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Review

Caffeinated energy drinks—A growing problem

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Abstract

Since the introduction of Red Bull in Austria in 1987 and in the United States in 1997, the energy drink market has grown exponentially. Hundreds of different brands are now marketed, with caffeine content ranging from a modest 50 mg to an alarming 505 mg per can or bottle. Regulation of energy drinks, including content labeling and health warnings differs across countries, with some of the most lax regulatory requirements in the U.S. The absence of regulatory oversight has resulted in aggressive marketing of energy drinks, targeted primarily toward young males, for psychoactive, performance-enhancing and stimulant drug effects. There are increasing reports of caffeine intoxication from energy drinks, and it seems likely that problems with caffeine dependence and withdrawal will also increase. In children and adolescents who are not habitual caffeine users, vulnerability to caffeine intoxication may be markedly increased due to an absence of pharmacological tolerance. Genetic factors may also contribute to an individual's vulnerability to caffeine-related disorders including caffeine intoxication, dependence, and withdrawal. The combined use of caffeine and alcohol is increasing sharply, and studies suggest that such combined use may increase the rate of alcohol-related injury. Several studies suggest that energy drinks may serve as a gateway to other forms of drug dependence. Regulatory implications concerning labeling and advertising, and the clinical implications for children and adolescents are discussed.

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Keywords: Caffeine; Energy drink; Adolescents; Overdose; Withdrawal; Dependence; Alcohol; Gateway drug

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1. Introduction

In 2006, annual worldwide energy drink consumption increased 17% from the previous year to 906 million gallons, with Thailand leading the world in energy drink consumption per person, but the U.S. leading the world in total volume sales (Zenith International, 2007). Although “energy drinks” first appeared in Europe and Asia in the 1960s, the introduction of “Red Bull” in Austria in 1987 and in the U.S. in 1997 sparked the more recent trend toward aggressive marketing of high caffeine content “energy drinks”. Since its inception, the energy drink market has grown exponentially, with nearly 500 new brands launched worldwide in 2006 (Johnson, 2006), and 200 new brands launched in the U.S. in the 12-month period ending July 2007 (Packaged Facts, 2007). From 2002 to 2006, the average annual growth rate in energy drink sales was 55% (Packaged Facts, 2007) (Fig. 1). The total U.S. retail market value for energy drinks (from all sources) was estimated to be \$5.4 billion in 2006 and has shown a similar annual growth rate over this same period (47%) (Packaged Facts, 2007). These drinks vary widely in both caffeine content (ranging from 50 to 505 mg per can or bottle) and caffeine concentration (ranging from 2.5 to 171 mg per fluid ounce) (Table 1). For comparison, the caffeine content of a 6 oz cup of brewed coffee varies from 77 to 150 mg (Griffiths et al., 2003). The main active ingredient in energy drinks is caffeine, although other substances such as taurine, riboflavin, pyridoxine, nicotinamide, other B vitamins, and various herbal derivatives are also present (Aranda and Morlock, 2006). The acute and long-term effects resulting from excessive and chronic consumption of these additives alone and in combination with caffeine are not fully known. Although the full impact of the rise in popularity of energy drinks

has yet to be realized, the potential for adverse health consequences should be considered and may be cause for preemptive regulatory action.

2. Regulatory aspects

The regulation of beverages to which caffeine is added has been challenging, partly because of the widespread and long-term use of beverages such as coffee and tea in which caffeine is a natural constituent. Nonetheless, several countries have enacted measures to regulate the labeling, distribution, and sale of energy drinks that contain significant quantities of caffeine. The European Union requires that energy drinks have a “high caffeine content” label (European Union, 2007) and Canada requires labels indicating that Red Bull should not be mixed with alcohol and that maximum daily consumption not exceed two 8.3 oz cans (Health Canada, 2005). Norway restricts the sale of Red Bull to pharmacies, while France (until recently) and Denmark have prohibited the sale of Red Bull altogether (Ari Kapner, 2004).

The history of the regulation of caffeine containing beverages in the U.S. serves as an illustrative example of the complexity of the regulatory issues involved in their sale, use, and promotion. Historically, the U.S. Food and Drug Administration (FDA) has regulated caffeine-containing soft drinks as foods. In 1980, citing health concerns about caffeine, the FDA proposed to eliminate caffeine from soft drinks (Food and Drug Administration, 1980). In response, soft drink manufacturers justified adding caffeine to soft drinks on the basis that caffeine was a flavor enhancer (PepsiCo Inc., 1981), although the scientific basis for that claim has since been challenged (Griffiths and Vernotica, 2000; Keast and Riddell, 2007). If caffeine had not been accepted as a flavor enhancer, but had been regarded as a psychoactive ingredient, soft drinks might have been regulated by the FDA as drugs. However, the FDA approved caffeine and limited the maximum caffeine content of cola-type soft drinks to 0.02% caffeine, or 71 mg/12 fluid oz (Food and Drug Administration, 2003).

Although drink manufacturers initially complied with the FDA caffeine limits, the marketplace has changed dramatically since the introduction of energy drinks. At least 130 energy drinks now exceed 0.02% caffeine (Energyfiend website, 2008), including one that contains 505 mg in a 24 oz can (the equivalent of 14 cans of a typical cola or several cups of coffee) (Table 1). Many manufacturers are not subject to the prior caffeine limits by claiming that their new products fall under the 1994 Dietary Supplement Health and Education Act, which classifies products deriving from herbs and natural sources as dietary supplements rather than drugs (Ari Kapner, 2004). Other manufacturers appear to be ignoring the FDA caffeine limits and FDA has not enforced the limits. The FDA has been lax in regulating the caffeine content of energy drinks and does not require warning labels advising proper use or the amount of caffeine in the product, as it does for over-the-counter (OTC) caffeine-containing stimulants. According to the FDA (Food and Drug Administration, 2007a), over-the-counter stimulant drug prod-

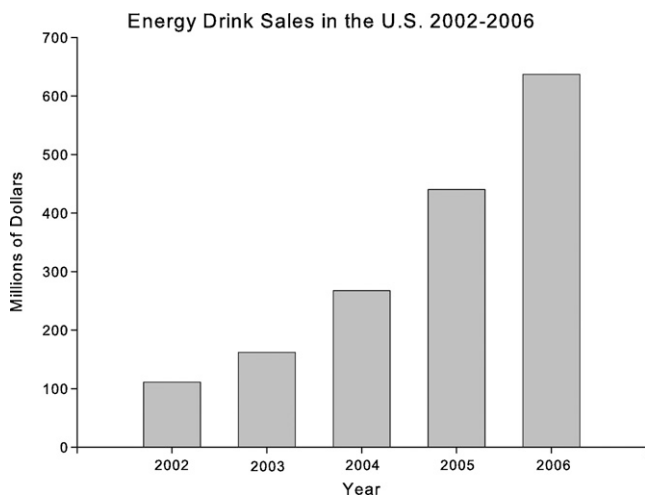


Fig. 1. Energy drink sales in millions of dollars in the United States from 2002 to 2006. Data are based on scanner data from over 32,000 stores such as supermarkets, drug stores, and discount merchandisers other than Wal-Mart. Data are from retailers with \$2 million or more in annual sales but exclude: club-stores/warehouse clubs, convenience stores, dollar/variety stores, foodservice, vending, concession sales and specialty channels/retailers of all types (e.g., gourmet/specialty food stores, hardware/home improvements stores, military exchanges) (Packaged Facts, 2007 used with permission).

Table 1
Energy drinks in the United States

	Ounces per bottle or can	Caffeine concentration (mg/oz)	Total caffeine (mg)
Top selling energy drinks^a			
Red Bull	8.3	9.6	80
Monster	16	10	160
Rockstar	16	10	160
Full throttle	16	9	144
No Fear	16	10.9	174
Amp	8.4	8.9	75
SoBe Adrenaline Rush	8.3	9.5	79
Tab Energy	10.5	9.1	95
Higher caffeine energy drinks^b			
Wired X505	24	21	505
Fixx	20	25	500
BooKoo Energy	24	15	360
Wired X344	16	21.5	344
SPIKE Shooter	8.4	35.7	300
Viso Energy Vigor	20	15	300
Cocaine Energy Drink	8.4	33.3	280
Jolt Cola	23.5	11.9	280
NOS	16	16.3	250
Redline RTD	8	31.3	250
Blow (Energy Drink Mix)	8	30	240
Lower caffeine energy drinks^b			
Bomba Energy	8.4	8.9	75
HiBall Energy	10	7.5	75
Airforce Nutrisoda Energize	8.5	5.9	50
Whoop Ass	8.5	5.9	50
Vitamin Water (Energy Citrus)	20	2.5	50
High concentration energy drinks^b			
RedLine Power Rush	2.5	140	350
Ammo	1	171	171
Powershot	1	100	100
Fuel Cell	2	90	180
Classic soft drinks			
Coca-Cola Classic	12	2.9	34.5
Pepsi Cola	12	3.2	38
Dr Pepper	12	3.4	41
Mountain Dew	12	4.5	54

Data on drink volume and caffeine content were obtained from the manufacturer via product label, website, or personal communication with manufacturer representatives. The one exception was that the caffeine content for BooKoo Energy was obtained from the energyfiend website (Energyfiend website, 2008) which indicates the information was obtained from a Boo-Koo representative. When the authors contacted the BooKoo company directly, a BooKoo representative refused to disclose the drink's caffeine content but did indicate that accurate information for the caffeine content of BooKoo Energy was available online.

^a Top selling energy drinks in the U.S. 2006, listed sequentially as a percentage of market share (Packaged Facts, 2007, used with permission).

^b Examples of energy drinks drawn from the hundreds of energy drink products currently marketed in the U.S., listed sequentially on total caffeine content.

ucts must contain the following warnings and directions on the product label:

- The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.
- For occasional use only. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a (select one of the following: “physician” or “doctor”).
- Do not give to children under 12 years of age.

- Directions: Adults and children 12 years of age and over: oral dosage is 100–200 mg not more often than every 3–4 h.

It is a striking inconsistency that, in the U.S. an OTC stimulant medication containing 100 mg of caffeine per tablet (e.g. NoDoz) must include all the above warnings, whereas a 500 mg energy drink can be marketed with no such warnings and no information on caffeine dose amount in the product.

3. Advertising

Energy drinks are promoted for their stimulant effects and claim to offer a variety of benefits including increased attention,

endurance and performance, weight loss, and “having fun, kicking butt and making a difference” (Bookoo website, 2008). The majority of these claims however, remain to be substantiated. The most consistent result to emerge is that caffeine reduces performance decrements due to reduced alertness (e.g. conditions of fatigue, or sleep deprivation) (Bonnet et al., 2005). Other studies have shown that, relative to placebo, caffeine can increase long-term exercise endurance, and improve speed and/or power output (Graham, 2001; Doherty and Smith, 2004; Doherty et al., 2004; Wiles et al., 2006). However, because many of the studies claiming to demonstrate performance enhancement by caffeine have been confounded by caffeine withdrawal, there is debate over whether caffeine has net positive or performance enhancing effects (e.g. improved mood, alertness or mental function) (Haskell et al., 2005; Childs and de Wit, 2006) or whether these effects are due to the reversal of caffeine withdrawal symptoms (James, 1998; Heatherley et al., 2005; Rogers et al., 2003, 2005; James and Rogers, 2005). Based on preclinical literature that clearly documents the behavioral stimulant effects of caffeine (Dews, 1984), it seems quite likely that caffeine enhances human performance on some types of tasks (e.g., vigilance) (Stafford et al., 2007), especially among non-tolerant individuals. Among high-dose habitual consumers, performance enhancements above and beyond withdrawal reversal effects are likely to be modest at best (James and Rogers, 2005).

Advertising of energy drinks is targeted primarily towards young males, with alluring product names such as “Full Throttle”, “AMP Energy” and “Cocaine”. These advertising campaigns promote the psychoactive, performance-enhancing, and stimulant effects of energy drinks and appear to glorify drug use. In a survey of 795 undergraduate students, self-reported measures of masculinity and risk taking behaviors were positively associated with frequency of energy drink consumption (Miller, 2008).

One of the more blatant examples of such advertising tactics is found in the drink additive “Blow”. This “energy drink additive” is packaged in glass vials and shipped with a mirror and plastic credit cards in an apparent attempt to model cocaine use. Blow founder Logan Gola describes the product as “sexy, edgy and fun” (PR Newswire Association, 2007). The energy drink “Cocaine” was initially marketed as “The Legal Alternative” with its product name displayed as a white granular substance which resembled cocaine powder (Food and Drug Administration, 2007b; Cocaine website, 2008), and with video clips on the company website showing consumers “snorting” its liquid product. Recently, the FDA claimed jurisdiction over both “Cocaine” (Food and Drug Administration, 2007b) and “Blow” (Food and Drug Administration, 2008), informing the companies that their products were marketed as an alternative to an illicit street drug, not a dietary supplement, and subject to regulation as a drug. In early 2008, the manufacturer re-released “Cocaine”, with revised product claims, yet retaining the drink’s characteristic moniker, “Cocaine” still prominently displayed as a white powdery substance resembling cocaine powder (Cocaine website, 2008; Kotaku website, 2008). The product “Blow” currently remains on the market.

The marketing of energy drinks as products to be used for their stimulant and recreational effects stands in marked contrast to the marketing of soft drinks. For decades, advertising for soft drinks has been restricted to rather innocuous and somewhat ambiguous claims such as those used to promote Coca-Cola: “The pause that refreshes” (Pendergast, 1993). As mentioned previously, in response to an FDA proposal to eliminate caffeine from soft drinks, soft drink manufacturers justified adding caffeine by calling it a flavor enhancer (PepsiCo Inc., 1981). After claiming that caffeine was added just for its flavor, manufacturers were likely reluctant to publicly promote their products as stimulants for fear of jeopardizing their regulatory rationale for adding caffeine. No such restraint is exercised on promotion of energy drinks, many of which are regulated under the 1994 dietary supplement act.

4. Caffeine toxicity/overdose

Concern regarding the caffeine content of energy drinks is prompted by the potential adverse consequences of caffeine use. One such adverse effect is caffeine intoxication, a recognized clinical syndrome included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and the World Health Organization’s International Classification of Diseases (ICD-10) (American Psychiatric Association, 1994; World Health Organization, 1992a,b). Caffeine toxicity is defined by specific symptoms that emerge as a direct result of caffeine consumption. Common features of caffeine intoxication include nervousness, anxiety, restlessness, insomnia, gastrointestinal upset, tremors, tachycardia, psychomotor agitation (American Psychiatric Association, 1994) and in rare cases, death (Garriott et al., 1985; Kerrigan and Lindsey, 2005; Mrvos et al., 1989). The symptoms of caffeine intoxication can mimic those of anxiety and other mood disorders (Greden, 1974).

The consumption of energy drinks may increase the risk for caffeine overdose in caffeine abstainers as well as habitual consumers of caffeine from coffee, soft drinks, and tea. The potential for acute caffeine toxicity due to consumption of energy drinks may be greater than other dietary sources of caffeine for several reasons:

- (1) Lack of adequate labeling: As mentioned earlier, many energy drinks do not label their product with the amount of caffeine, and are not required to display warning labels advising proper use. Consumers may be completely unaware of the amount of caffeine they are ingesting.
- (2) Advertising: Many energy drinks are marketed with claims of performance enhancing effects although, as discussed previously, the existence and extent of such effects is subject to debate. Red Bull, for example, advertises several benefits of consumption including improved performance, endurance, concentration and reaction speed, and increased metabolism (Red Bull website, 2008). Consumers may falsely believe that “more is better” and ingest multiple servings of these products. As an added risk, some energy drinks encourage rapid consumption of their products. For instance, “Spike Shooter” claims “the flavor’s so good,

you'll want to slam the whole can" (Spikeshooter website, 2008).

- (3) Consumer demographics: Since there are no restrictions on the sale of energy drinks, adolescents and children (who may be inexperienced and less tolerant to the effects of caffeine) may be at an increased risk for caffeine intoxication.

Forty-one cases of caffeine abuse from caffeine-enhanced beverages were reported to a U.S. poison control center from 2002 to 2004 (McCarthy et al., 2006). Another U.S. poison control center reported nine cases of adverse reactions to the energy drink Redline from January 2004 to March 2006. Eight of the nine patients were male, the youngest being 13 years of age. The symptoms were: nausea/vomiting (56%), tachycardia (44%), hypertension (100%) (for patients evaluated in a health care facility), jittery/agitated/tremors (67%), dizziness (44%), chest pain (11%) and bilateral numbness (11%) (Walsh et al., 2006). In a survey of 496 college students, 51% reported consuming at least one energy drink during the last month (Malinauskas et al., 2007). Of these energy drink users, 29% reported "weekly jolt and crash episodes", 22% reported headaches, and 19% reported heart palpitations from drinking energy drinks (Malinauskas et al., 2007).

Media reports have also highlighted several cases of caffeine intoxication resulting from energy drink consumption. A 28-year-old motorcycle (motocross) athlete nearly died when his heart stopped during a competition. He had consumed eight cans of Red Bull over a 5 h period (Dasey, 2007). "Spike Shooter" has been removed from several U.S. convenience stores, and banned from local high schools when students became sick after consuming cans of the product that were purported to have been given away at a promotional event (Brooks, 2007; Simon and Mosher, 2007). Similar action has been taken at another U.S. high school after two student athletes fainted after drinking "Speed Stack" (Lunen, 2007). Local store owners have also banned the selling of energy drinks to minors, after three teenage boys displayed signs of caffeine intoxication after rapidly ingesting "BooKoo" energy drink (Lunen, 2007).

In addition to caffeine intoxication, the consumption of energy drinks has been linked to seizures (Iyadurai and Chung, 2007), acute mania (Machado-Vieira et al., 2001), and stroke (Worrall et al., 2005). Deaths attributed to energy drink consumption have been reported in Australia, Ireland and Sweden (Ari Kapner, 2004). Considerable debate has ensued as to whether these fatalities were a direct result of energy drink consumption.

5. Caffeine dependence

The DSM-IV-TR defines substance dependence using a generic set of cognitive, physiological, and behavioral symptoms, including the inability to quit, use despite harm, using more than intended, withdrawal, and tolerance. Although DSM-IV-TR specifically excludes caffeine from its diagnostic schema for substance dependence, the World Health Organization's International Classification of Diseases (ICD-10) includes this diagnosis (World Health Organization, 1992a,b). While there

is debate regarding the extent of reinforcing effects and abuse potential of caffeine, there is compelling evidence that caffeine can produce a substance dependence syndrome in some people (Bernstein et al., 2002; Hughes et al., 1998; Jones and Lejuez, 2005; Oberstar et al., 2002; Richards et al., 2004; Strain et al., 1994; Svikis et al., 2005). For example, studies in adults (Richards et al., 2004; Strain et al., 1994) and adolescents (Bernstein et al., 2002; Oberstar et al., 2002) have shown high rates of endorsement of inability to quit, use despite harm, and withdrawal. A population-based survey showed that 30% of a sample of 162 caffeine users fulfilled diagnostic criteria for substance dependence when applied to caffeine (Hughes et al., 1998). The prevalence of caffeine dependence may increase as a result of marketing campaigns promoting the use of energy drinks among adolescents. By analogy with tobacco and alcohol use, the earlier the onset of smoking or drinking, the greater the risk for later dependence (Moolchan et al., 2000; Liepman et al., 2002).

6. Caffeine withdrawal

Symptoms of caffeine withdrawal have been described in the medical literature for more than a century (Griffiths and Woodson, 1988). There have been at least 66 studies of caffeine withdrawal in the medical literature, the majority of which have been published within the last 10 years (Juliano and Griffiths, 2004). The symptoms of caffeine withdrawal, the most common of which is headache, begin 12–24 h after the last dose of caffeine (Driesbach and Pfeiffer, 1943; Lader et al., 1996; Juliano and Griffiths, 2004). In double-blind studies, about 50% of individuals report headache which may be severe in intensity (Silverman et al., 1992; Juliano and Griffiths, 2004). In addition to headache, other caffeine withdrawal symptoms include tiredness/fatigue, sleepiness/drowsiness, dysphoric mood (e.g., miserable, decreased well-being/contentedness), difficulty concentrating/decreased cognitive performance, depression, irritability, nausea/vomiting, and muscle aches/stiffness (Griffiths et al., 1990; Juliano and Griffiths, 2004). These withdrawal symptoms may be severe in intensity, and the incidence of clinically significant distress and impairment in daily functioning due to caffeine withdrawal is 13% in experimental studies (Juliano and Griffiths, 2004). Caffeine withdrawal is recognized as an official diagnosis in ICD-10 and a research diagnosis in DSM-IV-TR. Studies have also documented caffeine withdrawal in teenagers (Hale et al., 1995; Bernstein et al., 2002; Oberstar et al., 2002) and children (Bernstein et al., 1998; Goldstein and Wallace, 1997), the incidence of which may increase substantially with the aggressive marketing of energy drinks to these age groups.

7. Combined use of caffeine and alcohol may be problematic

There is an association between the heavy use of caffeine and the heavy use of alcohol (Istvan and Matarazzo, 1984; Kozlowski et al., 1993), and the ingestion of energy drinks in combination with alcohol is becoming increasingly popular (O'Brien et al.,

2008; Oteri et al., 2007), with 24% of a large stratified sample of college students reporting such consumption within the past 30 days (O'Brien et al., 2008). In the previously mentioned survey of 496 college students, 27% reported mixing alcohol and energy drinks in the past month. Of those that mixed energy drinks and alcohol, 49% used more than three energy drinks per occasion when doing so (Malinauskas et al., 2007). In a survey of 1253 college students, energy drink users were disproportionately male and consumed alcohol more frequently than non-energy drink users (Arria et al., 2008).

One study showed that ingestion of a caffeinated energy drink (Red Bull) with vodka reduced participants perception of impairment of motor coordination in comparison to vodka alone, but did not significantly reduce objective measures of alcohol-induced impairment of motor coordination, reaction time, or breath alcohol concentration (Ferreira et al., 2006). These results are consistent with other studies investigating caffeine–alcohol interactions (Marczinski and Fillmore, 2006). Thus, when mixing energy drinks and alcohol, users may not feel the symptoms of alcohol intoxication. This may increase the potential for alcohol-related injury. Indeed, a recent survey of college students found that in comparison to those who consumed alcohol alone, students who consumed alcohol mixed with energy drinks had a significantly higher prevalence of alcohol-related consequences including: being taken advantage of, or taking advantage of another student sexually, riding in an automobile with a driver under the influence of alcohol, or being hurt or injured (O'Brien et al., 2008). In addition, mixing energy drinks with alcohol was associated with increased heavy episodic drinking and episodes of weekly drunkenness (O'Brien et al., 2008). The recent introduction of pre-mixed caffeine–alcohol combination drinks may exacerbate these problems (Simon and Mosher, 2007) and has prompted regulatory action. Accordingly, as part of a legal settlement reached in 2008 with State Attorneys in 11 states in the U.S., Anheuser-Busch has agreed to stop the manufacture and sale of caffeinated alcoholic beverages (Idaho Office of the Attorney General website, 2008).

8. Relationship of caffeine to dependence on other substances

Studies in adult twins show that lifetime caffeine intake, caffeine toxicity and caffeine dependence are significantly and positively associated with various psychiatric disorders including major depression, generalized anxiety disorder, panic disorder, antisocial personality disorder, alcohol dependence, and cannabis and cocaine abuse/dependence (Kendler et al., 2006). Studies in adult twins examining caffeine use, alcohol use, and cigarette smoking concluded that a common genetic factor (polysubstance use) underlies the use of these three substances (Swan et al., 1996, 1997; Hettema et al., 1999), although another twin study suggested that caffeine and nicotine were associated with genetic factors unique to these substances (Kendler et al., 2007). A study examining the co-occurrence of substance use among drug abusers concluded that dependence on caffeine, nicotine and alcohol were governed by the same factors (Kozlowski et al., 1993). In a study of caffeine depen-

dent adults, Strain et al. (1994) reported a clustering of histories of caffeine, nicotine, and alcohol dependence. In a study of pregnant women, those who fulfilled criteria for a diagnosis of caffeine dependence and who had a family history of alcoholism were six times more likely to have a lifetime history of alcohol abuse or dependence (Svikis et al., 2005).

More specifically, with regard to cigarette smoking, human and animal studies show that caffeine increases the reinforcing effects of nicotine (Gasior et al., 2002; Jones and Griffiths, 2003; Shoaib et al., 1999; Tanda and Goldberg, 2000). Epidemiology studies show that cigarette smokers consume more caffeine than nonsmokers (Parsons and Neims, 1978; Swanson et al., 1994), an effect that may be partially due to increased caffeine metabolism among cigarette smokers (Parsons and Neims, 1978). Self-administration studies show that cigarette smoking and coffee drinking covary temporally within individuals (Emurian et al., 1982; Lane, 1996), although acute caffeine administration does not always increase cigarette smoking (Chait and Griffiths, 1983). As described above, twin and co-occurrence studies suggest links between caffeine use and smoking (Kozlowski et al., 1993; Swan et al., 1996, 1997; Hettema et al., 1999). A study of pregnant women showed that those who met criteria for caffeine dependence were nine times more likely to report a history of daily cigarette smoking compared to those who did not meet dependence criteria (Svikis et al., 2005).

Whether caffeine serves as a gateway to other forms of drug dependence as suggested by some studies (Collins et al., 1997; Pallanti et al., 2006) bears further investigation (Packaged Facts, 2007). With regard to energy drinks in particular, one study of 1253 college students found that energy drink consumption significantly predicted subsequent nonmedical prescription stimulant use (Arria et al., 2008). It is plausible that the use of energy drinks that are promoted as alternatives to illicit drugs (e.g. “Blow” and “Cocaine”) may, in fact, increase interest in the use of such drugs.

9. Vulnerability to caffeine affected by tolerance and genetic factors

Vulnerability to caffeine intoxication after bolus caffeine doses, such as those delivered in energy drinks, is markedly affected by pharmacological tolerance. Tolerance refers to a decrease in responsiveness to a drug as a result of drug exposure. Daily administration of very high doses of caffeine (e.g. 750–1200 mg/day) can produce complete or partial tolerance to caffeine's subjective, pressor, and neuroendocrine effects (Robertson et al., 1981; Evans and Griffiths, 1992; Griffiths and Mumford, 1996). Thus, individuals such as children and adolescents who do not use caffeine daily, are at greater risk for caffeine intoxication due to energy drink consumption than habitual caffeine consumers.

Genetic factors are relevant to vulnerability to both caffeine intoxication as well as caffeine dependence and withdrawal. Studies comparing monozygotic versus dizygotic twins have shown higher concordance rates for monozygotic twins for caffeine intoxication, total caffeine consumption, heavy use, caffeine tolerance, and caffeine withdrawal, with heritabilities

ranging between 35% and 77% (Kendler and Prescott, 1999; Swan et al., 1997). Linkage studies have shown that polymorphisms in the adenosine A_{2A} receptor gene and in adenosine deaminase are associated with individual differences in caffeine consumption and caffeine's effects on EEG, anxiety, and sleep (Alsene et al., 2003; Cornelis et al., 2007; Retey et al., 2007).

10. Conclusions and implications

The consumption of high caffeine content energy drinks has increased markedly in recent years. Regulation of energy drinks, including content labeling and health warnings has differed across countries, with among the most lax regulatory requirements in the U.S., which is also the largest market for these products. The absence of regulatory oversight has resulted in aggressive marketing of energy drinks, targeted primarily toward young males, for psychoactive, performance-enhancing and stimulant drug effects. There are increasing reports of caffeine intoxication from energy drinks, and it seems likely that problems with caffeine dependence and withdrawal will also increase. The combined use of caffeine and alcohol is increasing sharply, which studies suggest may increase the rate of alcohol-related injury. Given that clinical pharmacology and epidemiological studies demonstrate an association of caffeine use with dependence on alcohol, nicotine, and other drugs, and one study showed that energy drink use predicts subsequent non-medical use of prescription stimulants, further study of whether energy drink use serves as a gateway to other forms of drug dependence is warranted.

One limitation of the present review is that the great majority of the knowledge about caffeine intoxication, withdrawal, and dependence is derived from studies of coffee consumption. However, studies that have examined these phenomena in the context of caffeine delivered via soft drinks or capsules have shown similar results (e.g. Juliano and Griffiths, 2004; Strain et al., 1994). Thus, there is no reason to suppose that delivery of caffeine via energy drinks would appreciably alter these processes.

These observations have several regulatory and clinical implications. Considering the variable and sometimes very high caffeine content of energy drinks, in combination with the aggressive marketing to youthful and inexperienced consumers, it would be prudent to require full disclosure of the amount of caffeine and other ingredients in energy drinks on the product labeling. Product label warnings about risks when used alone and in combination with alcohol would also be appropriate. Restrictions on advertising and the aggressive marketing of energy drinks to youthful and inexperienced users should also be considered. The promotion of the use of drugs for their recreational and stimulant properties sends a potentially harmful message to adolescents that glamorizes and encourages drug use. Ingesting an energy drink to enhance athletic performance may not be far removed from the nonmedical use of anabolic steroids or pharmaceutical stimulants such as methylphenidate or amphetamine to gain a competitive advantage. Along the same lines, the rapid onset of stimulant effects provided by energy drinks may encourage users to seek out the more intense effects of prescription and illicit stimulants. Finally, it is important for clinicians to

be familiar with energy drinks and the potential health consequences associated with their use. Recognizing the features of caffeine intoxication, withdrawal, and dependence may be especially relevant when treating younger persons who may be more likely to consume energy drinks.

Conflict of interest

Dr Reissig owns stock in PepsiCo Corporation. Dr Strain owns stock in Starbucks and PepsiCo Corporations, is an investigator on several grants from the National Institute on Drug Abuse (NIDA), and has been a consultant to various pharmaceutical companies on issues about drug abuse liability. Dr Griffiths owns a single share of stock from the Coca-Cola Company, and is an investigator on grants or contracts from NIDA, the Council on Spiritual Practices, the Heffter Research Institute, and the Fetzer Institute. He has also been a consultant to or received grants from the various pharmaceutical companies on issues about drug abuse liability.

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