Hypertension in an Adolescent Secondary to Performance-Enhancement Supplement Use

Journal of Pharmacy Technology
2014, Vol. 30(3) 81–86
© The Author(s) 2013
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122513503790
pmt.sagepub.com

Robin M. Milton, DPh¹, Merry Kelly-Rehm, MS, RN², Nancy Brahm, PharmD, MS, BCPP, CGP¹, and Mark D. Fox, MD, PhD, MPH¹

Abstract

Objective: To describe the effects of performance-enhancing supplements and caffeine on the blood pressure (BP) of an adolescent male. **Case Summary:** An adolescent male presented to his primary care provider for a preseason athletic physical. On physical exam, his BP was 162/90, exceeding the 99th percentile for his age. It had been elevated during the previous 2 yearly physicals. He was referred to the Pediatric Preventive Cardiology Clinic for follow-up. Illegal substance use and renal trauma were ruled out. During the evaluation, the patient acknowledged using energy drinks and performance-enhancing supplements, the majority of which were caffeine-based. His intention was to continue the use of supplements, so lisinopril was initiated. On follow-up, however, the patient reported supplement discontinuation, intermittent medication adherence, and lower home-based BP readings. He was subsequently lost to follow-up. An objective causality assessment revealed that the adverse drug event was probable. **Discussion:** When working with adolescent patients, it is particularly important to conduct an in-depth interview reflecting lifestyle choices. Use of performance-enhancing supplements and caffeine for adolescent athletes has been well reported in the literature. Adolescent use of supplements may be driven by misguided beliefs and lack of knowledge about potentially detrimental health effects, such as altered heart rate and elevated BP. Little evidence-based research is available to provide treatment guidance for clinicians regarding potential effects. **Conclusions:** A thorough patient history, including specific questions probing for any recent or chronic use of nutritional supplements, including energy drinks, will help identify substances that may contribute to BP variations. Even mild BP elevations in adolescents should lead clinicians to further investigate supplement use and include specific questions on any product use within the past 24 hours, several days, or longer. Adolescents may not consider the potential for adverse health effects when ingesting performance-enhancing supplements or energy drinks.

Keywords

adverse reactions, cardiology, drug information, hypertension, medication safety, pediatrics

Introduction

Use of supplements as energy boosters and performance enhancers for athletes has been a topic of concern, particularly the potential for supplements to adversely affect cardiovascular (CV) function.^{1–3} Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the burden of proof lies with the federal Food and Drug Administration (FDA) and the federal government to demonstrate that a dietary supplement is unsafe. This is unlike the regulatory process for both prescription and over-the-counter medications where manufacturers are required to demonstrate safety and efficacy before receiving FDA approval.⁴ The DSHEA has received opposition from health care organizations such as the American Society of Health System Pharmacists that would like to have an FDA regulatory

scheme in place for the safety and efficacy of dietary supplements.⁵ The ingredients of dietary supplements marketed for weight loss and/or increased endurance may be associated with a variety of potentially adverse effects on CV function, particularly heart rate (HR) and blood pressure (BP). Often little evidence-based research is available to support claims for the ingredients or provide guidance for clinicians regarding potential effects if combinations are used.^{6–8}

¹The University of Oklahoma, Tulsa, OK, USA

²The University of Tulsa, Tulsa, OK, USA

Corresponding Author:

Nancy Brahm, PharmD, MS, BCPP, CGP, University of Oklahoma College of Pharmacy, 4502 E. 41st Street, 2H17, Tulsa, OK 74135-2512, USA.
Email: nancy-brahm@ouhsc.edu

The potential for adverse effects from supplements may be underestimated by users. In a survey of patient knowledge about the possible adverse effects, more than 40% of the respondents thought these agents did not have the potential for adverse health effects.⁵ Use of supplements as performance enhancers for adolescent athletes has been well reported in the literature and may be driven by misguided beliefs by these adolescents. In a study of 157 students (ages 11-19), health literacy skills by use of the Internet were evaluated. Many students in the study cited difficulty distinguishing relevant health information from false statements.⁹

We report the case of an adolescent athlete referred to the Pediatric Preventive Cardiology Clinic (PPCC) by his primary care provider (PCP). The use of the 9 ingredients in dietary supplements he reported consuming was identified. We provide a review of these ingredients from case reports and evidence-based research reporting changes in CV function where a change in CV status or a CV-related adverse event was defined as a change in HR and/or BP.

Case Report

A 17-year-old white male was referred by his PCP to the PPCC for evaluation and management of hypertension following elevated readings over the course of 3 years of athletic physicals. The most recent reading was 162/90 mm Hg. This placed him in the 99th percentile for his age and gender, or greater than 2 standard deviations from the mean.¹⁰ In the referral request, the PCP indicated additional BP readings were also elevated to the level of Stage 2 Hypertension per JNC-7 guidelines.¹¹ Specific information on how BP was taken was not included in the referral information. The patient presented to the PPCC 1 week following the referral. When evaluated by the physician in the PPCC, past medical history was unremarkable. The usual childhood illnesses and occasional athletic injury were reported. Specifically, there was no history of urinary tract infection and no history of renal trauma or other insult. The hypertension workup was unrevealing with all laboratory values for a complete blood count, comprehensive metabolic panel with lipids, thyroid stimulation hormone level, and glycated hemoglobin within normal ranges. The renal ultrasound and echocardiogram were also normal. In addition, no laboratory test-supplement interactions were identified.

The patient was a competitive baseball player. He had regular preparticipation physical exams that, based on information contained in the referral request, reported 2 mildly elevated BP readings during the 2 years prior to referral. Copies of the medical record were not provided. The patient reported no medication use, either prescription or over-the-counter. The patient denied tobacco, alcohol, or illicit drug use (including steroids) and stated that he consumed 1 to 2 caffeinated beverages per day. The size(s) of the beverages and other specific information were not provided by the patient.

On physical exam, the patient's height measured 184.5 cm (90th percentile), weight 101.3 kg (99th percentile), with an increase of 7.8 kg over 15 months. The body mass index (BMI) was 29.8 kg/m². Blood pressure was 152/84 mm Hg in the right arm (manually) and 142/78 mm Hg in the left arm (manually), with a normal lower extremity BP. Both readings met criteria for Isolated Systolic Stage 1 hypertension in adults.¹¹ In accordance with his age, a systolic reading of 132 for this patient, based on gender and height-specific norms, placed him in the 90th to 95th percentile and met the criteria for pediatric hypertension.¹² The remainder of the physical exam was unremarkable.

On further questioning, the patient indicated that he had been engaged in a rigorous strength and conditioning program to enhance his prospects for a collegiate or professional baseball career. As part of his training regimen, he had been using dietary supplements. A thorough patient intake interview identified the use of 9 ingredients in supplements he reported consuming: ashwagandha, β -phenylethylamine, caffeine-based substances (coffee bean extract, guarana, kola nut, tea extracts, and yerba mate), creatine, and 1,3-dimethylamylamine (DMAA). Because these products were sold in vitamin shops, the patient did not consider reporting his supplement use important. Supplement use information was not contained in the referral information. He was reticent to reveal more information.

It was recommended that he discontinue use of dietary supplements and focus his weight training on submaximal, dynamic training¹³ with lower weights and higher repetitions per set. During the course of the clinic evaluation, he reported his intention was to continue the use of supplements; therefore, antihypertensive therapy was initiated in June with lisinopril 10 mg daily, the rationales being because the least intermittent reading were in excess of the 99th percentile and this was a highly competitive athlete. Lisinopril was selected for its known effectiveness, good safety and side effect profiles, and unlikeliness to limit his exercise tolerance. The adult starting dose of 10 mg was selected, and it was presumptively believed he was likely to be highly renin sensitive. Additionally, the patient was counseled on lifestyle modifications. On follow-up 1 month later (July), he reported intermittent compliance with the lisinopril. His BP had stabilized to 124/74 mm Hg. The patient indicated he did not like taking medicine and did not see a difference in home readings whether taking medication or not. After 1 month without supplements and without a maximal weight lifting regimen, his home readings were in the 120s/70s range. Considering patient compliance issues and systolic readings remaining at prehypertensive levels, the clinical plan, based on consultation with the PCP, was to discontinue lisinopril in 6 weeks (the end of September), 2 weeks prior to his follow-up appointment in the PPCC. The PCP was reluctant to stop the BP regimen altogether but thought a reasonable approach was to have a

washout period of 2 to 3 weeks prior to the planned follow-up clinic appointment. The patient was lost to follow-up after the July appointment. Criteria for the Naranjo Adverse Drug Reaction Probability Scale¹⁴ were applied and indicated a probable relationship (7 of 12) between the use of the supplements and elevated BP.

Discussion

In the United States, dietary supplements are not subjected to the strict regulatory approval process required by the FDA for prescription and over-the-counter medications.⁴ Because of this, double-blind placebo-controlled trials may be unavailable for clinician review and evaluation. A 2013 national representative survey sample (n = 1579) on the rationale for dietary supplement use was conducted. Respondents were 18 years or older, with 37.8% reporting use in the past 2 years and 13.9% reporting regular dietary supplement use. For the cohort of supplement users within the past 2 years, 40.8% stated improvement in “overall energy levels” as the rationale for use.¹⁵ In a study published in 2007 with 804 patients surveyed, 6% of these patients were at risk for potential dietary–drug interactions.¹⁶

Many consumers may not consider caffeine a dietary supplement. In terms of energy drink use, by 2006 the United States was identified as the worldwide leader in total sales volume.¹⁷ Analyzing results from self-report surveys, energy drink consumption was reported by approximately one third to one half of responders. Ages ranged from 10 years old to college students.¹⁸

The purpose of supplement use by our patient was to improve athletic performance. Products used for performance enhancement are often referred to as “ergogenic” agents. Dietary supplements are included in this category.

Caffeine is the most widely consumed behaviorally active substance in the world.¹⁹ The overuse of caffeine, whether acute or chronic, is termed caffeinism.¹⁹ The risk of developing clinically significant caffeinism becomes high when individual intake exceeds 500 mg/day. Energy drinks, beverages containing caffeine, taurine, vitamins, and dietary products have become increasingly popular, with young males the targeted users.¹⁷ Energy drinks, marketed to enhance alertness and/or energy, can be found under brand names such as Red Bull, Spike Shooter, and Full Throttle and contain varying amounts of caffeine.²⁰ The caffeine content can range from approximately 60 mg per container up to 400 mg.¹⁸

Growing in trendiness among adolescents and young adult athletes are caffeine-containing performance enhancers. The potential contribution that caffeine adds to performance enhancers is a possible ability to maintain aerobic breakdown of carbohydrates for extended periods of time during exercise.^{21,22} Serious problems associated with caffeine use typically require extremely high doses. The amount of caffeine needed to cause death in an average

male is 5 to 10 g.¹⁹ Problems may arise when high doses of caffeine are consumed by individuals with cardiac conditions, sometimes unknown to the patient, for which stimulants are contraindicated. Hypertrophic cardiomyopathy, the most common genetic cardiomyopathy in children and young adults, is of particular concern because of the risk of hypertension, syncope, arrhythmias, and sudden death.²³ In a study of coffee and caffeine intake, participants (n = 12, all women) experienced increases in HR following coffee intake and an increase in diastolic BP when encapsulated caffeine was ingested. The amount of caffeine in the coffee was approximately 130 mg, and the capsule contained 134 mg caffeine.²⁴ As a dose-dependent central nervous system (CNS) stimulant, caffeine increases the HR and force of contraction.¹⁹ This increased work load on the heart can be harmful for individuals with preexisting cardiac function or arrhythmias. Confounding these risk factors is the practice of consuming more than one performance enhancer or energy drink simultaneously, bringing individual doses of caffeine up to these very high, often dangerous, doses.

One example of consequences of caffeine ingestion is that of a 14-year-old female who ingested two 24-ounce energy drinks, a total of 480 mg caffeine, in 1 day. The following day, she went into cardiac arrest and died 6 days later. Her physician felt her preexisting heart condition, mitral valve prolapse, posed little health risk in the absence of caffeine.²⁵

Unbeknownst to many consumers, natural products containing caffeine or caffeine-like ingredients may be found in performance-enhancement supplements. While not always labeled as such, green and black tea, kola nut, guarana, coffee bean extract, and yerba mate are common caffeine-containing ingredients found in supplements marketed as performance enhancers.

Guarana, derived from *Paullinia cupana* seeds, contains “relatively large amounts” of caffeine, estimated to be between 2.5% and 7%. Reported adverse CV effects include heart palpitations, irritability, and anxiety.^{26,27} Guarana, however, is infrequently used as a single ingredient.²⁷ It is often used in combination with alkaloids with sympathomimetic properties, such as synephrine, found in bitter orange (*Citrus aurantium*). The potential for adverse CV-related consequences with the combination of bitter orange extract and guarana was reported in one study.²⁶ If used in combination with caffeine or other agents with similar properties, these CV effects may be enhanced. However, in an additional randomized, placebo-controlled crossover, double-blinded study (n = 23), CV effects were not reported with the combination of caffeine, bitter orange extract, and green tea extract. It should be noted that this was an industry-sponsored trial where the overall participant age range was 24.5 ± 7.4 with a BMI range of 26.6 ± 3.8 .²⁸

Synephrine, an alkaloid that is present naturally in plants, is also available as a synthetic drug. A component of

performance enhancers, it may be listed as “Bitter Orange,” or *C aurantium*, on product labels. Synephrine was introduced into the nutritional supplement market to replace ephedra, which was banned by the FDA in 2004 because of a consistent link to increased HR and adverse events. One hundred and forty adverse events that occurred between 1997 and 1999 were evaluated in 2000. Sixty-two percent of these adverse events were possibly or definitely linked to ephedra.²⁹ Structurally similar to ephedrine, synephrine has been associated with suspected adverse CV events including myocardial infarctions and ischemic strokes.³⁰

Kola nut is the fruit derived from the evergreen Kola trees that are native to the tropical rainforests of Africa. Kola nut contains approximately 2% to 3.5% of a xanthine similar to caffeine and 1.0% to 2.5% of theobromine as active agents. Both the xanthine and the theobromine mimic the pharmacological properties of caffeine, including stimulation of the CNS and respiratory system. Cardiac stimulation, coronary dilation, smooth muscle relaxation, and diuresis also may occur.³¹

Yerba mate, also called “mate,” is a xanthine derivative containing caffeine, theobromine, and theophylline. The caffeine content in yerba mate varies between 0.7% and 1.7% of dry weight, although variations in processing influence the amount of bioactive caffeine present in each product.³² A plant from the subtropical region of South America, yerba mate is one of the main sources of caffeine in some South American regions. It, too, possesses CNS stimulant effects.³³

Information on tea extracts as an additional source of caffeine was reviewed. Variations in tea occur because of differences in growing conditions, fermentation processes, and processing. Both caffeine and L-theanine occur naturally in tea. In a study of young adults ($n = 44$) consuming a beverage with the combination of these ingredients (97 mg L-theanine, 40 mg caffeine), systolic BP was slightly elevated.³⁴ Rogers et al found theanine attenuated BP effects secondary to caffeine intake.³⁵ The processing methods used to create green tea extracts account for the high amounts of caffeine and catechin polyphenols often associated with this variety of tea. A synergistic effect is suggested with caffeine.³⁶ Oolong tea, a traditional Chinese tea, contains (or can be metabolized into) caffeine, theophylline, and theobromine.³⁷ In a study that compared the caffeine content of 77 different teas, the investigators found “no observable trend in caffeine concentration due to the variety of tea.”³⁸ These findings accentuate the difficulty of assessing the caffeine content of various performance-enhancement supplements by simply looking at the ingredients listed on a product label.

Green coffee bean extract is created from coffee beans that have not yet been roasted. Instead, the beans are soaked and concentrated to form an extract. When compared to roasted coffee beans, green coffee beans have a higher level of chlorogenic acid, a chemical with a possible link to health benefits for heart disease, weight loss, and diabetes.

In a randomized, placebo-controlled crossover study evaluating the efficacy and safety of a green coffee bean extract in overweight subjects, significant reductions were observed in body weight, BMI, and percent body fat. Additionally, insignificant decreases in HR and systolic and diastolic BP were observed. The mechanism of action for these effects is unknown but is thought to be related to the chlorogenic acid and its metabolite, caffeic acid.³⁹ Perhaps counterintuitive to the average consumer’s perception, green coffee bean extract has a relatively low amount of caffeine when compared to roasted coffee beans.

β -Phenylethylamine, an additional supplement ingredient reviewed, is an endogenous brain amine that has been characterized as an endogenous amphetamine.⁴⁰ In a series of animal experiments, the CV effects of increased mean aortic BP, total peripheral vascular resistance, and left ventricular contractility were demonstrated. The authors concluded that β -phenylethylamine showed positive inotropic effects as well as vasoconstriction, potentially via norepinephrine release.⁴¹ These effects also may be present with supplement use, although dose–effect relationship information was not found. The effects of caffeine–phenylethylamine combinations were reviewed as well. Animal-based research indicated that this combination was associated with amphetamine-response cueing and suggested that an additive effect may be present.⁴² Specific information on CV effects was not reported in these animal studies, although, as mentioned earlier, increased HR is well documented as one of the effects of caffeine use.

Ashwagandha (*Withania somnifera*, Dunal), a commonly used herb in ayurvedic medicine in India, has been investigated for its effects on the endocrine system, the cardiopulmonary system, and the CNS.⁴³ Performance enhancement has not been proven. Additionally, there are few systematic toxicity studies available for this chemical and concerns about the poor quality of the studies that have been completed.⁴³

Creatine effects were also reviewed. Creatine is phosphorylated to phosphocreatine that provides energy to the muscles. Phosphocreatine provides muscle with the major energy source during the first 10 seconds of anaerobic activity and is, therefore, considered the limiting factor in short, high-intensity activities.⁶ Short-term oral creatine supplement use on exercise performance, BP, and renal function was evaluated. In a small ($n = 35$) placebo-controlled study of healthy, active duty, military personnel (20 men and 15 women; age range = 22–36 years) either 20 g/day of creatine or taurine (placebo arm) was used for 7 days. No significant differences were found in 2-minute push-up counts between the groups ($P = .437$; power = .98). The authors did report a significant increase in serum creatinine levels ($P < .001$) for the creatine group compared to the placebo group with no adverse changes in BP observed. They concluded short-term creatine supplement use appeared to be safe but did

not enhance push-up performance.⁴⁴ They also suggested caution with use of creatine supplement doses greater than 3 to 5 g/day in persons at risk for renal impairment, such as those with preexisting hypertension and/or diabetes.⁴⁵

Methylhexanamine (DMAA) has been marketed as a dietary supplement and is often used in combination with other ingredients, including caffeine.⁴⁶ One small study (n = 10) of healthy volunteers ingesting a combination of (a) caffeine 250 mg and DMAA 50 mg or (b) caffeine 250 mg and DMAA 75 mg found elevated BP in a dose-related manner. Heart rate was not increased.⁴¹ Following FDA receipt of 42 adverse event reports on products containing DMAA, in April 2012, the FDA sent warning letters to companies marketing products containing DMAA noting that it is known to narrow blood vessels and arteries, which can elevate BP and lead to CV events.⁴⁷

Increased use of supplements to enhance performance presents a number of problems for both clinicians and patients. Obstacles that should be addressed include, but are not limited to, patient misperceptions of safety, inclusion of similar ingredients with often synergistic adverse effects within one product, CV-related adverse effects that are sometimes life-threatening, and the lack of research or evidence-based studies regarding safety and efficacy. Thorough medication histories specifically covering possible use of supplements and product counseling can help identify problems associated with use. Work to improve health literacy among adolescents and young adults should also be a consideration among health professionals.

Conclusion

Clinicians may encounter patients who fail to report or under-report dietary and/or performance enhancement products that they may use on an episodic or chronic basis. Requesting patients to list current medications may not elicit all products used. Practitioners are encouraged to thoroughly interview the patient and ask specific questions regarding over-the-counter products, dietary supplements for weight loss or performance enhancement, energy drinks, or products that may be used to address a chronic or perceived health need. Inquiring about product or supplement use within the past 24 hours, several days, or longer may assist in determining if additional intervention or follow-up is needed to identify possible explanations related to the presenting complaint.

Authors' Note

This case report was accepted for a poster presentation at the 2013 annual meeting of the College of Psychiatric and Neurologic Pharmacists; April 21-24, 2013; Colorado Springs, CO.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Bent S, Tiedt TN, Odden MC, Shlipak MG. The relative safety of ephedra compared with other herbal products. *Ann Intern Med.* 2003;138:468-471.
2. Akay S, Ozdemir M. Acute coronary syndrome presenting after pseudoephedrine use and regression with beta-blocker therapy. *Can J Cardiol.* 2008;24:e86-e88.
3. Samenuk D, Link MS, Homoud MK, et al. Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc.* 2002;77:12-16.
4. Food and Drug Administration. Regulatory Information: Dietary Supplement Health and Education Act of 1994. <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148003.htm#sec4>. Accessed August 8, 2013.
5. Kroll DJ. ASHP statement on the use of dietary supplements. *Am J Health Syst Pharm.* 2004;61:1707-1711.
6. Calfee R, Fadale P. Popular ergogenic drugs and supplements in young athletes. *Pediatrics.* 2006;117:e577-e589.
7. Jenkinson DM, Harbert AJ. Supplements and sports. *Am Fam Physician.* 2008;78:1039-1046.
8. Williams MH. Dietary supplements and sports performance: introduction and vitamins. *J Int Soc Sports Nutr.* 2004;1:1-6.
9. Bell A, Dorsch KD, McCreary DR, Hovey R. A look at nutritional supplement use in adolescents. *J Adolesc Health.* 2004;34:508-516.
10. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program. *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* (NIH Publication No. 05-5268). Bethesda, MD: National Heart, Lung, and Blood Institute. www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf. Revised May 8, 2005. Accessed August 8, 2013.
11. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206-1252.
12. Graham L. AAP updates policy statement on athletic participation by children and adolescents with systemic hypertension. *Am Fam Physician.* 2010;82:1285.
13. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation.* 2001;104:1694-1740.
14. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239-245.
15. Blendon RJ, Benson JM, Botta MD, Weldon KJ. Users' views of dietary supplements. *JAMA Intern Med.* 2013;173:74-76.
16. Bush TM, Rayburn KS, Holloway SW, et al. Adverse interactions between herbal and dietary substances and prescription

- medications: a clinical survey. *Altern Ther Health Med*. 2007;13:30-35.
17. Reissig CJ, Strain EC, Griffiths RR. Caffeinated energy drinks—a growing problem. *Drug Alcohol Depend*. 2009;99:1-10.
 18. Seifert SM, Schaechter JL, Hershorin ER, Lipshultz SE. Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics*. 2011;127:511-528.
 19. Doering PL, Li RM. Substance-related disorders: alcohol, nicotine, and caffeine (Chapter 75). In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill; 2011. <http://www.accesspharmacy.com/content.aspx?aID=7987625>. Accessed August 8, 2013.
 20. Torpy JM, Livingston EH. *JAMA* patient page. Energy drinks. *JAMA*. 2013;309:297.
 21. Juhn MS. Ergogenic aids in aerobic activity. *Curr Sports Med Rep*. 2002;1:233-238.
 22. Acker-Hewitt TL, Shafer BM, Saunders MJ, Goh Q, Luden ND. Independent and combined effects of carbohydrate and caffeine ingestion on aerobic cycling performance in the fed state. *Appl Physiol Nutr Metab*. 2012;37:276-283.
 23. Colan SD, Lipshultz SE, Lowe AM, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *Circulation*. 2007;115:773-781.
 24. McMullen MK, Whitehouse JM, Shine G, Whitton PA, Towell A. The immediate and short-term chemosensory impacts of coffee and caffeine on cardiovascular activity. *Food Funct*. 2011;2:547-554.
 25. TODAY Health. Teen girl dies of “caffeine toxicity” after downing 2 energy drinks. <http://www.today.com/health/teen-girl-dies-caffeine-toxicity-after-downing-2-energy-drinks-506441>. March 21, 2012. Accessed August 19, 2013.
 26. Hess AM, Sullivan DL. Potential for toxicity with use of bitter orange extract and guarana for weight loss. *Ann Pharmacother*. 2005;39:574-575.
 27. Kennedy DO, Haskell CF, Wesnes KA, Scholey AB. Improved cognitive performance in human volunteers following administration of guarana (*Paullinia cupana*) extract: comparison and interaction with Panax ginseng. *Pharmacol Biochem Behav*. 2004;79:401-411.
 28. Seifert JG, Nelson A, Devonish J, Burke ER, Stohs SJ. Effect of acute administration of an herbal preparation on blood pressure and heart rate in humans. *Int J Med Sci*. 2011;8:192-197.
 29. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med*. 2000;343:1833-1838.
 30. Bouchard NC, Howland MA, Greller HA, Hoffman RS, Nelson LS. Ischemic stroke associated with use of an ephedra-free dietary supplement containing synephrine. *Mayo Clin Proc*. 2005;80:541-545.
 31. Shapiro K. *Natural Products: A Case-Based Approach for Health Care Professionals*. Washington, DC: American Pharmacists Association; 2006:196-198.
 32. Bastos DHM, Oliveira DM, Matsumoto RLT, Carvalho PO, Ribeiro ML. Yerba mate: pharmacological properties, research and biotechnology. *Med Aromat Plant Sci Biotechnol*. 2007;1:37-46.
 33. Heck CI, de Mejia EG. Yerba Mate Tea (*Ilex paraguariensis*): a comprehensive review on chemistry, health implications, and technological considerations. *J Food Sci*. 2007;72:R138-R151.
 34. Giesbrecht T, Rycroft JA, Rowson MJ, De Bruin EA. The combination of L-theanine and caffeine improves cognitive performance and increases subjective alertness. *Nutr Neurosci*. 2010;13:283-290.
 35. Rogers PJ, Smith JE, Heatherley SV, Pleydell-Pearce CW. Time for tea: mood, blood pressure and cognitive performance effects of caffeine and theanine administered alone and together. *Psychopharmacology (Berl)*. 2008;195:569-577.
 36. Dulloo AG, Seydoux J, Girardier L, Chantre P, Vandermader J. Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord*. 2000;24:252-258.
 37. Ashihara H, Gillies FM, Crozier A. Metabolism of caffeine and related purine alkaloids in leaves of tea (*Camellia sinensis* L.). *Plant Cell Physiol*. 1997;38:413-419.
 38. Chin JM, Merves ML, Goldberger BA, Sampson-Cone A, Cone EJ. Caffeine content of brewed teas. *J Anal Toxicol*. 2008;32:702-704.
 39. Vinson JA, Burnham BR, Nagendran MV. Randomized, double-blind, placebo-controlled, linear dose, crossover study to evaluate the efficacy and safety of a green coffee bean extract in overweight subjects. *Diabetes Metab Syndr Obes*. 2012;5:21-27.
 40. Greenshaw AJ. beta-Phenylethylamine and reinforcement. *Prog Neuropsychopharmacol Biol Psychiatry*. 1984;8:615-620.
 41. Liang CS, Sprecher D. Cardiovascular actions of beta-phenylethylamine. *Am J Physiol*. 1979;236:H592-H595.
 42. Holloway FA, Michaelis RC, Huerta PL. Caffeine-phenylethylamine combinations mimic the amphetamine discriminative cue. *Life Sci*. 1985;36:723-730.
 43. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): a review. *Altern Med Rev*. 2000;5:334-346.
 44. Armentano MJ, Brenner AK, Hedman TL, et al. The effect and safety of short-term creatine supplementation on performance of push-ups. *Mil Med*. 2007;172:312-317.
 45. Kim HJ, Kim CK, Carpentier A, Poortmans JR. Studies on the safety of creatine supplementation. *Amino Acids*. 2011;40:1409-1418.
 46. Bloomer RJ, Harvey IC, Farney TM, Bell ZW, Canale RE. Effects of 1,3-dimethylamylamine and caffeine alone or in combination on heart rate and blood pressure in healthy men and women. *Phys Sportsmed*. 2011;39:111-120.
 47. Food and Drug Administration. FDA challenges marketing of DMAA products for lack of safety evidence. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302133.htm>. Accessed August 8, 2013.