel sounds were normoactive in all 4 quadrants.

Laboratory testing included urine pregnancy test to verify pregnancy status prior to initiating oral contraception, as well as annual screening for chlamydia and gonorrhea per

clinical screening guidelines. Diagnoses included initial encounter and prescription for contraceptives, negative pregnancy test, screenings for bacterial sexually transmitted infections (STIs), and high risk heterosexual behavior. Documented counseling that occurred during encounter included family planning and forms of available contraception with risks and benefits of each method, education and prevention of STIs, healthy body mass index (BMI), healthy dietary and lifestyle modifications to maintain healthy weight and general health, and potential risks related to use of over-the-counter weight loss supplements.

With confirmation of negative pregnancy test and no identified risks factors or contraindications, an oral monophasic combined oral contraceptive (COC) was initiated per patient's preference. She was instructed to use condoms as a barrier method for the first week of oral contraceptive, as well as with all sexual encounters for STI prevention. Patient will be contacted regarding results of STI screenings when made available. She was instructed to monitor for signs of abdominal pain, chest pain, headaches, visual changes/disturbances, or severe leg pain due to risks of blood clots while taking COCs, and to seek medical attention if these symptoms should develop. Common side effects or reactions that may occur and should resolve were discussed and included nausea, vomiting, breast tenderness, and bleeding irregularities. Discussed clinical recommendations for cervical screenings after the age of 21 years old, and monthly self-breast examinations were recommended for her own body awareness. Encouraged to continue regular physical activity, maintain a well-balanced meal and adequate hydration in regards to overall health and weight management. Informed of current BMI, which indicates she's underweight, and highly encouraged to discontinue the use OTC Xenadrine due to potential health risks. Tobacco use was discussed and highly discouraged, as well as encouraged to limit alcohol use due to identified high risk sexual behaviors and safety

concerns correlated with excessive alcohol intake. Will complete a follow-up appointment in three months to evaluate adherence and adjustment to medication, as well as discuss any questions, concerns, or side effects, and will anticipate scheduling an annual physical examination with clinical Pap smear and breast examination after reaches 21 years of age in 1 year.

Literature Review

As health care providers, it is our responsibility to initially evaluate the quality of research prior to implementing it into our clinical practice. To assist with evaluating various studies and research, the evidence-leveling system created by the American Association of Critical Care Nurses (AACN) in 2008-2009 was used in this process, which identifies six separate levels of evidence with Level A as the highest level of evidence (e.g. meta-analysis and meta-synthesis) and Level M as the lowest level of evidence (e.g. manufacturer recommendations) (Armola et al., 2009). Each research study that is discussed will have a level of evidence identified.

Online resources available through the University of North Dakota's (UND) Harley E. French Library of the Health Sciences was utilized to complete the online literature search required to address the identified area of clinical interest and included CINAHL, PubMed, and the Cochrane Library. The main concepts or terms utilized during this literature search included "ephedra-free", "weight loss products", and "weight loss products, dietary supplements"; however, the term "ephedra-free" produced more specific results, and due to limited available data, no additional limitations in regards to date of publication, etc., were applied. At the conclusion of this literature search, fourteen research articles, including 3 randomized clinical trials (Level B evidence) and 11 case reports (Level E evidence) were identified as applicable to

the chosen research question of: what potential health risks have been associated with the use of OTC ephedra-free weight loss products.

This area of clinical interest was deemed pertinent upon completing an initial encounter with a 20 year old female college student that had presented as a new patient to the family planning office requesting to start an oral contraceptive. With the patient's medical history, family history, review of systems and physical examination unremarkable for any pertinent findings or contraindications, an oral contraceptive was initiated. However, the occasional use of OTC ephedra-free Xendarine was reported upon review of her current medications, which she believed were safe to consume and had denied any associated symptoms or side effects. With the well-known banning of ephedrine-containing dietary supplements from the market in 2004 due to its serious adverse events, this case highlights the need for further research to identify any reported adverse events or potential health risks that have been associated with the use of OTC ephedra-free weight loss supplements in order to improve clinical awareness, knowledge, and competency regarding the use of these weight loss supplements to provide current and appropriate patient education regarding its use, monitoring should patients choose to continue these supplements despite medical advice, and improve reporting of adverse events to the FDA.

As mentioned previously, manufacturers of dietary supplements are no longer allowed to produce products containing the ingredient ephedrine due to the serious cardiovascular and neurological risks and adverse events that were identified. This resulted in the production of "ephedra-free" supplements using a combination of ingredients, such as guarana, bitter orange or Citrus aurantium, ma huang, cocoa, Coleus forskolii and synephrine as substitutes for ephedrine. These ingredients have been found to have similar chemical and pharmacological properties as its predecessor ephedrine, yet there has been few research studies that have evaluated the safety

of these products (Foster et al., 2013; Moaddeb, Tofade, & Bevins, 2011; Retamero, Rivera, & Murphy, 2011).

Unfortunately, only a few randomized controlled trials (RCTs) have been conducted to determine the adverse effects of ephedra-free weight loss supplements required to provide sufficient evidence to prove their efficacy and safety. Results from a RCT published in 2005 determined there was no significant change in either blood pressure or systemic vascular resistance index (SVRI) among healthy volunteers that were administered a single dose of Metabolife Ephedra-Free (Min, McBride, Kardas, Ismali, Sinha, Kluger, & White, 2005). In contrast, significant increases in blood pressure measurements and irregular atrial/ventricular events were noted on an electrocardiograph (ECG) compared to baseline readings following the administration of multiple daily doses of several different ephedra-free products, as evidenced by two additional randomized studies (Foster et al., 2013; & Haller, Benowitz, & Jacob, 2005). Other associated symptoms included nausea and vomiting that were linked to a heavy contamination of bacillus species among two separate supplements (Foster, 2013). These "findings suggests that prolonged use of certain "ephedra-free" supplements may alter cardiac electrophysiology" compared to a one-time dose, as well as have the potential risks associated with herb-drug interactions and microbial contamination (Foster et al., 2013, p 271).

Furthermore, numerous case reports of associated adverse effects of rhabdomyolysis, psychosis, hypertensive urgency with presenting blood pressure of 234/130, malignant hypertension with aortic dissection, malignant hypertension with hypertensive retinopathy, ventricular fibrillation, ST-segment elevation myocardial infarction, exercise-induced syncope with QT prolongation, left middle cerebral artery vasospasm with stroke, and ischemic stroke have been associated with ephedra-free supplements since they became available to consumers.

In most of these cases, symptoms related to the adverse event developed after consuming the supplements for a prolonged period of time that ranged from a couple of weeks to numerous months. Among these reported cases, most had no predisposing medical history that would have accounted for or contributed to the development of these adverse events, and symptoms resolved without recurrence after the discontinuation of the ephedra-free supplement. In these patient cases, the probability that the adverse events were, indeed, associated with the patient's reported use of an ephedra-free supplement prior to the onset of symptoms was established with the use of the clinical tool Naranjo adverse drug reaction probability scale (Ahmed, 2009; Bouchard, Howland, Greller, Hoffman, & Nelson, 2005; Burke, Seda, Allen, & Knee, 2007; Carol, 2013; Holmes & Tavee, 2008; Moaddeb, Tofade, & Bevins, 2011; Nasir, Durning, Fergunson, Barold, & Haigney, 2004; Retamero, Rivera, & Murphy, 2011; Stephenson & Sarlay, 2009; Thomas, Munir, McIntyre, & Ferguson, 2009; & Willis, Moawad, Hartzell, Iglesias, & Jackson, 2006). Even though case reports have limited ability to identify causation, the pertinent research findings gained from the available randomized controlled trials (RCTs) and numerous case reports found in medical literature establish a strong association of serious cardiovascular and neurological health risks with the prolonged use of ephedra-free weight loss supplements or products that are similar to those previously reported with ephedrine, which has clinical implications for the safety of its consumers and our patients.

Learning Points

In conclusion, research findings have established a strong association of serious cardiovascular and neurological health risks with the prolonged use of ephedra-free weight loss supplements or products. It is the responsibility and recommendation for all healthcare providers to ask patients about their use of supplements and document with each encounter, as well as

provide education regarding the use of dietary supplements and associated health risks that have been identified. Since the Food and Drug Administration (FDA) is no longer required or allowed to verify the safety and efficacy of dietary supplements before they are released on the market, it is imperative that healthcare providers continue to monitor and report any adverse events to the FDA, which can be completed online through the adverse event reporting program known as MedWatch located on the FDA's website. Increased reporting of adverse events will not only help the FDA identify any safety risks related to these supplements, but it also provides the opportunity to help advocate for improved regulation of dietary supplements by the FDA.

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