

# Energy Drinks: The New Eye-Opener For Adolescents

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The availability of caffeine-containing energy beverages, combined with aggressive marketing and urban legend, has promoted their widespread use, particularly among adolescents. The caffeine content of these products is presently unregulated. Rapid growth in the consumption of these supplements has resulted in increasing reports of caffeine poisoning. This article provides a review of caffeine's pharmacokinetics and describes the clinical manifestations and management of caffeine toxicity. Suggestions for future research are also offered.

Clin Ped Emerg Med 9:35-42 © 2008 Published by Elsevier Inc.

**KEYWORDS** energy drink, adolescents, caffeine, guarana, taurine, carnitine, withdrawal

By promising immediate energy and decreased fatigue, energy drink brands have created a \$3.5 billion yearly industry [1]. Aggressive marketing campaigns featuring celebrities and athletes target adolescents and young adults. A culture of blogs, urban legends, and “underground” chic has further increased their appeal. In 2006, more than 30% of adolescents reported using energy drinks, an increase of more than 3 million teens in 3 years [2]. The wide availability of the beverages, from grocery stores, convenience stores and school bookstores makes them readily accessible for purchase by adolescents, even though the products often retail for more than twice the price of “traditional” soft drinks. Although the media has clearly identified the trend toward increasing adolescent energy drink use, little medical literature describes this phenomenon. The goals of this article include identifying major ingredients of energy drinks, as well as a discussion of the pharmacology and toxicology of caffeine.

## Caffeine

The key ingredient in most energy drinks is caffeine, supplemented by a wide variety of amino acids, B vitamins, and herbal supplements [3]. Caffeine is found in a wide variety of beverages and pharmaceuticals, and has been called the most commonly used psychoactive substance in the world [4]. Major sources in the North American diet include coffee and tea for adults, and carbonated sodas, energy drinks, and chocolate for children and adolescents. A range of caffeine concentrations are found in brewed coffee (56-100 mg/100 mL), instant coffee and tea (20-73 mg/100 mL), and colas (9-19 mg/100 mL) [5]. Smaller amounts can be found in chocolate (5-20 mg/100 g) and cocoa (7 mg/5 oz cup) [6]. In addition, over-the-counter medications such as NoDoz and Midol contain between 100 and 200 mg of caffeine per tablet [6].

Average caffeine consumption in the United States and Canada ranges from approximately 1 mg/kg per day in children to 3 mg/kg per day in adults [7,8]. Intake has been known to be much higher in certain European countries such as Denmark, where consumption reaches 7 mg/kg per day [3]. Canadian recommendations for daily caffeine are no more than 85 mg for children aged 10 to 12 years, no more than 300 mg in women of childbearing age, and no more than 400 to 450 mg in the remaining adult population [9].

The Food and Drug Administration has limited the caffeine content of sodas to 65 mg per 12 oz (18 mg/100 mL); however, energy drinks are not currently subject

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**Table 1** Energy drink products with caffeine content, selected additional ingredients and calories per container.

Product	Caffeine content	Container size	Caffeine per container	Also Contains	Calories per container
Full Throttle (Original)	300 mg/L	16 ounces	144 mg	Guarana, taurine, carnitine, ginseng	200
Monster (Original)	**	16 ounces	**	Guarana, taurine, carnitine, ginseng, inositol, glucuronolactone	200
Mountain Dew Amp Energy	295.8 mg/L	8.4 ounces	71 mg	Guarana, taurine, ginseng	120
Diet Pepsi Max	194.5 mg/L	12 ounces	46 mg	Ginseng	0
Red Bull	320 mg/L	8.4 ounces	80 mg	Taurine, inositol, glucuronolactone	110
Rockstar Energy Drink	333.3 mg/L	16 ounces	160 mg	Guarana, taurine, carnitine, ginseng, inositol, ginko, milk thistle	280
SoBe No Fear	362.5 mg/L	16 ounces	174 mg	Guarana, taurine, carnitine, ginseng, inositol, grape seed extract	260
Coffee (Brewed)	420 mg/L	8 ounces	100 mg	N/A	0-5
Coca-Cola	95 mg/L	8 ounces	34 mg	N/A	97

\* All product information derived from manufacturer websites or product label \*\* Listed as "energy blend" – caffeine content unknown.

to the same Food and Drug Administration regulations [10]. Energy drinks such as Red Bull and SoBe No Fear often contain between 14 and 31 mg of caffeine per 100 mL [10]. Although their caffeine concentration (in milligrams per milliliter) may be similar to coffee, energy drinks are often packaged in significantly higher volumes, resulting in increased caffeine intake. SoBe No Fear contains 141 mg of caffeine per 16 oz (473 mL) bottle, the equivalent of 1 1/2 cups of brewed coffee, or 4 cans of regular Coca-Cola (Table 1).

## Guarana and Other Caffeine-Containing Ingredients

Guarana is derived from the seeds of *Paullinia cupana*, a South American plant known for its stimulant properties. Guarana contains large amounts of caffeine (4%-8%), theobromine, theophylline, and a high concentration of tannins [11]. Although caffeine concentration may vary widely in guarana preparations, 3 to 5 g of guarana provides approximately 250 mg of caffeine [12]. The effects of guarana ingestion are necessarily similar to caffeine; however, the duration of action may be much longer with guarana because of the presence of saponins and tannins [13].

Besides guarana, other caffeine-containing herbal ingredients found in energy drinks include kola nut, tea, yerba mate, and cocoa [14]. Inclusion of these ingredients does not necessitate caffeine labeling, and their presence may not be included in calculations of caffeine content. They nonetheless contribute to the overall caffeine content of a beverage.

## Taurine

Taurine, the most abundant amino acid in animal tissue, is produced by the metabolism of methionine and cysteine

[15]. Taurine plays a role in multiple metabolic processes, ranging from osmoregulation to antioxidation to glycolysis [16]. Dietary sources include meat, dairy products, and fish; an average diet provides 20 to 200 mg of taurine daily [16]. In addition, the belief that taurine is essential during neonatal development led to its supplementation of infant formula in the early 1980s, even though this practice has never been rigorously studied [17]. Taurine is an essential amino acid in cats where its deficiency leads to retinal degeneration [18]. As a dietary supplement, taurine is marketed for promotion of biliary health, eye health, and prevention and treatment of congestive heart failure. Little is known regarding the effects of high-dose or long-term taurine use in children and adolescents.

## Ginseng

Ginseng, or *Panax ginseng*, is an East Asian herb that has been used for centuries to improve memory and stamina [19]. Although little medical literature supports these uses, ginseng has been incorporated into a variety of energy drinks. Although adverse effects associated with ginseng use tend to be mild, more serious complications have been reported, including diarrhea, vaginal bleeding, severe headache, and Stevens-Johnson syndrome [20,21]. Many of these effects may be attributed to contaminants; agranulocytosis in 4 patients taking ginseng had been linked to unreported phenylbutazone and aminopyrine contained in the preparation [22]. Herb-drug interactions in ginseng use include decreased international normalized ratio when concomitantly used with warfarin and the theoretical risk of hypoglycemia when used with antidiabetic agents [23,24]. A ginseng abuse syndrome has also been reported, characterized by morning diarrhea, hypertension, rashes, insomnia, and irritability [25]. Little is known regarding the effects of ginseng in children and adolescents [26].

## Carnitine

Carnitine is an amino acid derivative that plays a vital role in the  $\beta$ -oxidation of fatty acids. Carnitine is found in significant quantities in the average diet, but both congenital and acquired deficiency states exist, which are often characterized by profound muscle weakness [26,27]. Supplementation of the active isomer (levocarnitine) has been reported for a number of illnesses, including primary carnitine deficiency, end-stage renal disease, valproate toxicity, and dementia. Adverse effects described in carnitine supplementation include nausea, vomiting, abdominal pain, and diarrhea [28]. In patients with a known seizure disorder, an increase in seizure frequency has been described with carnitine use; in addition, de novo seizures have been reported with carnitine supplementation [29]. One study described no significant change in muscle carnitine stores of athletes during strenuous exercise, whereas others demonstrate no increase in exercise tolerance with carnitine supplementation [30-32]. However, energy drink and bodybuilding supplement manufacturers continue to promote carnitine as a means to burn fat and increase stamina [33].

## Pharmacokinetics of Caffeine

Caffeine, or 1,3,7-trimethylxanthine, is rapidly and completely absorbed after oral ingestion, with nearly 100% bioavailability [34]. Ingested caffeine reaches peak plasma concentration within approximately 30 to 120 minutes, depending on gastric contents. Caffeine is 10% to 35% protein bound and is rapidly redistributed from blood to all tissues [35]. It readily crosses the blood-brain barrier and placenta, and can be found in breast milk [36,37]. Its volume of distribution is 0.61 L/kg [38].

Caffeine is metabolized chiefly in the liver via cytochrome P-450 isozyme CYP 1A2 [34]. In adults, the major primary metabolite is 1,7-dimethylxanthine (paraxanthine); other primary metabolites include 3,7-dimethylxanthine (theobromine) and 1,3-dimethylxanthine (theophylline) [39]. These dimethylxanthines are physiologically active metabolites that likely contribute to the clinical effects of caffeine [6]. Repeated demethylation followed by hydroxylation leads to the final metabolites of 1-methylxanthine and 1-methyluric acid, respectively, leaving only 1% to 5% of ingested caffeine to be excreted unchanged in the urine [34].

Caffeine elimination follows Michaelis-Menten kinetics with an elimination half-life ranging from 3 to 6 hours in healthy individuals [5]. Multiple factors, including age, sex, and concomitant exposures, can affect time to elimination. In neonates, the elimination half-life is extremely prolonged, nearing 100 hours, but approaches adult ranges by 6 months of age [40]. The half life has also been reported to be 20% to 30% shorter in females but is prolonged 2- to 3-fold during the third trimester

of pregnancy [41-43]. The presence of hepatic disease or CYP 1A2 inhibitors (such as estrogen-containing oral contraceptives, disulfiram, and cimetidine) can prolong methylxanthine elimination [44,45]. In contrast, cigarette smoking results in a 2-fold increase in the rate of caffeine elimination; smoking cessation transiently leads to more than a 200% increase in serum caffeine levels [5,6,46].

## Pharmacology

As a member of the methylxanthine family, caffeine is a structural analog of adenosine and a functional adenosine receptor antagonist [47]. Antagonism at presynaptic alpha-1 receptors leads to an increase in peripheral catecholamine release with subsequent activation of postsynaptic  $\beta$ -adrenergic receptors [48]. The resulting norepinephrine, dopamine, and serotonin release in the brain reverses the centrally mediated adenosine effects of sedation and anticonvulsant activity [6]. Caffeine also inhibits phosphodiesterase, which breaks down intracellular cyclic adenosine monophosphate, a postsynaptic second messenger responsible for  $\beta$ -adrenergic stimulation. This also leads to increased adrenergic tone in the peripheral and central nervous systems [49].

## Clinical Manifestations, Toxicity

In 2005, more than 4600 calls were made to the American Association of Poison Control Centers (Washington, DC) for questions regarding caffeine. Of those, 2600 involved patients younger than 19 years, and 2345 required treatment in a health care facility. There were no deaths attributed to caffeine in 2004 or 2005 [50,51]. There are no available data on the proportion of these calls credited to energy drink use.

Most caffeine intoxications are mild; adverse effects, such as nausea and palpitations, begin at low doses and serve to prevent further intake. The quantities of caffeine contained in single servings of energy drinks are not generally high enough to produce severe symptoms; however, at least one death has already been attributed to energy drink use [52]. Patients with preexisting cardiac pathology or a history of seizures may be at greater risk. In addition, the popularity of energy drinks has led to increased marketing of caffeine supplements in pill form (ie, Venom Hyperdrive). The simultaneous and excessive use of these products may lead to serious adverse effects.

The primary clinical manifestations of caffeine exposure and overdose result from the effects of adrenergic stimulation. In small doses, patients experience the desired effects of heightened arousal and improved mood and cognition. Caffeine-containing energy drinks have been demonstrated to improve reaction times, increase aerobic and anaerobic endurance, and decrease driver sleepiness

[53-55]. The additive effects of other stimulant ingredients, such as taurine, require further study [55].

However, even in low doses (>3 mg/kg per day), caffeine can have undesirable adverse effects, including headache [26]. In one study of children and adolescents with daily headaches and excessive soda consumption (>1.5 L daily; average caffeine intake, 192.88 mg/d), 33 of 36 subjects experienced complete resolution of headache with caffeine abstinence. The remaining 3 subjects described a marked decrease in headache frequency [56]. These headaches may be attributed to caffeine itself or caffeine withdrawal [57].

Larger caffeine exposures are associated with increased adverse effects, including nausea, irritability, palpitations, and insomnia. Caffeine has been demonstrated to increase the number of awakenings during sleep, sleep latency (the time to onset of sleep), and sleep interruptions [58,59]. The magnitude and long-term effects of caffeine-induced insomnia in children and adolescents are unknown. After accidental or intentional overdose, one of the initial symptoms is often profound emesis. Caffeine-induced vomiting may be refractory to treatment with traditional antiemetics. Patients may also experience gastroesophageal reflux symptoms and abdominal pain.

Despite its large therapeutic window, massive overdoses of caffeine may result in life-threatening toxicity. The lethal dose of caffeine has been described as 5 to 10 g in healthy adults; however, this number may be lower in individuals with preexisting cardiac or seizure disorders [60]. Multiple vital sign abnormalities have been described in the setting of caffeine toxicity, including hyperthermia, tachypnea, tachycardia, and blood pressure lability [61,62]. Hyperthermia results from increased adrenergic tone and subsequent metabolic demands, whereas tachypnea is caused by caffeine stimulation of medullary respiratory centers. This effect forms the basis of caffeine therapy for neonatal apnea.

## Cardiovascular

In the setting of caffeine toxicity, sinus tachycardia is almost always present, and supraventricular tachycardia has been commonly described; the latter may result from adenosine antagonism [63]. Several tachyarrhythmias, including atrial and ventricular ectopy, atrial fibrillation, ventricular tachycardia, and ventricular fibrillation, have been described in caffeine-poisoned patients [52,64-67]. Ventricular fibrillation refractory to resuscitation attempts was reported in one patient with a history of mitral valve prolapse; underlying structural disease may increase risk of dysrhythmia [52]. Excessive caffeine use has also been associated with one case of myocardial infarction in a young woman with no cardiac risk factors. The authors postulated that coronary artery vasospasm is the mechanism for ischemia [66,68]. The link between long-term caffeine use and myocardial infarction remains controversial; however, one recent study describes a close temporal association between coffee drinking and myocardial infarction.

## Central Nervous System

Central nervous system toxicity may initially manifest with irritability that progresses to lethargy and coma. Myoclonic jerks, clonus, hallucinations, and opisthotonos have been described in the setting of acute caffeine toxicity [69-72]. Caffeine-induced seizures may occur at low doses in susceptible individuals or as a result of overdose. One case series of 4 adults with new-onset seizures questioned an association with heavy energy drink use [64]. The consumed ingredients shared by these 4 patients included caffeine, guarana, taurine, inositol, carnitine, and vitamins. Each of these patients reported no further seizure activity after abstinence from energy drink use. Cerebral edema and markedly elevated intracranial pressures have also been reported [71].

## Renal

Caffeine is a well-known diuretic; however, long-term use may result in diminished diuretic effect [73]. Regardless, energy drinks should not be mistaken for sports drinks, whose primary purpose is rehydration in the setting of exercise or fluid loss [26]. Caffeine use also leads to hypokalemia, which may be profound (<2.5 mmol/L). The proposed mechanisms for caffeine-induced hypokalemia include adrenergic  $\beta_2$ -receptor agonism and diuresis [69].

## Musculoskeletal

Rhabdomyolysis is an unusual complication of caffeine toxicity that has been reported after massive overdose. One proposed mechanism for muscle injury is tetanic contraction of skeletal muscle, resulting from sequestration of intracellular calcium [74]. Caffeine-induced rhabdomyolysis has produced serum creatine phosphokinase levels of more than 28 000 IU/L and long-term renal impairment [74,75]. In addition, hypokalemic paralysis has been reported in the setting of excessive caffeine use [76]. Hypokalemia itself may precipitate or worsen rhabdomyolysis.

## Laboratory Findings

Hypokalemia is the sine qua non laboratory abnormality in caffeine intoxication. The presentation of vomiting, tachycardia, and hypokalemia should prompt a search for methylxanthine or other  $\beta$ -agonist exposure (ie, albuterol, clenbuterol). Hyperglycemia is common in caffeine toxicity, secondary to increased lipolysis, glycogenolysis, and gluconeogenesis [77]. Leukocytosis, mild metabolic acidosis, ketonuria, hypophosphatemia, and hypocalcemia have also been described [61].

Qualitative testing for caffeine has limited use; the substance is nearly ubiquitous. Quantitative analysis of serum caffeine levels is readily performed at most institutions that care for neonates; however, the magnitude

of caffeine toxicity is determined clinically, and serum levels in acute intoxication have little use but may be useful in confirming the diagnosis.

## Management

Treatment of patients with caffeine toxicity must begin with careful and immediate assessment of the patient's airway, breathing, and circulation. Intravenous access must be established and noninvasive monitoring devices used. Oxygen should be administered if necessary, and a fingerstick glucose level should be rapidly obtained. Serum electrolytes, including calcium and phosphorus, should be obtained. Serial electrocardiograms are indicated in any patient with palpitations, chest pain, or vital sign abnormalities.

Although activated charcoal does adsorb caffeine, patients demonstrating caffeine toxicity after energy drink ingestion often present to care more than 1 hour after ingestion, because they experience unexpected symptoms. Given the rapid absorption of caffeine, there will be little benefit to administration of single-dose charcoal in clinical settings. Multiple-dose activated charcoal has proven to be effective in enhancing the elimination of theophylline [78,79]. The structural and pharmacologic similarities of caffeine and theophylline provide for a theoretical benefit in caffeine toxicity; however, rigorous support for this practice has not yet been demonstrated. In any event, multiple-dose activated charcoal would be difficult to administer because of the repeated emesis that is common in methylxanthine toxicity. Contraindications to activated charcoal include seizures, emesis, and the potential for aspiration due to lack of definitive airway maintenance [80,81].

Other methods of enhanced elimination, such as charcoal hemoperfusion, hemodialysis, and exchange transfusion, have been used in the treatment of caffeine toxicity. Charcoal hemoperfusion has historically been the most effective method for enhanced elimination of caffeine and other methylxanthines, decreasing the half-life to approximately 2 hours [82,83]. However, charcoal hemoperfusion is no longer widely available. Hemodialysis has been used with success and carries the additional benefits of availability, familiarity, and safety [71,84]. Patients who are considered too unstable for hemodialysis, such as those with hypotension, may benefit from continuous venovenous hemofiltration; however, its use has not yet been reported in methylxanthine toxicity. Other modalities, such as peritoneal dialysis and exchange transfusion, have been used with success in methylxanthine toxicity but have limited applicability [70,71].

## Cardiovascular

Hypotension resulting from adrenergic  $\beta_2$ -receptor-mediated vasodilatation should initially be treated with crystalloid resuscitation using either 0.9% sodium chloride solution or lactated Ringer's solution in serial

intravenous boluses of 20 mL/kg. Refractory hypotension is an indication for vasopressors, such as phenylephrine or norepinephrine, which lack  $\beta_2$ -adrenergic agonist activity. Vasopressin use has also been reported [84]. If hypotension persists,  $\beta$ -adrenergic antagonists such as esmolol, propranolol, and metoprolol have been found, albeit counterintuitively, to be a successful treatment modality for hypotension by overcoming  $\beta_2$ -adrenergic agonism [85,86].

Benzodiazepines may be used in the treatment of supraventricular dysrhythmias; by decreasing peripheral catecholamine release and concomitant postsynaptic  $\beta$ -receptor stimulation, benzodiazepines may also facilitate rate control in sinus tachycardia [63]. Calcium channel blockers and  $\beta$ -adrenergic antagonists are also effective in treating these tachyarrhythmias [86,87]. Management of ventricular dysrhythmias centers on the use of lidocaine and amiodarone for stable monomorphic ventricular tachycardias, with sotalol and procainamide as potential treatment alternatives [62,88]. Comparative studies performed on the efficacy of various antiarrhythmics in caffeine poisoning have found  $\beta$ -adrenergic antagonists, such as esmolol and propranolol, as well as calcium channel blockers, such as verapamil, to be effective in abolishing potentially lethal ventricular dysrhythmias associated with caffeine poisoning [52,89]. Any unstable patient manifesting a malignant dysrhythmia should be treated via traditional advanced cardiac life support protocols.

Metabolic derangements, such as hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia, should be corrected [90]. In the presence of electrocardiogram abnormalities, such as T-wave deflections or QTc prolongation, electrolytes such as potassium and calcium should be repleted [91].

## Central Nervous System

Milder neurologic symptoms, such as insomnia, anxiety, restlessness, and tremor, can all be appropriately treated with benzodiazepines, such as diazepam (0.1 mg/kg initial dose) or lorazepam (0.05-0.1 mg/kg initial dose). Benzodiazepines should also be the first-line therapy for caffeine-induced seizures [52,67]. If seizure activity is refractory to benzodiazepine therapy, barbiturates are indicated [92]. We recommend the addition of a barbiturate if more than 0.5 mg/kg of diazepam or 0.1 mg/kg of lorazepam is given without cessation of seizures. The use of barbiturates may necessitate endotracheal intubation to support central nervous system and respiratory depression. In the intubated patient, propofol can be initiated with a 125 to 300  $\mu$ g/kg continuous infusion titrated to effect; however, propofol should not be administered routinely in children younger than 3 years. Phenobarbital may also be used; its safety in children has been well documented. A loading dose of 10 to 20 mg/kg can be given. Phenytoin has not been

found to demonstrate any benefit in treating methylxanthine-induced seizures [93-95]. Emergent critical care and/or neurology consultation is warranted in patients with status epilepticus refractory to therapy; continuous electroencephalogram monitoring may be indicated.

### Musculoskeletal

Rhabdomyolysis must be treated aggressively with continuous infusion of isotonic crystalloid solutions to maintain a urine output of 2 to 3 mL/kg/h [75,96]. As mentioned previously, judicious use of benzodiazepines is indicated to control muscle contractions and seizures.

### Withdrawal

The caffeine withdrawal syndrome has been well described, with symptoms including yawning, fatigue, depression, anxiety, and headache with cessation of caffeine [97]. Withdrawal symptoms generally occur within 12 to 24 hours of cessation, peak at 20 to 48 hours, and may last for up to 1 week [98]. One study of children demonstrated decreased reaction time during the caffeine withdrawal period. In addition, the children displayed decreased attention for up to 1 week after cessation of caffeine use [97]. The implications of prolonged inattention in school-aged children are very concerning; further implications as to variability in caffeine intake and attention require additional study.

### Future Research

Several areas require investigation to further characterize the effects of long-term energy drink use in children and adolescents. One of the most worrisome is the combination of energy drinks with alcohol. Urban legend and pop culture have contributed to the mystique that energy drinks may prevent the depressant effects of intoxication when consumed with alcohol [99]. Instead, a recent study described no change in alcohol effects when combined with energy drinks [100]. The potential risk for injury or excessive intoxication in adolescents combining energy drinks and alcohol is very concerning. Another area of needed research is the long-term neuropsychiatric sequelae of energy drink use, as well as the overall impact of insomnia in children and adolescents. Another is the contribution of energy drinks to the epidemic of childhood obesity and psychiatric illness, including attention-deficit/hyperactivity disorder. Finally, a vital area of investigation is that of addiction research in adolescents chronically using energy drinks, given adult literature that links caffeine dependence to both tobacco and alcohol use [101-104].

From a policy perspective, there are currently no regulations that require the reporting of caffeine content on energy drink product labels. However, significant momentum is building for legislation requiring accurate labeling.

### Summary

Clinicians should screen for energy drink use among their patients. Screening can identify symptoms related to toxicity and give patients greater understanding of the risks of high-dose and long-term energy drink use. When caffeine toxicity is suspected, immediate consultation with a regional poison control center or toxicologist is recommended. Clinicians should report all suspected cases of energy drink toxicity to a poison control center because the pooled data generated by poison control center and clinician-initiated surveillance will provide the data to drive federal analysis and legislation on these products.

### Acknowledgments

The authors gratefully acknowledge the assistance of Dr Edward W. Boyer and Mr William B. Hendee in the preparation of the manuscript.

### References

1. Shute N. Over the limit?. US News and World Report. Available at: <http://health.usnews.com/usnews/health/articles/070415/23caffeine.htm> Posted April 15, 2007. [Accessed September 15, 2007].
2. Foxnews.com. Teens abusing energy boosting drinks, doctors fear. Available at: <http://www.foxnews.com/story/0,2933,226223,00.html> Posted October 31, 2006. [Accessed August 23, 2007].
3. Dlugosz L, Bracken MB. Reproductive effects of caffeine: a review and theoretical analysis. *Epidemiol Rev* 1992;14:83-100.
4. Gilbert R, Marshman J, Schwieder M, et al. Caffeine content of beverages as consumer. *Can Med Assoc J* 1976;114:205-8.
5. Nawrot P, Jordan S, Eastwood J, et al. Effects of caffeine on human health. *Food Addit Contam* 2003;20:1-30.
6. Benowitz NL. Clinical pharmacology of caffeine. *Annu Rev Med* 1990;41:277-88.
7. Ellison R, Singer M, Moore L, et al. Current caffeine intake of young children: amount and sources. *J Am Diet Assoc* 1995;95:802-4.
8. Hughes JR, Oliveto AH. A systematic survey of caffeine intake in Vermont. *Exp Clin Psychopharmacol* 1997;5:393-8.
9. Health Canada. It's your health: caffeine. Available at: [http://www.hc-sc.gc.ca/fyh-vsv/food-aliment/caffeine\\_e.html](http://www.hc-sc.gc.ca/fyh-vsv/food-aliment/caffeine_e.html) Posted February 2006. Updated September 2007. [Accessed September 10, 2007].
10. McCusker RR, Goldberger BA, Cone EJ. Caffeine content of energy drinks, carbonated sodas, and other beverages. *J Anal Toxicol* 2006; 30:112-4.
11. Henman AR. Guarana (*Paullinia cupana* var. *sorbilis*): ecological and social perspectives on an economic plant of the central Amazon basin. *J Ethnopharmacol* 1982;6:311-38.
12. Guarana. In: AltMedDex System [intranet database]. Greenwood Village CVG (Colo): Thomson Micromedex; 2007. Available at: <http://www.micromedex.com/products.altm.de>.
13. Food Safety Promotion of Board. A review of the health effects of stimulant drinks: a final report from the Food Safety Promotion Board. Available at: [www.safefoodonline.com/article.asp?article=236](http://www.safefoodonline.com/article.asp?article=236) [Accessed September 14, 2007].
14. Haskell CF, Kennedy DO, Wesnes KA, et al. A double-blind, placebo-controlled, multi-dose evaluation of the acute behavioural effects of guarana in humans. *J Psychopharmacol* 2007;21:65-70.
15. Brosnan JT, Brosnan ME. The sulfur-containing amino acids: an overview. *J Nutr* 2006;136(6 Suppl):1636S-40S.
16. Stapleton PP, Charles RP, Redmond HP, et al. Taurine and human nutrition. *Clin Nutr* 1997;16:103-8.

17. Heird WC. Taurine in neonatal nutrition—revisited. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F473-4.
18. MacDonald ML, Rogers QR, Morris JG. Nutrition of the domestic cat, a mammalian carnivore. *Annu Rev Nutr* 1984;4:521-62.
19. Coon JT, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. *Drug Saf* 2002;25:323-44.
20. Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. *Ann Intern Med* 2002;136:42-53.
21. Dega H, Laporte JL, Frances C, et al. Ginseng as a cause for Stevens-Johnson syndrome. *Lancet* 1996;347:1344.
22. Ries CA, Sahud MA. Agranulocytosis caused by Chinese herbal medicines. Dangers of medications containing aminopyrine and phenylbutazone. *JAMA* 1975;231:352-5.
23. Vuksan V, Sievenpiper JL. Herbal remedies in the management of diabetes: lessons learned from the study of ginseng. *Nutr Metab Cardiovasc Dis* 2005;15:149-60.
24. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health Syst Pharm* 1997;54:692-3.
25. Siegel RK. Ginseng abuse syndrome. Problems with the panacea. *JAMA* 1979;241:1614-5.
26. Braganza S, Larkin M. Riding high on energy drinks. *Modern medicine*. Available at: <http://www.modernmedicine.com/modernmedicine/article/articleDetail.jsp?id=426763>. Posted May 15, 2007. [Accessed September 15, 2007].
27. Lheureux PE, Penalzo A, Zahir S, Gris M. Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care* 2005;9:431-40.
28. Russell S. Carnitine as an antidote for acute valproate toxicity in children. *Curr Opin Pediatr* 2007;19:206-10.
29. Carnitor. Carnitor (levocarnitine) tablets and oral solution, and Carnitor SF sugar-free oral solution package insert. Available at: <http://www.carnitormetabolic.com/>. [Accessed on September 20, 2007].
30. Soop M, Bjorkman O, Cederblad G, et al. Influence of carnitine supplementation on muscle substrate and carnitine metabolism during exercise. *J Appl Physiol* 1988;64:2394-9.
31. Decombaz J, Gmuender B, Sierro G, et al. Muscle carnitine after strenuous endurance exercise. *J Appl Physiol* 1992;72:423-7.
32. Brass E. Supplemental carnitine and exercise. *Am J Clin Nutr* 2000;72:618s-23s.
33. Bodybuilding.com. L-Carnitine information and product listing: an amino acid that helps with fat loss. Available at: <http://www.bodybuilding.com/store/lcarn.html>. [Accessed September 20, 2007].
34. Arnaud MJ. The pharmacology of caffeine. *Prog Drug Res* 1987;31:273-313.
35. Sawynok J, Yaksh TL. Caffeine as an analgesic adjuvant: a review of pharmacology and mechanisms of action. *Pharmacol Rev* 1993;45:43-85.
36. Tyralla EE, Dodson WE. Caffeine secretion into breast milk. *Arch Dis Child* 1979;54:787-800.
37. Berger A. Effects of caffeine consumption on pregnancy outcome. A review. *J Reprod Med* 1988;33:945-56.
38. Baselt RC. Disposition of toxic drugs and chemicals in man. 5th ed. Foster City: Chemical Toxicology Institute; 2000.
39. Fligner CL, Opheim KE. Caffeine and its dimethylxanthine metabolites in two cases of caffeine overdose: a cause of falsely elevated theophylline concentrations in serum. *J Anal Toxicol* 1988;12:339-43.
40. Aranda JV, Collinge JM, Zinman R, et al. Maturation of caffeine elimination in infancy. *Arch Dis Child* 1979;54:946-9.
41. Eskenazi B, Fenster L, Swan S, et al. Caffeine use during pregnancy: how much is safe? *JAMA* 1993;270:47 [author reply 47-8].
42. Hinds TS, West WL, Knight EM, et al. The effect of caffeine on pregnancy outcome variables. *Nutr Rev* 1996;54:203-7.
43. Karen G. Caffeine during pregnancy? In moderation. *Can Fam Phys* 2000;46:801-3.
44. Denaro CP, Wilson M, Jacob P, et al. The effect of liver disease on urine caffeine metabolite ratios. *Clin Pharmacol Ther* 1996;59:624-35.
45. Nix DE, Di Cicco RA, Miller AK, et al. The effect of low-dose cimetidine (200 mg twice daily) on the pharmacokinetics of theophylline. *J Clin Pharmacol* 1999;39:855-65.
46. Brown CR, Jacob P, Wilson M, et al. Changes in rate and pattern of caffeine metabolism after cigarette abstinence. *Clin Pharmacol Ther* 1988;43:488-91.
47. Fredholm BB. On the mechanism of action of theophylline and caffeine. *Acta Med Scand* 1985;217:149-53.
48. Vestal RE, Thummel KE, Musser B, et al. Cimetidine inhibits theophylline clearance in patients with chronic obstructive pulmonary disease: a study using stable isotope methodology during multiple oral dose administration. *Br J Clin Pharmacol* 1983;15:411-8.
49. Benowitz NL, Osterloh J, Goldschlager N, et al. Massive catecholamine release from caffeine poisoning. *JAMA* 1982;248:1097-8.
50. Watson WA, Litovitz TL, Rodgers GC, et al. 2004 Annual report of the American Association of Poison Control Centers toxic exposure surveillance system. *Am J Emerg Med* 2005;23:589-666.
51. Lai MW, Klein-Schwartz W, Rodgers GC, et al. 2005 Annual report of the American Association of Poison Control Centers' national poisoning and exposure database. *Clin Toxicol (Phila)* 2006;44:803-932.
52. Cannon ME, Cooke CT, McCarthy JS. Caffeine-induced cardiac arrhythmia: an unrecognized danger of healthfood products. *Med J Aust* 2001;174:520-1.
53. Alford C, Cox H, Wescott R. The effects of red bull energy drink on human performance and mood. *Amino Acids* 2001;21:139-50.
54. Reyner LA, Horne JA. Efficacy of a 'functional energy drink' in counteracting driver sleepiness. *Physiol Behav* 2002;75:331-5.
55. Horne JA, Reyner LA. Beneficial effects of an "energy drink" given to sleepy drivers. *Amino Acids* 2001;20:83-9.
56. Hering-Hanit R, Gadot N. Caffeine-induced headache in children and adolescents. *Cephalalgia* 2003;23:332-5.
57. Millichap JG, Yee MM. The diet factor in pediatric and adolescent migraine. *Pediatr Neurol* 2003;28:9-15.
58. Pollak CP, Bright D. Caffeine consumption and weekly sleep patterns in US seventh-, eighth-, and ninth-graders. *Pediatrics* 2003;111:42-6.
59. Karacan I, Thornby JI, Anch M, et al. Dose-related sleep disturbances induced by coffee and caffeine. *Clin Pharmacol Ther* 1976;20:682-9.
60. Caffeine. In POISINDEX System. Thomson Micromedex. Available at: <http://www.thomsonhc.com> [Accessed July 19, 2007].
61. Rivenes SM, Bakerman PR, Miller MB. Intentional caffeine poisoning in an infant. *Pediatrics* 1997;99:736-8.
62. Chopra A, Morrison L. Resolution of caffeine-induced complex dysrhythmia with procainamide therapy. *J Emerg Med* 1995;13:113-7.
63. Hoffman R. Methylxanthines. In: Goldfrent LE, Flomenbaum NE, Lewin NA, et al, editors. Goldfrank's toxicologic emergencies. 8th ed. New York (NY): McGraw-Hill; 2006.
64. Iyadurai SJ, Chung SS. New-onset seizures in adults: possible association with consumption of popular energy drinks. *Epilepsy Behav* 2007;10:504-8.
65. Josephson GW, Stine RJ. Caffeine intoxication: a case of paroxysmal atrial tachycardia. *JACEP* 1976;5:776-8.
66. Forman J, Aizer A, Young CR. Myocardial infarction resulting from caffeine overdose in an anorectic woman. *Ann Emerg Med* 1997;29:178-80.
67. Shum S, Seale C, Hathaway D, et al. Acute caffeine ingestion fatalities: management issues. *Vet Hum Toxicol* 1997;39:228-30.
68. Baylin A, Hernandez-Diaz S, Kabagambe EK, et al. Transient exposure to coffee as a trigger of a first nonfatal myocardial infarction. *Epidemiology* 2006;17:506-11.

69. Dietrich AM, Mortensen ME. Presentation and management of an acute caffeine overdose. *Pediatr Emerg Care* 1990;6:296-8.
70. Perrin C, Debruyne D, Lacotte J, et al. Treatment of caffeine intoxication by exchange transfusion in a newborn. *Acta Paediatr Scand* 1987;76:679-81.
71. Walsh I, Wasserman GS, Mestad P, et al. Near-fatal caffeine intoxication treated with peritoneal dialysis. *Pediatr Emerg Care* 1987;3:244-9.
72. Mrvos RM, Reilly PE, Dean BS, et al. Massive caffeine ingestion resulting in death. *Vet Hum Toxicol* 1989;31:571-2.
73. Maughan R, Griffin J. Caffeine ingestion and fluid balance: a review. *J Hum Nutr Diet* 2003;16:411-20.
74. Emohare O, Ratnam V. Multiple cardiac arrests following an overdose of caffeine complicated by penetrating trauma. *Anaesthesia* 2006;61:54-6.
75. Wrenn KD, Oschner I. Rhabdomyolysis induced by a caffeine overdose. *Ann Emerg Med* 1989;18:94-7.
76. Appel CC, Myles TD. Caffeine-induced hypokalemic paralysis in pregnancy. *Obstet Gynecol* 2001;97(5 Pt 2):805-7.
77. Leson CL, McGuigan MA, Bryson SM. Caffeine overdose in an adolescent male. *J Toxicol Clin Toxicol* 1988;26:407-15.
78. Arimori K, Nakano M. Transport of theophylline from blood to the intestinal lumen following i.v. administration to rats. *J Pharmacobiodyn* 1985;8:324-7.
79. Shannon M, Amitai Y, Lovejoy Jr FH. Multiple dose activated charcoal for theophylline poisoning in young infants. *Pediatrics* 1987;80:368-70.
80. Golej J, Boigner H, Burda G, et al. Severe respiratory failure following charcoal application in a toddler. *Resuscitation* 2001;49:315-8.
81. Graff GR, Stark J, Berkenbosch JW, et al. Chronic lung disease after activated charcoal aspiration. *Pediatrics* 2002;109:959-61.
82. Woo OF, Pond SM, Benowitz NL, et al. Benefit of hemoperfusion in acute theophylline intoxication. *J Toxicol Clin Toxicol* 1984;22:411-24.
83. Nagesh RV, Murphy KA. Caffeine poisoning treated by hemoperfusion. *Am J Kidney Dis* 1988;12:316-8.
84. Holstege CP, Hunter Y, Baer AB, et al. Massive caffeine overdose requiring vasopressin infusion and hemodialysis. *J Toxicol Clin Toxicol* 2003;41:1003-7.
85. Biberstein MP, Ziegler MG, Ward DM. Use of beta-blockade and hemoperfusion for acute theophylline poisoning. *West J Med* 1984;141:485-90.
86. Price K, Fligner D. Treatment of caffeine toxicity with esmolol. *Ann Emerg Med* 1990;19:44-6.
87. Whitehurst VE, Joseph X, Vick JA, et al. Reversal of acute theophylline toxicity by calcium channel blockers in dogs and rats. *Toxicology* 1996;110:113-21.
88. American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112(24 Supplement).
89. Strubelt O, Diederich KW. Experimental treatment of the acute cardiovascular toxicity of caffeine. *J Toxicol Clin Toxicol* 1999;37:29-33.
90. Rudy DR, Lee S. Coffee and hypokalemia. *J Fam Pract* 1988;26:679-80.
91. Shannon M. Hypokalemia, hyperglycemia and plasma catecholamine activity after severe theophylline intoxication. *J Toxicol Clin Toxicol* 1994;32:41-7.
92. Goldberg MJ, Spector R, Miller G. Phenobarbital improves survival in theophylline-intoxicated rabbits. *J Toxicol Clin Toxicol* 1986;24:203-11.
93. Marquis JF, Carruthers SG, Spence JD, et al. Phenytoin-theophylline interaction. *N Engl J Med* 1982;307:1189-90.
94. Blake KV, Massey KL, Hendeles L, et al. Relative efficacy of phenytoin and phenobarbital for the prevention of theophylline-induced seizures in mice. *Ann Emerg Med* 1988;17:1024-8.
95. Hoffman A, Pinto E, Gilhar D. Effect of pretreatment with anticonvulsants on theophylline-induced seizures in the rat. *J Crit Care* 1993;8:198-202.
96. Kamijo Y, Soma K, Asari Y, et al. Severe rhabdomyolysis following massive ingestion of oolong tea: caffeine intoxication with coexisting hyponatremia. *Vet Hum Toxicol* 1999;41:381-3.
97. Bernstein GA, Carroll ME, Dean NW, et al. Caffeine withdrawal in normal school-age children. *J Am Acad Child Adolesc Psychiatry* 1998;37:858-65.
98. Griffiths RR, Woodson PP. Caffeine physical dependence: a review of human and laboratory animal studies. *Psychopharmacology (Berl)* 1988;94:437-51.
99. CBS News. Study: Red Bull won't tame booze. Available at: <http://www.cbsnews.com/stories/2006/03/27/health/webmd/main1443856.shtml>. Posted March 27, 2006 [Accessed August 25, 2007].
100. Ferreira SE, de Mello MT, Pompeia S, et al. Effects of energy drink ingestion on alcohol intoxication. *Alcohol Clin Exp Res* 2006;30:598-605.
101. Bernstein GA, Carroll ME, Thuras PD, et al. Caffeine dependence in teenagers. *Drug Alcohol Depend* 2002;66:1-6.
102. Ogawa N, Ueki H. Clinical importance of caffeine dependence and abuse. *Psychiatry Clin Neurosci* 2007;61:263-8.
103. Strain EC, Mumford GK, Silverman K, et al. Caffeine dependence syndrome. Evidence from case histories and experimental evaluations. *JAMA* 1994;272:1043-8.
104. Swanson JA, Lee JW, Hopp JW. Caffeine and nicotine: a review of their joint use and possible interactive effects in tobacco withdrawal. *Addict Behav* 1994;19:229-56.