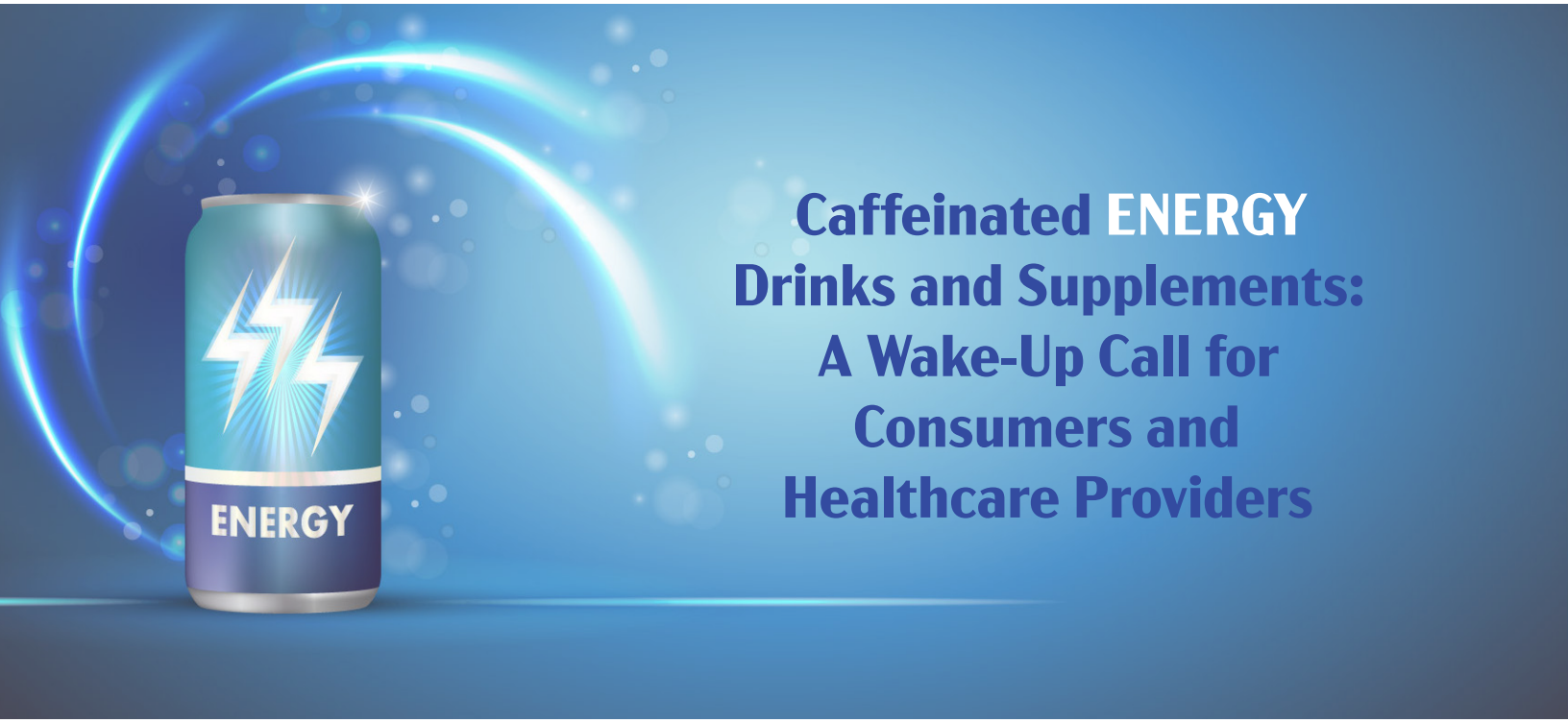

Caffeinated ENERGY Drinks and Supplements: A Wake-Up Call for Consumers and Healthcare Providers

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Energy drinks have been one of the fastest growing products in the beverage and supplement industries. Their ubiquity in society has grown exponentially over the last two decades, with over 500 new brands launching since 2006. These drinks are touted to improve mental and physical performance of the consumer via the addition of energy-enhancing ingredients such as caffeine, taurine, herbal extracts, sugar, and B vitamins.[1] Despite their prevalence and proposed benefits, concerns have been raised regarding the safety of consuming these products. Serious cardiovascular and neurological adverse events have been reported in connection to energy drinks, as well as a number of highly publicized deaths. As a result, the ease of accessibility of these products, especially to minors and young adults, has been called into question.

Caffeine, the most popular ingredient amongst these beverages, is a naturally occurring methylxanthine alkaloid. After oral ingestion, it is rapidly absorbed from the gastrointestinal tract into the bloodstream and readily distributed throughout the body. The primary mechanism of action of caffeine is the antagonism of adenosine receptors, which indirectly results in the release of norepinephrine, dopamine, and serotonin in the brain as well as increased levels of circulating catecholamines.[2] The psychostimulant effects of caffeine can cause the consumer to feel more energetic and awakened, but like with any drug there also exists the risk of toxicity and overdose with excessive use. Consuming a large quantity of caffeine over a short time frame can result in physical and mental manifestations of acute caffeine intoxication. Patients may report feeling anxious or restless, be unable to sleep, or display symptoms of psychomotor agitation. Other physical findings will often include an elevated heart rate, tremor, diarrhea, diuresis, or nausea and vomiting.[3] In the most severe of overdose cases, patients may even present with hemodynamic instability, a hypertensive crisis, cardiac arrhythmias, or seizures, which have the potential to be fatal.[4]

Despite the health risks associated with the overconsumption of caffeine, energy drinks and similar energy supplements are not regulated any differently by the Food and Drug Administration (FDA) than conventional food or beverages. Minors, who are often unaware of the dangers of caffeine intoxication, are therefore able to freely purchase any quantity of these products without limitation. Public pressure over the last decade to address these specific safety concerns for minors has led some companies to make changes to their labels and marketing tactics. For example, companies

that are members of the American Beverage Association follow a set of guidelines implemented in 2014 to encourage responsible use of energy drinks. Under these guidelines, beverages must be labeled with the caffeine amount per serving and a warning for special populations (children, pregnancy, caffeine-sensitive), and companies agree to not market their products to children under the age of 12.[5] However, it is important to note that these extra regulations are neither universal nor mandatory; companies can voluntarily offer warnings and information to keep consumers safe but are not legally obligated to.

Self-regulation of beverage companies coupled with a lack of significant government oversight has resulted in the aggressive marketing of energy drinks targeted towards 18- to 35-year-olds. Unsurprisingly, this population tends to be the largest consumer of energy drinks and supplements.[6] The allure of a quick fix to revitalize energy and increase performance makes overtired college students and working adults the prime population to target for sales. One survey conducted among college students found that approximately half of participants consumed at least one energy drink per month to make up for their lack of sleep and increase energy levels.[7] Results from another survey found that up to 15% of 16- to 24-year-olds reported consuming energy drinks on a weekly basis.[8] The high prevalence of energy drink use within these populations presents an increased risk of caffeine-related harm, especially if one ingests the alkaloid from other sources. In general, 400 milligrams of caffeine per day is considered the upper limit of safe consumption for the average adult.[9] Notably, the caffeine levels in most energy drinks typically range from 100 to 300 mg per serving. Thus, having more than one beverage or even enjoying a cup of coffee on the same day can exceed what is considered a safe daily limit.

Long QT syndrome is a heart signaling disorder, either congenital or acquired, that can cause fast, chaotic heartbeats (arrhythmias).

There have been several highly publicized cases in which individuals unknowingly consumed large amounts of caffeine and suffered fatal consequences. The most recent of these occurred in October 2023 when a lawsuit was filed against Panera Bread for the wrongful death of Sarah Katz, a 21-year-old college student.[10] Katz had consumed a large "Charged Lemonade" and went into cardiac arrest hours later. Katz had a known diagnosis of long QT syndrome and as a result actively avoided energy drinks and other highly caffeinated beverages. The lemonades, which can contain between 245 to 390 mg of caffeine, are equivalent to the caffeine content of two to three cans of Red Bull or three to four standard cups of coffee. Despite the large amounts, Panera's lemonades were not advertised as a highly caffeinated beverage, nor did they display a total caffeine amount per serving. This changed in the weeks following Katz's death: Panera Bread now displays advisories on their website and mobile app to consume Charged Lemonades in moderation due to the high amount of caffeine.

While devastating and preventable, Katz's death is not the only reported case of a fatality from Panera's Charged Lemonades. Although little information is currently available, another lawsuit regarding a 46-year-old man's death from cardiac arrest was filed against the company on December 4, 2023.[11] On October 9, Dennis Brown, who had a history of hypertension, collapsed on his walk home from work after consuming three Charged Lemonades earlier in the day. The lawsuit argues his cardiac arrest was triggered by the defective design of the beverage, and as a result, the company should be held liable. The public outcry following the deaths of both Katz and Brown has further highlighted the need for regulation surrounding the labeling and sale of highly caffeinated beverages. For certain populations with underlying health problems, a clearly marked "caffeine" label and subsequent warning could prove to be the difference between life and death. Consumers should be empowered with the knowledge of what is in their products in order to best protect themselves from harm.

In addition to the risk of intoxication or overdose, caffeine possesses the ability to interact with prescription medications, drugs of abuse, or other supplement products. Interactions may be pharmacodynamic or pharmacokinetic in nature and take place through a variety of mechanisms. An individual's preexisting conditions, disease states, or genetic makeup can impact their ability to metabolize caffeine, and as a result, "sensitivity" to caffeine can vary drastically from person to person.[12] Caffeine is primarily metabolized by CYP1A2, an enzyme with documented polymorphisms. Consequently, individuals who possess such genetic markers or concurrently take medications that modulate the activity of CYP1A2 will experience altered levels of metabolism. Inducers of CYP1A2 may impede the energizing effects of caffeine, while inhibitors of the enzyme can lead to potentially toxic levels of caffeine or another object drug within the body. For example, competitive inhibition of CYP1A2 occurs with concurrent administration of caffeine and clozapine, which can lead to increased concentrations and subsequent toxicity of clozapine.

Other prescription drugs display similar pharmacokinetic interactions with caffeine, including but not limited to atazanavir, cimetidine, fluvoxamine, ciprofloxacin, and theophylline.[12] It is imperative that practitioners acknowledge the potential for significant drug interactions between prescription medications and certain foods, beverages, or supplements. To maintain efficacy and reduce the risk of toxicity from either caffeine or a prescribed medication, patients taking drugs with CYP1A2 activity should be asked about their energy drink consumption and counseled on the potential risks of caffeine intake while receiving therapeutic treatment. The prevalence of caffeine use within society and the potential for harm dictates that energy drinks, at the bare minimum, should be a talking point in the conversation between practitioner and patient.

Caffeine can also potentiate pharmacodynamic interactions with therapeutic medications. Interactions may have synergistic, additive, or antagonistic effects if consumed within a small enough time frame.[12] When paired with psychostimulant drugs like cocaine or amphetamine salts, caffeine can exhibit synergism—amplifying the sympathomimetic effects of both drugs. Patients mixing substances may experience acute tachycardia; hypertension; cardiac arrythmias; or, in severe cases, a myo-

cardial infarction.[13] Energy drinks can even be co-formulated with hidden sources of sympathomimetic compounds, like the legal herbal supplement bitter orange. Consequently, consumers may unknowingly expose themselves to a dynamic interaction by drinking a beverage with multiple active ingredients. In addition to other stimulants, caffeine may exhibit additivity with drugs that lower the seizure threshold. Caffeine excitatory effects have historically been used as a tool to induce and lengthen seizures during electroconvulsive therapy.[14] Therefore, ingestion of large doses of caffeine while on medication like bupropion or tricyclic antidepressants can place consumers at increased risk for a seizure.[12] Practitioners should ensure patients are counseled on the increased risks of cardiovascular and neurologic toxicity secondary to the high levels of caffeine contained in most energy drinks if prescribed one of the above drugs.

Drug interactions with caffeine are not limited to prescription medications. Recreational drugs like tobacco, cannabis, and alcohol can also modulate the metabolism of caffeine in the body. Polycyclic aromatic hydrocarbons, known inducers of CYP1A2, are found in the smoke of cigarettes and other combustible tobacco products.[15] Inhalation of tobacco smoke therefore reduces levels of caffeine by accelerating metabolism. Smokers who look to energy drinks for revitalization may not achieve the desired effects from one beverage, and in turn may consume larger quantities. Cannabinoids, like tobacco, may also modulate CYP1A2 activity, but the data in support of this hypothesis is not nearly as robust. One literature analysis, which examined in vitro studies exploring the pharmacokinetic effects of cannabinoids, concluded that THC, CBD, and CBN are likely inhibitors of CYP1A2.[16] Thus, pairing an energy drink with cannabis can potentially increase the risk of caffeine intoxication.

The recreational drug paired most frequently with energy drinks is alcohol. Alcohol-mixed energy drinks (AmEDs), like the notable Vodka Red Bull, are ubiquitous at bars and commonly consumed in social settings. Studies conducted in the United States revealed that in 2017, 10.6% of high school students and 31.8% of young adults age 19–28 had consumed an AmED in the last year.[17] Unfortunately, this popular pairing has the potential to be problematic. It is hypothesized that the stimulant effects of caffeine can mask the intoxicating effects of alcohol, leading consumers to believe they are less impaired than they truly are.[18] As a result, people may consume larger quantities of alcohol which can increase the risk of injuries, accidents, or acute ethanol poisoning. Furthermore, the mechanisms of both alcohol and caffeine modulate the neurotransmission of dopamine within the body. Increased dopamine stimulation from caffeine may potentiate the rewarding effects of alcohol, drawing users to consume more ethanol and continue consuming AmEDs in the future.[17] Fortunately, due to the recognized risks of ethanol alone and in combination with caffeine, the sale of beverages co-formulated with these two active ingredients is banned in the United States. As of 2010, the FDA deemed caffeine an unsafe food additive to alcoholic beverages and issued formal warnings to companies who sold such products.[19] However, this does not prevent bars or other public establishments from serving AmEDs. And as mentioned earlier, there is no mandate requiring energy drinks to warn against the concurrent consumption of alcohol.

Evidence revealing the negative and potentially lethal consequences surrounding the consumption of energy drinks highlights the need for tighter regulations of these products. Banning the sale of energy drinks to people under the age of 18, capping the total amount of caffeine per serving, proper labeling, and widespread public education are all potential means of preventing adverse outcomes from these beverages.[20] Other countries have already begun implementing progressive legislation to place more scrutiny on caffeinated beverages. As of 2014, all European countries have required manufacturers to display warning labels on beverages with >150 milligrams per liter of caffeine as "high caffeine content" in addition to other health warnings.[21] Until the United States can catch up and better regulate beverage companies, public education may prove the most effective means of keeping consumers safe. Unfortunately, it is estimated that only half of clinicians regularly provide counseling to adolescent patients on the risks associated with energy drink consumption.[22] Increasing the number of practitioners who incorporate energy drinks into their counseling conversations can help limit the harm these beverages may pose to unsuspecting patients.

Caffeine and other biologically active ingredients within these beverages may derive from plants but come with no guarantee of safety. Emphasizing the importance of reading nutrition labels and researching the caffeine contents in all beverages can help equip patients with the tools to keep themselves free from harm.

As trusted sources of information, healthcare providers have an important role in informing patients and other members of the public about the contents and potentially dangerous effects of energy drinks. Many are often unaware of the impact energy drink ingredients and consumption can have on both physical and mental health. The high caffeine content present within many of these drinks puts patients at risk for acute caffeine toxicity or interactions with drugs and medications. Strategic marketing of these "all natural" or "plant-based" products has deceived consumers into believing they are perfectly harmless. Healthcare providers must help combat this notion by making patients aware of the effects of excessive energy drink consumption. Caffeine and other biologically active ingredients within these beverages may derive from plants but come with no guarantee of safety. Emphasizing the importance of reading nutrition labels and researching the caffeine contents in all beverages can help equip patients with the tools to keep themselves free from harm. Healthcare providers must be proactive in advocating for the safe and responsible consumption of energy drinks, especially in children and young adults. Until stronger regulations are enforced on energy drink companies, healthcare workers will have to serve as the first line of defense against the dangers of energy drinks by educating consumers about their risks.

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