

ONLINE FIRST

Energy Drinks and Caffeine-Related Adverse Effects

Kent A. Sepkowitz, MD

IN 1911, UNDER AUTHORITY GRANTED BY THE RECENTLY enacted Food and Drug Act, US agents seized 40 kegs and 20 barrels of Coca-Cola syrup in Chattanooga, Tennessee.^{1,2} The group, led by chief chemist Harvey Wiley, considered the caffeine in Coca-Cola to be a significant public health hazard (both cocaine and alcohol had been removed from the recipe in the previous decade). The case continued for years. Eventually Coca-Cola decreased the caffeine content in this product and legal action was dropped.³

In 2012, the Food and Drug Administration (FDA) is again investigating a caffeine-containing product, the “energy drink,” because of safety concerns. Several types of these caffeinated drinks are linked to unexpected deaths in apparently healthy persons, raising calls for closer scrutiny and possible regulation. Drinks containing both caffeine and alcohol were considered unsafe by the FDA in 2010 because the caffeine obscured “some of the sensory cues individuals might normally rely on to determine their level of intoxication.”⁴

The swift change in public perception of energy drinks from harmless mild stimulant to lethal, unregulated drug is unprecedented. Energy drinks were introduced in the United States in 1997. Since then their popularity has increased: US residents consumed an estimated 2.3 billion energy drinks in 2005 and 6 billion in 2010.⁵ About 6% of young men in the United States report consuming a daily energy drink. In a recent survey of US overseas troops, 45% reported daily use.⁶ Sales of energy drinks in the United States increased 16% in a single year to almost \$9 billion in 2011.⁷

Product labels for most energy drinks do not list their caffeine content. Many energy drinks contain “natural” ingredients, such as ginkgo or milk thistle, allowing these drinks to be regulated as “dietary supplements” rather than as medications. The 1994 Dietary Supplement and Education Act classifies products containing herbs and other natural ingredients as supplements rather than drugs, allowing manufacturers to side-step disclosure of caffeine dose, even though some brands do provide the information.⁸ In contrast, caffeine-containing products such as No-Doz and Caffedrine,

marketed as over-the-counter drugs, are required to provide dose.

The millions of persons consuming energy drinks seek more energy, alertness, or stamina yet may be unaware of the amount of caffeine they are ingesting. Consequently, unintentional caffeine overdoses have resulted in serious illness and rare deaths from caffeine poisoning.^{8,9}

Caffeine poisoning has only recently been characterized. Swedish researchers conducted an extensive analysis defining toxic doses of caffeine.^{9,10} Of 5000 forensic autopsies performed in Sweden each year, 1% had caffeine levels exceeding 10 $\mu\text{g}/\text{mL}$. To place this in perspective, a single cup of standard brewed coffee results in blood caffeine levels of 1 to 2 $\mu\text{g}/\text{mL}$. In 16 years of autopsies, 20 cases had caffeine levels higher than 80 $\mu\text{g}/\text{mL}$, a dose considered potentially lethal.⁹ The cause of death for 12 of these patients (average age, 41 years) was caffeine intoxication, although several patients had other medications in their bloodstream.⁹ Arrhythmias were the most common cause of caffeine-related death.

Although blood levels of caffeine higher than 80 $\mu\text{g}/\text{mL}$ have been described, the corresponding dose of caffeine needed to reach that level is not known. Ingestion over a brief time of 3 to 10 g of caffeine might be lethal.^{9,10} Caffeine is well-absorbed and achieves peak blood levels 15 to 45 minutes following ingestion. Caffeine is quickly metabolized by the liver into active stimulants such as theophylline and theobromine. Alcohol and other medications can prolong the 5-hour half-life of caffeine and contribute to its toxic effects. Most current soft drinks and coffees, as well as energy drinks, have about 100 mg of caffeine per serving. A few energy drinks have up to 250 mg per serving (see the related table in the Patient Page).

To reach the possibly lethal dose of 3 g of caffeine, a person would need to ingest at least 12 of the highly caffeinated energy drinks within a few hours. It is not known how many energy drinks were ingested by patients thought to have energy drink-related deaths. A number of contributory factors require exploration. For example, drug-drug interactions relating to caffeine's toxic effects are incom-

Author Affiliations: Infectious Disease Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center and Weill-Cornell Medical College, New York, NY.
Corresponding Author: Kent A. Sepkowitz, MD, Infectious Disease Service, Department of Medicine, Infection Control, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (sepkowik@mskcc.org).

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pletely understood. Caffeine and a number of medications are metabolized via the cytochrome P450 1A2 pathway. Some fatalities might have resulted from heightened and prolonged caffeine levels attributable to multiple drugs being metabolized by the same metabolic pathway. The rate of drug metabolism varies from person to person and depends on body size, age, sex, and genetic factors. Some people may have cardiac or liver diseases that could increase susceptibility to caffeine-related adverse effects, making a routinely consumed amount of caffeine more dangerous. Some ingredients in energy drinks may confer toxicity or promote drug-drug interactions.

Given the increasing popularity of these products, physicians should ask their patients about their use of energy drinks, particularly young men who are the heaviest users. In addition, information that defines the caffeine content of most commercially available products should be provided (see related table in the Patient Page). A ceiling of less than 500 mg of caffeine per day is generally considered a safe daily dose. A lower daily dose or no caffeine ingestion should be considered for patients with heart disease or liver disease.

The appropriate role of the FDA and other regulators in the oversight of energy drinks is yet to be defined. A logical first step might be to require placing the caffeine content of energy drinks on their label. In Sweden, restriction of caffeine tablet sales from 250 to 30 pills per customer appeared to decrease the rate of fatal caffeine overdoses, sug-

gesting that deliberately restricting the sale of preparations with a high dose of caffeine might be an effective approach.⁹ Publicity about energy drink–related deaths should inform the public of the potential dangers of these products.

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