REVIEW ARTICLE

Energy Drinks; Impact of Use in Patients with Diabetes, Obesity, and/or other Cardiometabolic Spectrum Conditions.

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Abstract

Energy drinks (EDs) are a brand of non-alcoholic beverages that are typically distinguished from regular sweetened caloric beverages (SCBs) by their augmented carbohydrate and purine alkaloids/methylxanthines (usually either caffeine; 1,3,7 trimethylxanthine and/or theobromine; 3,7 dimethylxanthine) content touted as being able to boost energy levels. At initial inception they were dominantly consumed by young adults (with an initial strong male preponderance) but in the last few decades as their variety, main-stream acceptance and widespread marketing has increased their appeal and consumption has become widespread and virtually universal to the general population including virtually all age, gender and ethno-racial demographics. With increased widespread consumption concerns regarding their safety and potential impact on long term health have started being raised. This is particularly pertinent as their regulatory oversight and monitoring is often presently minimal.

Diabetes and Obesity represent two dominant halves of the global diabesity epidemic that afflicts over 650 million adults worldwide with over 40% of the adult population in the United States affected. The well documented cardiometabolic spectrum (CMS) of diseases that are associated comorbidities of diabesity are well documented and it is inevitable that the increasing consumption of EDs would involve these group of persons in adult, geriatric, adolescent and even pediatric populations.

This review summarizes and synthesizes the limited published data on the described and potential health impact of EDs use particularly in persons with and/or at risk for diabetes, obesity and other CMS diseases to make the case for need of more careful study, monitoring and scrutiny of the use of these beverages in these group of persons. After providing an overview of the history, epidemiology and major components of EDs we detail the major potential and reported systemic complications of their long-term intake especially in at risk populations discussing the modulating effects of genetics, present comorbidities and alcohol co-intake. The prominent roles of caffeine and carbohydrates in the potential poly-systemic effects of EDs and their reported toxidromes is also highlighted while acknowledging the limitations in the present body of published data in this area.

Keywords: Energy drinks, Sweetened Caloric beverages, Alcoholic beverages, Diabetes Mellitus, Obesity, Cardiometabolic syndrome, Caffeine

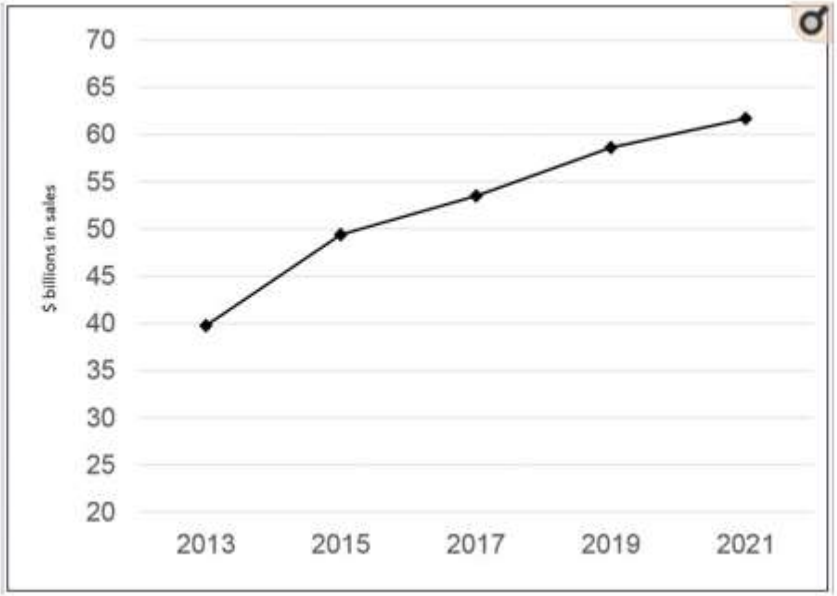
INTRODUCTION:

Overview of energy drinks (EDs) and broad classification (typical contents, types etc).

Energy drinks (EDs) are non-alcoholic drinks that differ from soft drinks or so called sweetened caloric drinks (SCBs) or sports drinks in that they contain comparatively high levels of caffeine and sugars in addition to added dietary supplements[1]. They are primarily sold in 8 -16 ounce containers, but some are sold as smaller, concentrated "shots" of 2 or 3 ounces. Energy beverages have had an increasing presence in the United States over the past few decades and now represent a significant percentage of beverage consumption.

The first energy drink released in the United States was "Dr. Enuf" in 1949, and the first European energy drink was Red Bull, launched in 1987 in Austria [2]. The energy beverage market has grown exponentially since Red Bull was brought to the United States in 1997, followed soon after by other major brands such as Rockstar (2001), Monster (2002), and Full Throttle (2004). In the United States, nearly 200 new brands of energy beverages were launched between 2006 and 2007. Regionally, the US is the largest consumer of energy beverages by volume (roughly 290 million gallons in 2007 or 3.8 qt per person per year) but a similar increase in energy beverage consumption has been reported worldwide [1]. Figure 1 below shows the secular trends of global EDs consumption with the projected future trajectory.

Figure 1: Projected trends in Energy Drinks (EDs) consumption World-wide



Business forecasts indicate that current popularity of EDs is unlikely to subside in the coming years. This global market is projected to top $60 billion in sales revenue within 5 years with attendant global appeal and consumption in virtually all age and demographic strata[3-7].

Manufacturers aggressively market energy beverages claiming that they increase energy, augment cognition, and improve physical performance; though there is no strong evidence to support such claims[1,2]. EDs manufacturers have gradually broadened their consumer focus from athletes to young people; they are currently actively targeting people between 15-30 years of age[2,3,6-17]. This population is generally healthy, relatively active, and includes a higher population of sports-enthusiasts and high-risk takers.

Epidemiology and History of Energy Drinks (EDs) and Sweetened Caloric Beverages (SCBs).

There is growing concern regarding the safety of energy beverages and how they are displayed alongside other sweetened caloric beverages (SCBs) or sport drinks such as Gatorade and Powerade. This can potentially mislead consumers into believing there is no distinction between these products. In

addition, the availability of energy beverages in most grocery or convenience stores makes it very easy for consumers to choose them without fully understanding what is in the energy beverage[18,19]. Ultimately, very little research has been focused on many of the ingredients found in EDs[20,21].

There are a multitude of ingredients that comprise energy beverages and many of these have not been subject to comprehensive studies. Furthermore, many of these ingredients are unregulated in the United States and are not subject to the stringent requirements of the US Food and Drug Administration (FDA). Interestingly, this contrasts with more conventional soft drinks which do fall under regulation by the FDA[7,8,15,20-22].

Generally, the dense carbohydrate content in EDs is far greater than is recommended for most physically active people[7,8,15,20-22]. Additionally, there are reports that suggest an association with energy beverage consumption and individuals who participate in high-risk behaviors, such as alcohol, tobacco, or marijuana use, high-risk sexual behavior, and aggressive behavior[7,8,15,20-22]. Due to the complex blend of ingredients in energy beverages, cause and effect is difficult to ascribe to one specific additive. Indeed, it may be the combination of certain ingredients rather than the singular contribution of an individual one that causes the overall effect.

History and Epidemiology of AMED (alcohol mixed with energy drinks).

In addition to the consumption of energy beverages, alcohol mixed with energy drinks (AMED) has become increasingly popular, despite scientific evidence suggesting that energy beverages may have deleterious health effects that can be aggravated by admixture with alcohol[23-30]. The danger of AMED first became apparent when pre-mixed caffeinated, alcoholic beverages such as *Four Loko* became popular. This brand was marketed aggressively for younger consumers in their 20s-30s with bright, colorful packaging that promoted the ability to mask the alcohol's effects while simultaneously intensifying the intoxication. This marketing demographic was also more likely to engage in high-risk behaviors [23-31]. The threat posed by this dangerous mix became increasingly evident after several reports emerged of college students hospitalized after excessive consumption. Finally, on November 17, 2010, the FDA issued a warning that AMED was a concern for public health. The high amount of caffeine added to malt alcoholic beverages was deemed an "unsafe food additive."

While energy drinks are often consumed alone, they are also frequently used as mixers for alcoholic beverages. Consumption of AMED beverages might not present a major public health concern if it were a rare practice. However, survey data gathered from college students when premixed caffeinated alcohol was still available (i.e., before November of 2010) indicated that about half of college students reported consumption of at least one ED each month and 54% of these ED users combined them with alcohol. Other survey data indicated that 25% of past 30-day alcohol drinkers consumed at least 1 AMED in the past month[27,32,33]. Survey data gathered around this same time period in a convenience sample of college students also found that consumption of AMED was common, with 1 in 10 college students reporting consumption of at least 1 AMED in the past 2 weeks. Another probability sample of college students surveyed in 2010 revealed that lifetime and past year AMED use prevalence rates were approximately 75% and 65%, respectively. Finally, athletes are a college

population that is likely to engage in heavy episodic drinking. One sample of student-athletes revealed that 37% had consumed AMED in the past year.

Several studies showed that AMED consumption is associated with a variety of additional risks when compared to alcohol alone. However, causal statements cannot be made based on these associations since the studies are not randomly assigning subjects to drink choices and then observing resulting behaviors. AMED consumption in epidemiological studies and field research is measured in participants who self-select these beverages. By contrast, experimental studies can manipulate whether subjects (human or animal) are receiving AMED versus alcohol to directly compare the pharmacological properties of these two types of beverages. However, it is important to highlight that the above work on the associations between AMED beverages and risky behaviors is very useful in designing appropriate experiments to better understand the potential attendant risks. Though pre-mixed caffeinated alcoholic beverages were discontinued in the US, the combined use of caffeine and alcohol continues through the informal impromptu combination of EDs with alcoholic beverages especially among adolescents and college students. The practice of mixing energy drinks with alcohol has been consistently linked to harmful drinking behaviors[30,32-35]. Martz et al used nationally representative survey data on 6,498 12th grade students and found AMED to be associated with many sociodemographic, academic, social and substance use factors[27,32,33]. In addition, AMED use was noted to be related to driving under the influence, which is a serious health concern. In another longitudinal study by Tucker et al, surveys were conducted in 696 adolescents from 16 middle schools in Southern California and AMED was also associated with high-risk behaviors such as drug use and substance use-related unsafe driving[29].

Interestingly, several studies have shown that the primary reason for AMED consumption is masking the taste of alcohol (55% in one study of US college students) and the flavor of the energy beverage itself (30%) (et al Obrien [36-39]. By comparison, few subjects reported consuming AMED for the purpose of increasing alcohol intake and masking the appearance of inebriation (5%).

The notion that AMED increases total alcohol consumption is controversial[40]. It has been hypothesized that the stimulant effect of caffeine may counteract the psycho-depressant effect of alcohol as the suggested putative mechanism for mediating this suggested effect. If true, then this may exacerbate the already well established negative consequences of excessive alcohol consumption[24-26,33,40]. A group of investigators performed a systematic review and metanalysis of 14 studies to compare alcohol consumption of AMED consumers with alcohol only consumers[29,30]. It was shown that AMED drinkers do drink significantly more alcohol in general, but they do this irrespective of whether alcohol is mixed with energy beverages or not. Prior research revealed that AMED consumers were primarily Caucasian, young adults and male[41,42]. They tended to have lower income and education levels, tended to be single, use illicit drugs, smoke tobacco products and/or cannabinoid products, and engage in high-risk taking behavior[40,43-51]. Other increased high-risk behaviors associated with AMED consumption include unprotected sex, and driving while intoxicated[39,43-46,49-58]. These differences between AMED and alcohol-only consumers may be caused by differences in underlying personality characteristics between the groups (such as risk-taking behavior)[53,55-58]. Recent research supports this by showing

that level of risk taking behavior is an independent predictor of binge drinking even after controlling for demographics and lifestyle factors[40,59].

Epidemiology of Energy Drinks (EDs) and associated Comorbidities.

Average consumption of sugar-sweetened beverages in the United States ranges from 6.8 servings per week among white women to nearly 12 servings per week among Mexican American men. Women generally consumed less than men[60,61].

The market value for energy drinks is continually growing and the annual worldwide energy drink consumption is progressively increasing. However, issues related to energy drink ingredients and the potential for adverse health consequences remain to poorly characterized. These drinks vary widely in both caffeine content (80 to >141 mg per can) and caffeine concentration as well as carbohydrate content and other potentially bioactive additives.

The drink and beverage patterns and trends among school-aged children in the US have been studied and tracked for years, and a recent study covered the period between 1989-2008 with the specific background that high intake of SCBs in childhood is linked to increased risk of obesity and type II diabetes later in life, so using three nationally representative surveys of dietary intake, they investigated beverage patterns and trends among US school aged children from 1989/91 to 2007/08. 3583 participants were included ages 6-11 y old. They reported per capita trends in beverage consumption, percent consuming, and amount per consumer for the following categories of beverages: SCBs, caloric nutritional beverages (CNB) and low calorie beverages (LCB). As part of the published results and recommendations they highlighted the progressive upward trends of SCBs consumption and the parallel increases in childhood obesity prevalence, as well as suggested educational and policy interventions[15]. No mention was however made in this report of EDs consumption in children in this cohort.

Another study to determine the physiologic and glycemic responses to EDs by people with type 1 diabetes was performed in 2015. In a double-blind randomized comparison of Red Bull, Red Bull Light and a control drink, 16 adults (11 females; average age 31.5 years) with type 1 diabetes and an average glycated hemoglobin (A1C) of 68 mmol/mol were given 750 mL of Red Bull, Red Bull Light and Suso Orange in a random order.

The results showed that consumption of Red Bull and Suso Orange were associated with an early sustained rise in blood glucose, which was augmented by Red Bull ($p=0.02$). A transient rise in systolic blood pressure (115.9 mm Hg to 124.5 mm Hg and 115.8 mm Hg to 125.9 mm Hg, respectively, both $p<0.01$) followed consumption of Red Bull and Red Bull Light. There were less consistent changes in diastolic blood pressure and heart rate so they stated that consumption of energy drinks can result in a significant carbohydrate load for people with diabetes, and patients must consider the need to adjust their insulin regimens appropriately. Based on this short term study it was thus concluded that Caffeine-containing EDs can cause a rise in blood pressure, which may be an important consideration for individuals at risk for diabetes-related complications[62].

On the other hand, participants from the Raine study in Australia were investigated in cross-sectional and prospective fashion to explore associations between frequency of EDs intake in young-adults and body mass index (BMI) and Metabolic Syndrome (MetS) and its components. No significant associations were found between frequency of ED-intake, and BMI, MetS or its individual components over

two years (ages 20-22 years). Though they advised that future studies should include volume of EDs consumed and longer follow-up [63]. Similar recommendations were made by the Indian Academy of Pediatrics based on their review of nationally available data of SCBs, EDs and related beverages and fast foods in India[13].

Death from cardiovascular disease in the US fell 32.7% from 1999–2009, and continued to decrease through 2014. Life expectancy in the US rose about 6 years from 1970–2000, and increased CVD survival was responsible for 3.9 of those years. Much of this improvement is from advances in treatment, but slightly over half is due to improving risk factors, particularly with statin drugs and improved diabetes control[60,61].

Diabetes mellitus affects ~10% of US adults, with ~ 95% of cases being type 2 diabetes mellitus. Type 2 diabetes mellitus is however becoming increasingly common in children and adolescents[12,60,61,64-73]. The prevalence of type 2 diabetes mellitus in children/adolescents has increased by 30.5% from 2001-2009, and now constitutes about half of all childhood diabetes. Diabetes mellitus is associated with reduced longevity; men and women with diabetes mellitus live an average of 7.5 and 8.2 years less[12,60,61,64-73].

From 2009-2012, ~ 33% of US adults ≥20 years old have hypertension. From 2003-2013, deaths from hypertension increased 8.2%. During this 10-year period, the corresponding values were a 14.4% increase in non-Hispanic Whites; a 1.7% increase in Hispanics; and a 9.1% increase in non-Hispanic Blacks[60,61,74].

From 2007-2012, the prevalence of CKD (stages 1–5) was 13.6%[60,61,74-79].

From the early 2000s, the national prevalence of metabolic syndrome in the United States peaked in 2001–2002 and began to fall. This was largely from decreases in prevalence among women. Generally, the national prevalence of hypertriglyceridemia and hypertension have decreased, but hyperglycemia and elevated waist circumference have increased[60,61]. With the high prevalence and growing incidence of the CMS diseases, the ongoing diabesity epidemic worldwide and the extension of these disease states from the prior demographic of middle age and geriatric populations to now affecting young adults, adolescents and even pediatric age groups it is inevitable that a growing proportion of these patients will be exposed to EDs that have progressively become among the most popular consumed beverages. This unfortunate confluence of expanding population groups is however fraught with considerable potential for potentially significant morbidity and mortality[1,2,7,8,14,17,22,80-106].

DISCUSSION:

Discussion of major Energy drinks (EDs) components and potential impact of these suggested by animal and targeted human studies (caffeine, glucose, sugar alcohols, taurine and other additives).

While EDs have a variety of ingredients with different concentrations and forms, Caffeine and glucose are the main drivers of the observed metabolic effects. One of the most studied ingredients of energy drinks is caffeine. Caffeine can be added to energy drinks as a purified caffeine or as a plant extract. Caffeine has been demonstrated to have performance enhancing capacity and capacity to induce impairment of insulin sensitivity. Current data from epidemiological studies however suggest that long term coffee consumption reduces incidence of type 2 diabetes. Studies results also suggest that

others components of coffee are biological active and can thus counteract the effect of caffeine by itself. This is one example of the complex nature of the caffeine in EDs. Thus findings from studies of coffee and tea cannot be equated to presumed metabolic impact of EDs Therefore, the impact of energy drinks containing caffeine could vary widely depending on the specific chemical composition of the products in question[107,108].

It is also important to appreciate that most of the studies of caffeine containing EDs have been conducted in a healthy adult populations. It is largely unknown what the effects of chronic EDs use in children and adolescents given the higher exposure in relation to body weight and body surface area. It is also unknown what the impact on growth, development and gonadal maturation could be and the possible predisposition for future metabolic and hemodynamic derangements . The potential impact of chronic EDs use in geriatric populations or even in younger adults with significant underlying cardiometabolic disease are also largely unknown. The preferences, sensitivity to and metabolism of caffeine is known to be affected by genetics, Weight and adiposity as well as demographic factors like age, sex, race, and ethnicity. In addition, environmental factors like diet, lifestyle, physical activity levels etc are known to impact caffeine processing and presumably would likely apply to the cardiometabolic effects of caffeine containing EDs[109-111].

Caffeine containing EDs alter the secretion of incretins by the gastrointestinal cells. Incretins are responsible for >50 % of the insulin secretion after a meal. The most studied incretins are the Glucagon like peptide 1 (GLP-1) and the Gastric inhibitory peptide (GIP)[112]. Secretion of GLP-1 is well known to blunt insulin resistance[113]. Coffee seems to independently stimulate GLP-1 secretion but this appears to happen independently from caffeine and not surprisingly this same effect has not been consistently demonstrated with caffeine containing EDs. Many ingredients of the EDs are absorbed in the small intestine; other ingredients get in contact with the large intestine and colon where alterations in the microbiota can occur. Changes in the gut microbiota has been associated with obesity and type 2 diabetes in various recently reported studies and cohorts[114]. Artificial sweeteners (which are included in some EDs) and chronic consumption of sugar (which is a natural consequence of most chronic EDs use because of their high carbohydrate content) are known to be associated with potentially deleterious changes in microbiota balance by affecting bacterial gut diversity and gene expression promoting metabolic dysfunction and obesity[115-117].

Caffeine is the most common ingredient found in EDs. It is often combined with taurine, glucuronolactone, guarana, sugar alcohols, amino acids, B vitamins, or various other additives to form what the manufacturer's market refers to as an "energy blend". When high doses of caffeine are combined with these other substances, the metabolic effects cannot always be predicted. Research has shown that some of these substances are important for proper body function, but the amounts contained in energy drinks often far exceed the recommended daily allowance[20,21]. We will briefly discuss the major components of the typical "energy blend" of EDs below.

Caffeine is an adenosine receptor antagonist and acts as a stimulant to the central and peripheral nervous system. It is largely responsible for the cognitive effects of energy beverages[2,107,118-121]. Caffeine reaches a peak plasma concentration within 30-120 minutes after consumption[119,121-124]. Most energy drinks contain 70-200 mg of caffeine per 16-oz serving. For comparison, an 8-oz cup of

coffee has approximately 80-100 mg of caffeine. Several studies have shown caffeine can raise heart rate and blood pressure in part from its sympathetic stimulation, though adverse effects (including insomnia, anxiety, gastrointestinal upset, headache, and tachyarrhythmias) generally do not manifest unless ingestion is greater than 200 mg[20,21,110,121,124-126].

Caffeine has also been shown to adversely affect arterial stiffness. In their report, Mahmud and Feely showed that the consumption of caffeinated coffee, but not decaffeinated coffee, acutely increased aortic stiffness in healthy individuals[1,127,128].

Conversely, when consumed in moderate quantities, caffeine has been shown to be an effective physical performance aid. Caffeine mobilizes fat stores and stimulates muscle to use fat as fuel which delays the depletion of muscle glycogen and allows for prolonged exercise. The critical period in glycogen sparing appears to occur during the first 15 minutes of exercise when caffeine has been shown to decrease glycogen utilization by as much as 50%. Thus, caffeine allows glycogen to be available during the later stages of exercise. The comparatively high caffeine content in EDs has a diuretic effect which is more pronounced in first time users (the kidneys eventually adapt in 3-5 days of use) but caffeine should be avoided during prolonged exercise in hot environments as it can predispose to dehydration[106,121,124].

Taurine is the most abundant intracellular amino acid in humans. It is involved primarily in the modulation of skeletal muscle contractile function and may attenuate exercise-induced damage. Taurine has other physiological functions in bile acid conjugation and cholestasis prevention; it works as an inotropic and chronotropic agent which may prevent arrhythmias and participates in central nervous system neuromodulation. It may improve exercise capacity and performance, but this has not been quantifiably demonstrated. However, the amounts of taurine found in popular energy beverages are far less than the amount expected to result in either therapeutic benefits or adverse events[20,129-131].

Guarana is a plant that is native to the Amazon and has historically been used for its caffeine-rich fruits to increase awareness and energy[132-137]. Guarana seeds contain more caffeine than any other plant in the world and also contain theobromine and theophylline (which are methyl Xanthine stimulants) thereby yielding a stronger stimulating effect than caffeine alone [2,138]. The amount of guarana found in energy beverages is less than the amount expected to deliver therapeutic benefits or cause adverse events. However, there have been case-reports of young subjects presenting to the emergency department with overdose of caffeine after over-consuming guarana-based energy beverages[132-137].

Glucuronolactone is a naturally occurring substance produced in small amounts within the body. It may assist the body's natural defense mechanism for eliminating carcinogens and tumor promoters. Toxicokinetic data on glucuronolactone in rats are in accordance with the limited human data. Unfortunately, little research has been done in humans and therefore a firm evidence based conclusion of whether glucuronolactone is harmful or beneficial in the form it is included in some EDs cannot be made[139-142].

Milk thistle extract (*Silybum marianum*) is a lipophilic extract that acts as an antioxidant by reducing free radical production and lipid peroxidation and may have hepatic antifibrotic activity. It has anecdotally been used to treat alcoholic liver disease, acute and chronic viral hepatitis, and toxin-induced liver diseases[143].

Milk thistle extract is included in some energy drinks, notably Rockstar, and purported as a liver-protectant agent which may imply anticipation for the product's use with alcohol which has already been discussed and alluded to. Even with direct oral supplementation of milk thistle extract though, in vitro studies have demonstrated that it is unlikely that enough of the ingredient could be absorbed to have any appreciable hepato-protective effect in humans[144].

EDs contain large amounts of sugar, usually in the form of glucose, high fructose corn syrup, or sucrose, which is the body's most basic currency for energy. Administration of glucose or other carbohydrates before, during, and after prolonged exercise has been shown to postpone fatigue, conserve muscle glycogen, and improve performance. The amount of sugar in a typical energy beverage is about 54 grams, which is about 13 teaspoons of sugar. Concerningly, long term exposure of the body to excessive amounts of simple sugar is known to be associated with development of obesity, insulin resistance, possibly fatty liver disease and ultimately type 2 diabetes[2,11,21,65,80,85,92,93,101,103,145-148]. We outline a few of these sweeteners below.

High-fructose corn syrup was first introduced to the food and beverage industry in the 1970s as a replacement for sucrose (simple table sugar) due to its improved stability and ease of use. It is a fructose-glucose dimer liquid sweetener that is derived from corn and often used as an alternative to sucrose (common table sugar). Today its use is nearly equivalent to sucrose in the United States (whereas 90% of the nutritive sweetener used worldwide is sucrose). Recent data suggests that its abundant consumption may be responsible for many cardiometabolic and other health problems[98,101,103,104,145,148-155]. Epidemic studies have shown that heavy consumption of high fructose corn syrup is associated with the development of cardiovascular and metabolic diseases. However, despite research proving its negative impact on human health, the use of high-fructose corn syrup is not presently not restricted[145,149-151,156].

Sucralose (*Splenda*) is a non-caloric high intensity sweetener that has been approved globally since 1998 by the FDA for use in foods and beverages[157-159]. It is about 600 times sweeter than sucrose. Unlike sucrose, sucralose is not metabolized for energy, therefore, sucralose does not affect blood glucose levels. It has not been shown to cause harm to humans (et al Omar, 2013). Inositol is a sugar-alcohol commonly used as a sweetener in foods as it has less caloric content than sucrose and has no demonstrable adverse effects with the exception of osmotic diarrhea at very high doses[160].

Maltodextrin is a polysaccharide that is digested by the body as a simple carbohydrate and is thus easily converted to instant energy. Although no causal relationship between the consumption of maltodextrin and negative health effects has been reported, this does not mean that overconsumption of maltodextrin has no effects. Regular intake can cause weight gain, impaired insulin sensitivity, and lipemic derangements. The use of maltodextrose in concentrated energy drinks may help reduce the risk of gastrointestinal distress compared to glucose or sucrose[161].

Ginseng is one of the most popular herbal supplements in the world. It is thought to increase energy, relieve stress, and improve memory by stimulating the hypothalamus and pituitary glands to secrete corticotropin though these claims have yet to be demonstrated. Some studies have demonstrated the benefit of preventing Type 2 diabetes with consumption of ginseng[162,163]. Some adverse effects associated with ginseng are hypotension, edema, palpitations, vertigo, headache,

insomnia, and mania. However, the amounts in energy beverages are far below the amounts expected to deliver therapeutic benefits or cause adverse effects. In a 2016 study involving young, healthy volunteers, ginseng did not have a significant impact on ECG or blood pressure parameters[102].

Ginkgo biloba extracts have been used in traditional Chinese medicine for centuries. It is alleged to have antioxidant properties, modify vasomotor function, and reduce thrombo-embolic events. However, no large well-controlled randomized trials have demonstrated clinical benefit[164].

L-carnitine and L-tartrate are amino acids made predominately by the liver and kidneys to increase metabolism. They have been shown to stimulate lipid metabolism. Recent evidence indicates L-carnitine plays a decisive role in preventing cellular damage and favorably affects recovery from exercise stress[165]. There is evidence of a beneficial effect in recovery from strenuous exercise, however, the amount of L-carnitine in energy beverages is likely not enough to see any appreciable effect in recovery. In addition, no advantage appears to exist in giving an oral dose greater than 2 grams of L-carnitine at one time, because absorption studies indicate saturation at this dose.

B-vitamins include Thiamine [B1], Riboflavin [B2], Niacin [B3], Pantothenic acid [B5], Pyridoxine hydrochloride [B6], Biotin [B7], Inositol [B8], and Cyanocobalamin [B12] which are water soluble vitamins required for proper cell function and energy production[166]. These B-vitamins are marketed as a crucial component needed to "unlock" the energy provided by the simple sugars in energy beverages. Thus, these energy drinks almost universally contain a high concentration of these B vitamins[166].
Table 1 below summarizes the major contents of 4 common and popular EDs.

Table 1: Major contents and ingredients of typical Energy Drinks (EDs).

Ingredient (mg) per 16 oz	Red Bull	Rockstar	Monster	Full Throttle
Caffeine	160	160	160	160
Carbohydrate (high fructose corn syrup, sucrose, sucralose, inositol, Maltodextrin)	58	63	54	58
Sugar (grams)	52	63	54	58
Taurine		Listed		Not Listed
Guarana		Listed		Not Listed
Glucuronolactone		Listed		
Ginseng extracts		Listed		
Ginkgo biloba extracts		Not Listed		
L-carnitine and L-tartrate		Listed		
Thiamine (B1)		Not Listed		
Riboflavin (B2)		Listed		

Niacin (B3)	200%	100%	200%	200%
Pantothenic acid (B5)	100%	100%	200%	50%
Pyridoxine hydrochloride (B6)	500%	100%	200%	200%
Biotin (B7)		Not Listed		
Cyanocobalamin (B12)	160%	100%	200%	200%
Milk Thistle extract (Silybum marianum)		Listed		
Calories	220	270	220	220

As concerns regarding the long term effects of chronic consumption of high glycemic index carbohydrates in SCBs and EDs has grown, in an attempt to assuage this, more and more EDs are substituting various lower caloric sugar substitutes (SS) and artificial sweeteners (AS) in their contents to maintain palatability while reducing total caloric load. While this review is not a treatise on SS and AS some understanding of this "niche" area of clinical nutrition is important in understanding the potential impact that these agents may have in the overall health profile of such EDs. In standard SCBs the use of SS and AS is designed to reduce total caloric content however their use in EDs is often additive to regular carbohydrates as the total elimination of the latter is perceived to negatively impact the "performance" enhancement, "energy boost" and "improved endurance" with reduced fatigue that these beverages are touted to offer.

While the AS and SS products are generally presumed safe with no credible rigorous data to suggest that they are associated with long term risks for cancer, caries, weight gain and/or cardiometabolic disease, they are closely monitored and regulated by the FDA and their equivalent regulatory bodies worldwide. Broadly speaking these agents can either be designated as GRAS (generally regarded as safe) or with FDA mandated and defined acceptable daily intake (ADIs) akin to the well established RDA norms for established dietary nutrients[167-171].

While the AS and SS products can be subclassified based on the caloric content as nutritive (low calorie) or non- nutritive (zero calorie), as a class these agents generally have much greater sweetness profiles and much less caloric content than regular sucrose, glucose or other common dietary sugars and carbohydrates[167-171]. While the list of available and approved AS and SS products is quite extensive and variable depending on geographic locations, here in the United States, the 6 high intensity sweeteners that are FDA approved with defined GRAS status and/or defined ADIs are saccharin(*sweet 'N low*) which is the oldest in the class in the market, aspartame (*Equal and Nutrasweet*), acesulfame potassium (*Ace-K and Sweet one*),sucralose (*Splenda*) which is the most popular and widely used such product in the United States, neotame and advantame. Other widely used AS and SS products are Stevia (*Truvia and Pure via*) which has a defined ADI, sugar alcohols Xylitol, sorbitol, mannitol and Isomalt which are all nutritive sweeteners as well as erythritol which is a much lower calorie sugar alcohol, monk fruit sweetener which is a zero calorie product with a GRAS designation and no specified ADI as well as allulose (*D-psicose and Dolcia prima*) which is a very low calorie sweetener[167-171].

Despite the comfort of FDA oversight, monitoring and surveillance of the AS and SS

industry it is important to understand that just like coffee is way more and often metabolically quite different from plain caffeine, any of these agents once added into the mixture of an EDs cocktail could potentially have different and distinct metabolic effects compared to when consumed alone in small amounts. There is an increasing body of published data for example that suggests that while coffee consumption may have beneficial effects on the gut microbiota profile, energy drinks including those with added AS and SS may have deleterious effects suggesting that the combination of ingredients in EDs may well overwhelm and counteract the putative beneficial effects of caffeine alone on the gut microbiome[92,117,172-174].

The EDs production industry is a financial juggernaut with progressively increasing consumer demand, market distribution and associated revenue generation. It would be nigh impossible to provide a comprehensive listing of available EDs but using annual revenue generation, extent of market distribution, estimates of bottles sold and estimates of popularity there are various published rankings of EDs available one of which is detailed below in table 2 to provide a snapshot idea of the huge revenue stakes involved in this growing industry[3-5].

Table 2: Top dozen ranked Energy Drinks (EDs) based on earned market revenue.

Rank	ED name	Est. Annual Generated Revenue (US $)	Base Headquarters
1	Red Bull	~ 6.13 B	Austria
2	Monster	~ 3.37 B	U.S.A.
3	Rockstar	~ 918M	U.S.A.
4	Eastroc Super drink	~ 350.12 M	China
5	NOS	~ 107.79 M	U.S.A.
6	Lucozade	~ 501.8 M	U.K.
7	Oronamin	~ 102.8 M	U.S.A./Japan
8	Burn	???	U.S.A.
9	Xyience	~ 25 M	U.S.A.
10	Zevia	~ 100 M	U.S.A.
11	Hi-Tiger	~ 10 B	China
12	Bang Energy	~ 200 M	U.S.A.

Health effects and Consequences of acute and chronic Energy drinks (EDs) use.

There are no long term studies on the effects of caffeine, taurine, and glucuronolactone on the body. Norway, France and Denmark have banned the sale of Red bull, partly in response to a study in rats that were fed taurine rich EDs and exhibited bizarre behavior, including anxiety and self-mutilation[20,21].

Few comprehensive literature reviews have been done to detail and explore the potential adverse health effects of energy drinks or link the adverse health effects with recommendations and guidelines for

limitation of energy beverages use in certain age groups or population type [1,13].

Verster and others in a series of studies and reports concluded that although some reports suggest that energy drinks lead to reduced awareness of intoxication and increased consumption, a review of the available literature shows that these views are not supported by direct or reliable scientific evidence[30,175-178]. It has also been suggested that a personality profile with higher levels of risk taking behavior may be the primary reason for increased alcohol and drug abuse per se, with the co-consumption of energy drinks being one of the many expressions of that type of lifestyle or personality[30,40,59,176-178].

In a prospective study, 508 AMED consumers were followed for 56 days[179-181]. Within-subjects, occasions of AMED consumption were compared to AO occasions. The analyses revealed that on AMED occasions significantly more alcohol was consumed. Interpretation is difficult as no data were presented regarding estimated or measured amounts of alcohol consumed on AMED and AO occasions, nor on the relative frequency of both types of drinking occasions. After controlling for estimated BAC, no significant differences in subjective intoxication were found.

Overall, review of the literature seems to suggest that, compared with alcohol alone, mixing alcohol with energy drink has little significant effect on total alcohol consumption, subjective intoxication, and alcohol-associated risk-taking behavior or other negative consequences. Alcohol itself seems to be the cause of many negative consequences of high alcohol intake per se. The literature is overwhelmingly consistent with the notion that AMED consumption is just one manifestation of an underlying trait for greater alcohol consumption along with a cluster of other risky behaviors[30,40,59,176-181].

While there is considerable complexity to understanding the pharmacodynamics of EDs and their effects in humans, a simplification of the concepts involved involves understanding that the vast majority of these products amount to variable **c**ocktails of **c**affeine and **c**arbohydrates with other additives (the concepts of the 3 Cs). The potential adverse reactions of the use of these beverages though not well studied in large carefully designed standardized randomized controlled prospective clinical trials can be anticipated based on what is already known about these two major ingredients in clinical medicine and therapeutics. Such adverse effects can be broadly classified as either acute or chronic with some potential effects being transitory or subacute in nature.

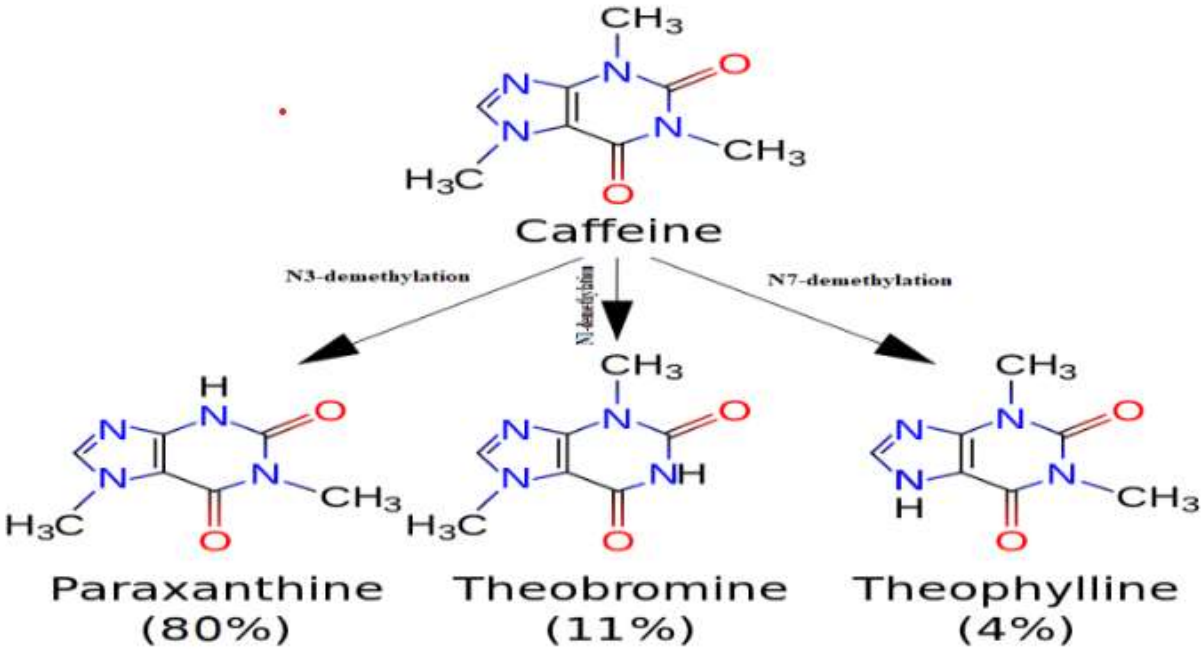
A 2019 longitudinal study by Dillon et al of 1,958 freshmen compared health behaviors between caffeine users and nonusers and EDs users and nonusers[182]. The data evaluated men and women separately. Eighty percent of the subjects reported current use of caffeine, with women more likely to report use than men (85% to 71%, $p < 0.0001$). In addition, there were significant differences by gender in the types of caffeinated beverages consumed. Women were more likely to report drinking coffee, tea, soda, and other caffeinated beverages than men, while men were more likely to report consuming EDs. Women who used any caffeine were more likely to use alcohol (64% vs. 53%, $p = 0.0297$), in comparison to women who did not consume caffeine. In addition, women who used any caffeine were more likely to report marijuana, sedative, stimulant, and tobacco use than women who did not use caffeine. EDs, regardless of frequency of use, were associated with all adverse health behaviors, but only among female students in this cohort.

More than half of the participants were Caucasians (52.7%), with African American (19.4%), Asian (15.2%), other races/ethnicities (12.7%) completing the racial admixture of the studied cohort. No ethno-racial distinction was apparent in any of the observed findings as regards caffeinated beverages vs EDs use.

Caffeine is one of three common methxanthines (purine alkaloids) that are ubiquitous in the common beverages of coffee and tea as well as in chocolate. The other two theobromine and theophylline are more common in tea and all three are phosphodiesterase inhibitors. While the beneficial effects of caffeine and other methylxanthines intake is well documented in healthy individuals including improved attention span and mild improvements in cognitive function and mild psychostimulation, excessive intake and/or excess serum levels are well described to cause the well defined toxidrome of caffeine toxicity.

To provide some guidelines in this regard the FDA has set a daily recommended daily allowance (RDA) of caffeine intake of ~ 400mg for healthy adults (the equivalent content of ~ 4 cups of regular coffee or 10 cans of a regular cola soda drink) [118]. It is important to remember that this RDA does not apply to pediatric populations nor patient populations with significant comorbidities that could affect the pharmacokinetics of caffeine. Specifically as shown in figure 2 below the major component of caffeine's metabolism to other less pharmaco-potent methylxanthines and their subsequent degradation occurs predominantly in the liver with small amounts of the original methyxanthines excreted unchanged in the urine[123,183]. It is also important to be aware that the mild innate diuretic effect of methlxanthines; theophylline > caffeine > paraxanthine > theobromine is also associated with increased urinary losses of sodium, chloride, calcium, phosphorus, magnesium and other urinary solutes with potential clinical consequences and implications for caffeine and other methylxanthine intake among patients with significant renal disease and/or renal functional deficits[123].

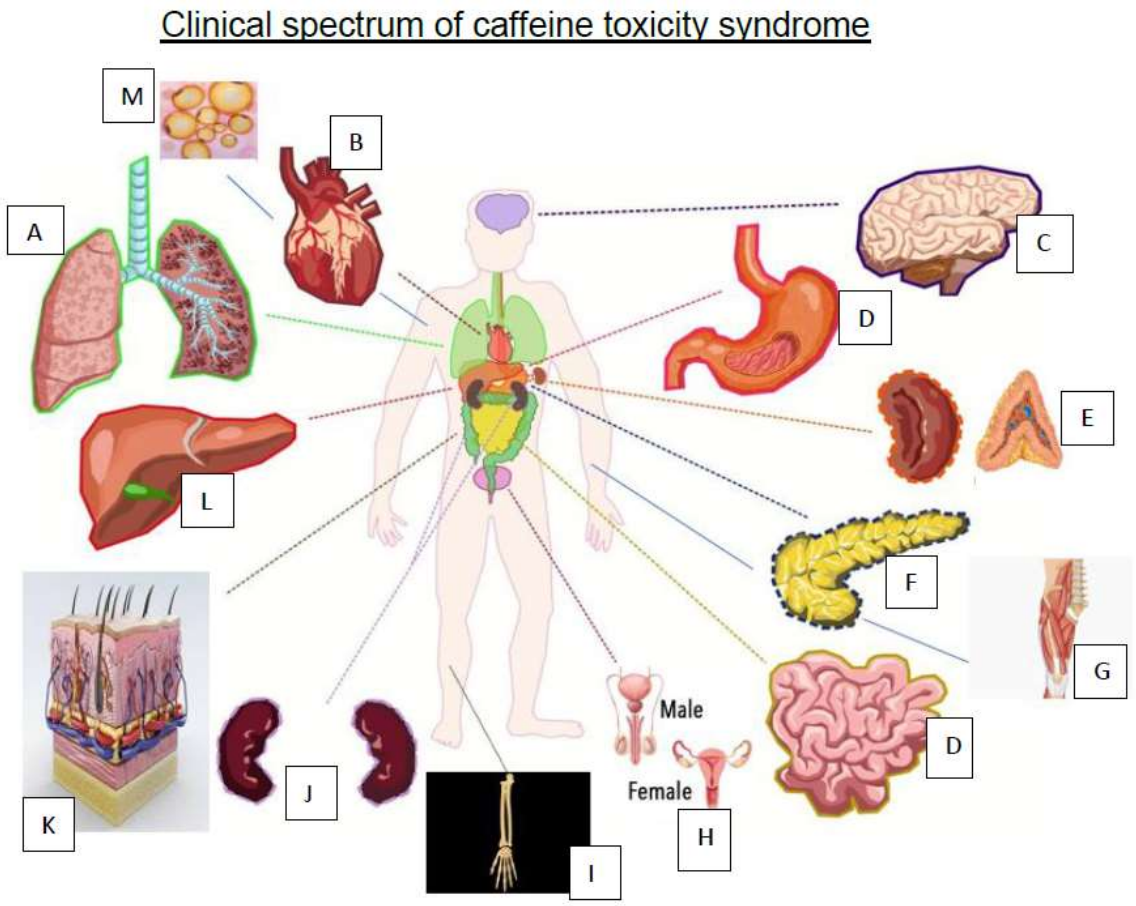
Figure 2: The metabolism of Caffeine



While this is typically associated with acute intoxication, one area of toxicology and therapeutics that provides an idea regarding the potential acute and possibly chronic consequence of EDs is the syndrome of caffeine toxicity. Figure 3 below demonstrates the spectrum of clinical presentations associated with caffeine toxicity which can be conceivably expected among susceptible patients who use excessive amounts of caffeine containing EDs[82,106,107,110,121,122,124,126].

Similarly, the potential toxic and pathogenic consequences of carbohydrate excess can be classified into acute effects associated with systemic glucotoxicity (often with associated lipotoxicity) as well as the more chronic consequences of long term carbohydrate excess (that can be conceived as carbo-toxicity)[65,86-88,145,146,184-186]. It is reasonable to anticipate that the potential clinical sequelae and toxidromes of long term EDs use in susceptible patients would be amalgam of the clinical presentations of both caffeine and carbohydrate excess as they are the dominant ingredients of these products[90,102,103,126,187-195].

Figure 3: The Caffeine toxicity syndrome spectrum.



A; Pulmonary - Tachypnea, bronchodilation, hyperventilation with consequent respiratory alkalosis, Respiratory failure in most severe cases
B; Cardiovascular- Sinus tachycardia, tachyarrthymias, atrial fibrillation, acute coronary syndromes, blood pressure elevation
C; Central Nervous system and Psyche - Agitation, confusion, delirium, hallucinations, psychosis, chronic insomnia, irritability, cephalgia, myoclonus, muscle cramps, seizures, garbled speech, hyperaggression, mania, panic disorder, techiopsiae, tinnitus, generalized anxiety, caffeine withdrawal state, caffeine dependence state, hyperpyrexia, Coma in most severe cases
D; Gastrointestinal tract - Gastritis, diarrhea, Gastroesophageal reflux disease, Gastric ulcers, dehydration
E; Spleen + Adrenals; leucocytosis and ACTH dependent hypercortisolemia, Increased cathecoleamines
F; Pancreas – hyperglycemia, insulin resistance
G; Skeletal Muscle – Rhabdomyolysis, fasciculations, myalgias
H; Gonads – Subfertility, miscarriages, possible teratogenesis
I; Bone + Bone Marrow – leucocytosis, decreased bone density and increased bone loss. Increased osteoporosis risk
J; Kidney – Diuresis, Polyuria, hypokalemia, hypophosphatemia, hypocalcemia
K; Skin – Flushing, hyperhidrosis, hypesthesia
L; Glycogenolysis, Gluconeogenesis
M; Adipocytes – Lipolysis

Figure 4 below shows the potential clinical spectrum of clinical presentations and disease states that could thus potentially result from chronic EDs use especially in susceptible patients and populations. Presumably, included in this subset would be pediatric and geriatric patients as well as patients who already have significant chronic diseases affecting the functional status of any of the major organs/tissue involved in the metabolism of the major components of EDs. This would include the vast majority of patients with significant CMS diseases like diabetes, obesity, fatty liver disease, obstructive sleep apnea, chronic obstructive pulmonary disease, dysmetabolic syndrome, prediabetes states and atherosclerotic vascular disease. In addition, other potentially high risk patient populations to consider would including patients with clinically significant underlying psychopathology including substance abuse and dependency states, chronic kidney disease and patients with genetic inherited disorders of metabolism that can impact the catabolism and elimination of methylxanthines, carbohydrates, sugar alcohols and/or specific amino acids like taurine[2,14,80,82,84,88,90,100-102,105,106,108,111,122,126,127,129,147,148,153,183,187,190-193,195-202].

Several studies demonstrate cardiac effects such as increased heart rate and blood pressure after consuming EDs[2,82,84,127]. This was attributed to the caffeine content of the energy drink. Additionally, other cardiac issues and arrhythmias have been documented following over-consumption of energy beverages[203]. Other studies suggest that consuming EDs impair endothelial function and stimulate platelet activity through arachidonic acid-induced platelet aggregation[2,82,84,91,127,187,204,205]. Recent reports also suggest an association between EDs overconsumption and arterial dilatation, aneurysm formation, dissection and rupture of large arteries[94,97,187,189,190,206,207].

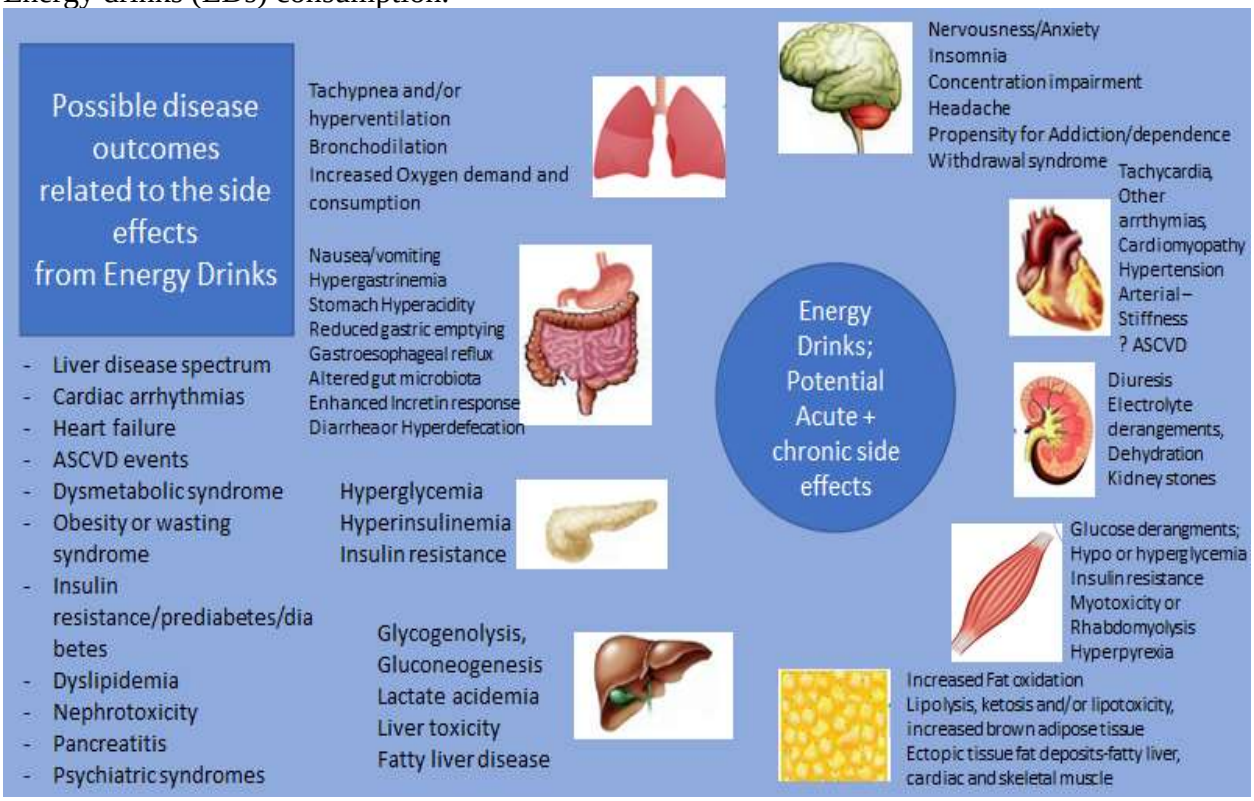
EDs can also impact neurologic function[2,53,107,122,183,206,208]. High caffeine intake can cause acute and chronic daily headaches by stimulating a pro-nociceptive state of cortical hyperexcitability. Four caffeine-induced psychiatric disorders have been defined including caffeine intoxication, caffeine-induced anxiety, caffeine-induced sleep disorder and caffeine related withdrawal disorder. Several reports suggest that energy drinks may contribute to ischemic stroke and epileptic seizures[1,20,94,122,209,210]. Hallucinations might be observed in individuals that consume more than 300 mg of caffeine per day, possibly from the high cortisol that occurs after ingesting high amounts of caffeine.

EDs also usually contain large amounts of carbohydrates which may increase the risk of obesity and type 2 diabetes[93,94,211]. Additionally, the high carbohydrate content in EDs may reduce the functional activity, diversity and gene expression of intestinal bacteria resulting in increased risk of obesity and metabolic syndrome[114,117,157,212].

The caffeine in EDs have been shown to enhance diuresis. Therefore, energy drinks should be avoided during prolonged exercise in a hot environment because of the potential for dehydration. Studies have reported that dehydration at a level of 1.5% during prolonged exercise may result in an increase in body temperature, heart rate and perceived rate of exertion with increased potential for heat exhaustion and malignant hyperpyrexic states with increased morbidity and even mortality potential especially in at-risk persons[17,106,121,126,141].

Figure 4 below provides a pictorial display of the spectrum of potential health consequences of acute and/or chronic EDs use especially in at-risk subjects.

Figure 4: Potential clinical spectrum of adverse effects and disease states attributable to chronic Energy drinks (EDs) consumption.



In view of the public health impact and importance of atherosclerotic cardiovascular disease in disease morbidity and mortality in adults, the question of the role and potential impact of EDs in modulating cardiovascular disease risk is an important one but unfortunately has not been well studied and characterized to date[2].

A study published in 2016 in Advances in Nutrition analyzed the impact of EDs on the cardiovascular system, their potential mechanisms and also analyzed well controlled, randomized crossover studies that used continuous beat-to-beat measurements and provided evidence that cardiovascular responses to the ingestion of energy drinks are best explained by the action of caffeine and sugar, with little influence from other ingredients. However, a role for other active constituents, such as taurine and glucuronolactone, cannot be ruled out[187].

Other studies suggest that EDs consumption can lead to an acute adverse hemodynamic profile with an augmented cardiac workload and diminished cerebral blood flow velocity, even during a mental stress test. These adverse changes are most likely caused by caffeine or by the effect of an interaction between caffeine and sugar on the cardiovascular system, whereas auxiliary substances apparently play a minor role. These cardio- and cerebrovascular changes in response to EDs have however only been studied in healthy young humans but not in those at highest risk of cardiovascular events or those with pre-existing hypertension and/or impaired cerebral circulation. The authors indicate that future studies should consider the following: *1*) the use of continuous blood pressure measurements, when possible; *2*) measuring hemodynamic responses for a minimum of 60 min ED post consumption; and *3*) maintaining a standard posture throughout the test. Given their global popularity and estimated market

value of >$40 billion, accurately assessing the potential adverse effects of EDs has important implications for the prevention and management of obesity, type 2 diabetes, and cardiovascular disease.

An important metanalysis was recently published analyzing the impact of acute energy drinks consumption on electrical heart disease. Although a toxicity threshold has been established for caffeine, the safety profile of whole EDs consumption has not yet been similarly defined. They conducted the study following the PRISMA guidelines. Three reviewers conducted two separate systematic searches on PubMed on October 24 and December 3, 2019. Out of 250 potential records, 43 prospective clinical studies assessing the effects of EDs on heart rate (HR) and other electrocardiographic (ECG) parameters were included. A meta-analysis was conducted. After EDs consumption, resting HR increased in 71.1 % of studies but was only significant in 38 %. QRS increased in all but two protocols; evidence on PR interval was contradictory, and corrected QT interval (QTc) increased compared to baseline in all but one study, exceeding the pathological limit value in two of them. T wave changes were seen in two studies, and one study reported a ratio of 5 to 1 in the number of ectopic beats[207].

One of the greatest difficulties in the interpretation of the published data on EDs use and their health impacts is the huge diversity in the publications. Beyond huge variances in study types and data sources, the paucity of true randomized studies especially long term ones and the ethical difficulties of even designing such studies including the difficulties in including exposure “blinding” in such trial designs make the interpretation of the published studies and data fraught with risks and limitations. There are also a wide range of covariates, ethno-demographic and anthropometric variables that have to be considered when interpreting and comparing the reports on EDs from various settings and populations. The huge diversity in types of EDs, amount, duration and frequency of consumption, co-administration with alcohol and/or SCBs as well as variables such as age, gender, race and ethnicity need to be considered in evaluating reported effects of EDs. It is also critically important to distinguish between clinical effects that can be rightly attributed to these agents in healthy young adults as opposed to clinical effects observed in patients with significant background comorbidities including but not restricted to cardiometabolic diseases and conditions like diabetes, essential hypertension, dyslipidemia, fatty liver disease, atherosclerotic vascular disease, heart failure etc.

Adding to this complexity are the wide worldwide differences in regulation, approval requirements and post marketing surveillance of EDs world-wide. While not directly consequent upon EDs themselves since they are artificial rather than natural food products/beverages these questions and considerations are important because of the potential of contamination by toxins that can result from the manufacturing process as has been so widely described with the far better screened and regulated pharmaceutical industry[213,214].Beyond the well described potential for some of these EDs to have microbial contaminants with the consequent infective enteritis syndrome, more insidious and concerning are reports of possible contamination with heavy metals and other bioactive agents with capacity to have chronic endocrine disruptor consequences[215-220].

In the United States the FDA lists caffeine as generally safe in concentration of <200 mg/kg. There are however caveats to this. Specifically in 2008 Maine, Kentucky and Michigan introduced legislation that banned the sale of highly caffeinated drinks to children <18 y old, but the bills were defeated, California is considering a bill to require special labels on

alcoholic beverages to avoid confusion with nonalcoholic beverages as well for caffeine containing beverages. In Canada they require warning labels, recommend a maximum daily consumption amount, and specifically advise against mixing ED with alcohol[17]. The rest of the world have widely different regulations regarding EDs. For example United Kingdom Committee on Toxicity investigated Red Bull and determined that it was safe for the general public but that children <16 y old should avoid drinks with high caffeine content. Finland states that drinks that contain >150 mg/L of caffeine must be labeled "not recommended for children, pregnant women or people sensitive to caffeine". In Norway, EDs can only be sold in pharmacies while in Sweden sales to children <15 are banned[17]. Argentina's senate has proposed banning EDs in nightclubs while Uruguay prohibits ED entirely, same as in Denmark. Other countries like France and Netherlands reviewed EDs safety and declared no risk.

On the other hand, the regulatory status of EDs in most of continental Africa is much less structured and largely patchwork to non-existent. This is of particular importance and potential relevance as Africa is witnessing an increased number of EDs consumers who are primarily concerned about their health, due to the increasing cost of healthcare facilities. Thus, the demand for the nutritive beverage in the form of drinks and mixers is expected to augment the growth of the market studied. Furthermore, to attract new consumers to the category, many players are investing in fruit-flavored energy drinks, especially those more familiar to the African population[221]. With the lack of strict regulation as to health claims that can be made regarding beverages and food products in most African countries it is expected that the use of EDs will continue to increasing and likely among all population age groups and demographics. However, rising concern over health issues associated with EDs including reports of various psychiatric disorders including major depression, generalized anxiety disorder, panic disorder, alcohol dependence, and cannabis and/or cocaine abuse/dependence in relation to concurrent EDs use presumably due to their high caffeine content may be a dampening factor in the market growth of these products in African countries [221].

Concluding Remarks;

The current twin pandemics of obesity and diabetes (the diabesity epidemic) is known to be a result of the toxic interaction between genetically at-risk populations and environmental factors of which dietary patterns and increased high density caloric intake with reduced physical activity levels play a major role. The recognition that intake of SCBs and alcoholic beverages can have an enabling effect both on incidence and prevalence of these CMS diseases has made regulation of their intake a central aspect of the public health policy and clinical counselling efforts worldwide. Often left unacknowledged however is the growing market share and consumption of EDs and their potential to be just as deleterious as these two caloric beverages. EDs generally being a variable cocktail of carbohydrates and caffeine with various other potentially bioactive ingredients because of their popularity in the main-stream media and their suggested utility for improving fatigue, concentration, endurance etc are now extensively used in populations and demographics outside the commonly presumed setting of young physically active adults.

The body of literature on their potential long term health effects is largely disjointed and widely variable but contains enough "signals" to raise the need for closer scrutiny and systematic study especially when used long

term in pediatric, adolescent and geriatric populations. There is enough reported clinical and public health based data on associations with their use to also raise concerns for their potential to induce and/or aggravate common CMS diseases and conditions including but not restricted to type 2 diabetes, obesity, atherosclerotic cardiovascular disease and related disorders like fatty liver disease and the dysmetabolic syndrome especially when imbibed in large amounts over extended periods of time. There is also growing cause for concern regarding their use in subjects who already have significant CMS disease burden in which their profile has to be considered as potentially bioactive pharmaceuticals rather than just recreational/nutritive beverages.

There is need for better designed studies to investigate the lingering questions regarding EDs and their long term safety especially in subject populations that are not healthy young adults. For public health data gathering and analyses, there is also a need to more rigorously and consistently capture information regarding types and amounts of EDs consumption much the same way it is presently done for SCBs and alcoholic beverages as part of the standard social and nutritive history taking process.

Till more complete and carefully obtained longitudinal prospective and cross-sectional data is available it is probably best based on the suggestions from the currently available body of data to adopt a stance of caution and erring on the side of safety regarding recommendations for EDs use in subject populations that are not healthy young adults. Even in the distinct demographic of "young healthy adults" counsel regarding moderate limited EDs use at the most is probably also justified and wise. Comparing secular trends over time between outcomes and CMS disease associations in countries with more strict EDs use restrictions versus with those with more liberal to non-existent regulation and oversight may yield important actionable public health information in the coming years. For now, while little definitive evidence for direct cause and effect is available there is ample reason for caution regarding widespread, long term use of EDs in general populations.

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