Published in final edited form as:
Nutr Rev. 2014 October ; 72(0 1): 98–107. doi:10.1111/nure.12127.

Energy Drinks Mixed with Alcohol: What are the Risks?

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Abstract

Energy drinks are popular beverages that typically include high levels of caffeine and other ingredients such as taurine, or caffeine-containing herbs, such as guarana. While energy drinks are often consumed alone, they are also frequently used as mixers for alcoholic beverages. This review summarizes what is known about the scope of use of alcohol mixed with energy drinks (AmED), the risks associated with AmED, and the objective laboratory data examining how AmED differs from alcohol alone. The weight of the evidence reveals that AmED beverages are riskier than alcohol alone and constitute a public health concern. AmED beverage consumption is frequent, especially in young and underage drinkers. AmED use is associated with elevated rates of binge drinking, impaired driving, risky sexual behavior, and risk of alcohol dependence when compared with alcohol alone. Laboratory research (human and animal) has demonstrated that AmED beverages lead to altered subjective states including decreased perceived intoxication, enhanced stimulation, and increased desire to drink/increased drinking compared to alcohol alone. Possible underlying mechanisms explaining these observations are highlighted.

Keywords

Alcohol; Energy drinks; Caffeine; Intoxication; Stimulation

Introduction

Energy drinks are popular consumer products advertised to decrease lethargy and increase energy levels. Energy drinks differ in volume and typical ingredients, but most are sweetened carbonated beverages that contain high levels of caffeine and other ingredients including, but not limited to, taurine, guarana, ginseng, glucuronolactone, and B vitamins.[1-3] While caffeine-containing energy drinks (CCED) are often consumed alone, they are frequently used as mixers for alcoholic beverages. It is common in bars to see patrons drinking cocktails such as a vodka Red Bull® or a Jagerbomb (a shot of the spirit Jagermeister® placed in a pint glass filled with an energy drink). Up until November of 2010, a variety of premixed caffeinated alcoholic beverages were available (with brand

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Declaration of Interest: The authors have no other competing interests to declare.

names including Four Loko®, Moonshot®, Sparks®, B-to-the-E®, and Joose®). The risks of alcohol mixed with energy drinks (AmED) were first noticed when these premixed beverages were on the market. Many underage and young adult drinkers were admitted to emergency rooms with high levels of intoxication after consuming these products, prompting physicians and scientists to raise concerns about the safety of these products.[4] The US Food and Drug Administration (FDA) promptly responded to such concerns by reviewing the available scientific data and expert opinion on combining energy drinks/caffeine with alcohol. After such review, the determination was made that caffeine was an unsafe food additive when combined with alcohol.[5] Concerns about caffeinated alcohol included the risk that consumers may underestimate how intoxicated they were even though caffeine does not alter blood alcohol content levels and thus would not reduce the risk of harms associated with drinking alcohol.[6-8] Elevated risks of alcohol poisoning, sexual assault, and impaired driving were also listed as potential concerns.[9] Given the reviewed scientific evidence and expert opinion, the FDA sent warning letters to alcohol manufacturers asking for their own scientific evidence that the addition of caffeine and other stimulants to alcohol was GRAS (generally recognized as safe).[10] Manufacturers of these products promptly responded to the warning letters by voluntarily removing caffeine and other stimulant ingredients from their alcoholic beverages.[11]

While the above history about the availability and then removal of premixed AmED products from the marketplace might suggest that the issue of AmED is now closed, the reality is that the removal of premixed caffeinated alcohol products from the market has just been replaced by consumer-made or bartender-made cocktails that mix energy drinks with alcohol. Consumers are now drinking cocktails that are pharmacologically similar to what was previously available in one product package. For example, Four Loko® (in the formulation available before November, 2010) contained alcohol, caffeine, taurine, and guarana. Many energy drink cocktails today contain the same ingredients in similar doses. Furthermore, the consumption of AmED is becoming more widespread around the world. Concerns from scientists and physicians about the safety of combining CCED with alcohol continue to rise as more data are gathered using a variety of different methodological approaches. Two examples are briefly mentioned before the weight of the evidence is discussed in the rest of this review. First, the Drug Abuse Warning Network, a public health surveillance system in the US, has been monitoring an increased incidence of negative medical outcomes associated with CCED consumption. From 2007 to 2011, emergency department visits in the US involving CCED doubled, with a subset of these visits involving AmED.[12] Second, concerns about AmED arise from recently published data of exposure to CCED that resulted in reports to the US National Poison Data System (NPDS) from 2010 to 2011. NPDS data compile calls to poison control centers. The number of cases involving AmED was 11% of all calls involving CCED. The AmED cases involved underage drinkers (68.2% were less than 20 years of age). Moreover, the incidence of moderate to major adverse effects of toxicity was 39.3% for AmED (as compared to 15.2% for CCED alone). The seriousness of the AmED cases was also reflected in outcomes, with 76.7% of AmED-related phone calls to poison control centers resulting in a referral to a health care facility (as compared to 26.4% of CCED alone phone calls referred to a health care facility).[13] Given that there is continued concern about the risks associated with AmED beverages, the

purpose of this review is to summarize what is known about the scope of use of AmED, the risks associated with AmED, and the objective laboratory data examining why AmED is riskier than consumption of alcohol alone. Certainly, the data coming from emergency room visits and calls to poison control centers justify taking a closer look at AmED beverages.

To summarize this broad and rapidly growing literature, frequency, associative, and causal data derived from a variety of methodological approaches is presented to provide a global picture of the risks associated with AmED.[14] As an overview, data regarding the scope of AmED use indicates that consumption of AmED is common worldwide, particularly in underage and young adult drinkers. Second, AmED consumption is associated with elevated rates of binge drinking, impaired driving, requiring medical treatment, risky sexual behavior, and risk of alcohol dependence when compared with alcohol alone. Finally, causal statements about how AmED can elevate the risks of alcohol consumption stem from data gathered from laboratory studies (human and animal). These laboratory studies indicate that AmED can alter subjective state (by decreasing perceived intoxication, enhancing stimulation, and increasing desire to drink) to a greater extent than alcohol alone. The possible underlying mechanisms accounting for these observations are discussed. In sum, this review highlights recent research that affirms the conclusion reached by the FDA in 2010: consumption of AmED beverages is riskier for the consumer than alcohol alone. However, more research is clearly needed and some knowledge gaps that need to be addressed by scientists will be discussed.

Scope of Use of AmED

Consumption of AmED beverages might not present a major public health concern if it were a rare practice. However, the data gathered on the scope of use of AmED suggest that AmED use is common, especially in underage and young adult drinkers. Prevalence data were first gathered from a variety of samples of college students, which often include a large portion of underage drinkers. 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 CCED each month and 54% of these CCED users combined them with alcohol.[15] Other survey data indicated that 25% of past 30-day alcohol drinkers consumed at least 1 AmED in the past month.[9] 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.[16] 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.[17] 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.[18]

The above studies reflect data collected on a single college campus or across several campuses. However, more recent comprehensive data are now available that provide a better view of the scope of use of AmED. The Monitoring the Future (MTF) Survey examines licit and illicit drug use in US high school students, college students, and young adults using a nationally-representative sample. The MTF data are considered to be one of the nation's

most reliable scientific sources of valid information on trends in drug use in these age groups. Data collected in the 2012 survey revealed that 10.9% of 8th graders, 19.7% of 10th graders, 26.4% of 12th graders, 33.8% of college students, and 36.7% of young adults (ages 19-28) reported consuming an AmED beverage at least once in the past year.[19,20] From the MTF data, one can conclude that AmED use is common, especially considering that these annual prevalence rates include data collected from individuals who do not consume alcohol.

On a broader scale, data gathered from a representative community sample in the US revealed that approximately 6% of the sample reported past year use of AmED. [21] In this sample, AmED users were more likely to be younger. AmED users were also more likely to be hazardous drinkers than other consumers of alcohol. Furthermore, some demographic groups are more likely to consume AmED. One field-based survey conducted in New York City nightclubs revealed that AmED consumers were more likely to be younger and male than consumers of alcohol alone. In addition, patrons of gay nightclubs also reported higher prevalence of AmED consumption than patrons of other nightclubs.[22] Survey research of an Australian community sample also revealed that AmED consumption is common in public venues, emphasizing that situational context could be something that should be more closely investigated.[23]

Scope of use of AmED in other countries appears to be similar to that observed in the US One recent survey of a large national sample of Brazilian college students (n = 12,711) indicated that almost 1 in 3 alcohol consumers reported drinking AmED in the past year.[24] A survey of Dutch college students (n = 6,002) indicated that approximately 1 in 5 college students consumed AmED.[25] Finally, a survey of Canadian college students revealed that almost 1 in 4 students reported consuming AmED in the past 30 days.[26] In sum, mixing energy drinks with alcohol is relatively common worldwide, especially in demographic groups such as adolescents and young adults (including college students).

Risks Associated with AmED

One common reported finding in epidemiological studies with origins in a variety of countries around the world is that AmED consumers are more likely than alcohol alone consumers to be heavy episodic (i.e., hazardous or binge) drinkers.[17,18,21,24,26-29] In addition, results from one national survey from Taiwan (n = 22,085) revealed that AmED consumers were more likely to be dependent on alcohol, when compared to alcohol alone consumers.[27] This observation bears some similarity to the finding from another study that weekly or daily CCED use in US college students was associated with alcohol dependence.[30] Of course, such data are challenging to interpret as the correlation provides no information regarding causality; it is unclear if hazardous drinkers are motivated to consume CCEDs or AmED products, whether CCEDs or AmED increase hazardous drinking, or whether some combination of these mechanisms are interacting. However, other studies have more specifically reported that AmED consumption is associated with greater quantity of alcohol consumed during a single episode when compared to episodes where alcohol is consumed alone.[23,28,31,32] Given these associations, it has been suggested that AmED consumption leads to increased alcohol consumption when compared to alcohol

alone. However, not all reports coincide with this observation. For example, one industry-supported survey of Dutch college students actually reported the reverse observation as students reported consumption of fewer alcohol drinks when consuming AmED compared with consumption of alcohol alone.[25] It is unclear why this Dutch report would differ from many other studies, but price of AmED drinks in that location or other cultural factors could be important and warrant further examination.

The observations from survey research that AmED consumption may lead to increased drinking also coincide with observations of patient admissions related to alcohol use in emergency departments. One study examined the medical records of emergency department visits for intoxication at one hospital to determine if visits followed consumption of Four Loko® (data were gathered in 2010 when Four Loko® was still available with caffeine, taurine, and guarana). Analyses revealed that the individuals who consumed Four Loko® were far younger than the legal drinking age (mean age was 16 years) and many required admission to hospital because of high blood alcohol concentrations leading to unconsciousness or altered mental state, emesis, seizures, and/or tachycardia. More than a third of the patients had blood alcohol levels greater than twice the legal limit.[4]

Field work is another means to confirm that survey data are reflecting actual behavior. One study of bar patrons leaving local bars asked participants to report what beverages they had consumed, whether or not they intended to drive home, and to provide a breath sample. Patrons who had consumed AmED were at a 3-fold increased risk of leaving the bar legally intoxicated (BrAC > .08 g%) and a 4-fold risk of intending to drive home intoxicated, compared to other drinking patrons.[33] Results from another field study revealed that caffeine appears to have a dose-dependent relationship with alcohol intoxication in bars, with highly intoxicated consumers being more likely to have consumed CCED or cola mixers with alcohol.[34] Another field study in 60 bars located in 4 European cities appeared to highlight the role that CCED played in heighted patron intoxication. The researchers observed that promotion of CCEDs in a given location was associated with higher levels of customer intoxication.[35]

Consistent with observations from field work, survey research has also found that AmED consumption is associated with additional risky behaviors beyond the association of AmED and heavy episodic drinking. Individuals who report AmED consumption also report engaging in a variety of risky behaviors and experiencing greater alcohol-related consequences, even after adjusting for the amount of alcohol consumed.[9,26,29,36,37] After adjusting for demographic variables, drinking variables, and risk-taking propensity, it has been reported that AmED users are more likely to be involved in high-risk traffic behaviors including driving after binge drinking.[24,26] Note that this association is similar to that observed in one field study where AmED consumers were more likely to report that they were going to drive home despite being intoxicated.[33] AmED users are also more likely to need medical treatment or be hurt or injured when drinking when compared to alcohol alone consumers.[9,26] In addition, several studies have reported that AmED use is associated with engaging in risky sexual behaviors when compared with alcohol alone.[17,37,38] AmED consumers have also been found to be more likely to use illicit drugs, including marijuana, cocaine, and ecstasy when compared with alcohol-alone consumers.[38] All of the above

studies control for the alcohol consumed (since alcohol use alone would elevate the risks for all of the above risky behaviors). Some, but not all, studies also control for risk-taking propensity and other demographic characteristics that are known predictors of risky behavior. Therefore, it appears that AmED increases a variety of health and safety risks above and beyond what would be observed with alcohol alone. However, findings are not universal in this area, with the results of one online survey of Australians revealing that risk behaviors were actually lower for AmED sessions compared to alcohol alone sessions.[39]

In sum, a variety of studies using different methodologies largely, although not universally, concur that AmED consumption is associated with a variety of 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 risks. The next section describes what is known from human and animal experimental studies regarding the risks of AmED consumption.

Laboratory Studies Examining AmED versus Alcohol Alone

Laboratory research involving both human and animal participants has examined the combined effects of alcohol and CCEDs or the combined effects of alcohol and caffeine (the primary stimulant found in CCEDs) when compared to alcohol alone. Interestingly, results from experimental studies are similar to the findings from survey and field work studies. Double-blind, placebo-controlled experimental studies examining whether AmED differs from alcohol alone suggest that AmED beverages are pharmacologically distinct from alcohol alone and elevate the risks associated with alcohol consumption by altering subjective state and increasing desire to drink more alcohol.

Human studies (including our own work) typically involve recruiting subjects to receive doses of alcohol, CCED, AmED, and placebo in a laboratory setting. Some studies incorporated within-subjects designs where participants randomly received all dose conditions, while other studies utilized between-subjects designs with participants being randomly assigned to one dose condition. In most studies, dose administration is double-blind and dose administration is based on body weight. After consuming the beverage, participants are typically asked to complete cognitive tasks to assess various aspects of performance and questionnaires that assess subjective state. Typically, these objective and subjective measures were assessed when blood alcohol concentration reached a moderate to intoxicating level (.05 - .08 g%), as assessed using a breathalyzer.

Across various human laboratory studies, there are important similarities and differences between AmED and alcohol. First, the similarities should be addressed. Blood alcohol concentrations do not differ when alcohol is administered with and without the CCED/

caffeine, rendering the objective level of intoxication to be similar.[6-8,31,40-45] Second, data from a variety of cognitive tasks reveal that behavior is often similarly impaired for alcohol and AmED, with a few exceptions. Studies have found that AmED (or alcohol combined with caffeine) produces similar impairments to alcohol with regard to decreased response inhibition,[7] increased choice response errors,[7-8,41-43] increased risk-taking,[41] and in terms of alcohol's slowing effects on simple reaction times,[6] coordinated responses,[6,8,43] and information processing.[43]

However, CCEDs or caffeine when mixed with alcohol can sometimes antagonize some of the alcohol-induced impairment of behavioral responses.[7-8,41-43,45] Such counteracting effects of CCED or caffeine on alcohol impairment might pose potential risks for increased abuse of alcohol. For example, in one study of the antagonistic effects of caffeine on alcohol impairment of motor control, it was found that repeated co-administrations of caffeine with alcohol over three days facilitated the development of tolerance to the impairment effect of alcohol alone.[46] Given that alcohol tolerance may contribute to abuse by encouraging the use of escalating doses, that finding raises concerns about the effects of long-term use of alcohol with caffeine, as in the case of AmED use. Other studies have found that AmEDs or caffeine mixed with alcohol can counteract some of the impairing effects of alcohol (i.e., slowing effects on reaction time), but not other effects of alcohol, such as reduced impulse control.[8] Such non-uniform counteraction of alcohol impairments from AmEDs could result in a dangerous combination. A consumer of alcohol alone is typically slow and impulsive. By contrast, a consumer of AmED is also impulsive but is able to react a little quicker. The AmED consumer may be more able to execute risky courses of action whereas an alcohol consumer may be less able to execute all risky impulses due to the slowed ability to execute actions.

The second concern with AmED consumption is revealed by examining the subjective responses from various questionnaires. AmED consumption (or alcohol and caffeine) results in several changes in subjective state that are riskier for the drinker when compared to alcohol alone including: 1) decreased perceived intoxication, 2) enhanced stimulation, and 3) increased desire to drink more alcohol. Decreased perceived intoxication for AmED versus alcohol alone has been demonstrated in at least two different laboratories.[8,41] If a consumer of AmED underestimates alcohol consumption, this increases the likelihood of other potentially risky behaviors such as continued drinking or the inappropriate decision to drive when it is not safe to do so.

Second, enhanced stimulation (or reduced sedation/fatigue) is an almost universal finding in most laboratory studies that have compared subjective state for AmED (or alcohol and caffeine) versus alcohol alone.[7-8,31,40-43,45] Drug-induced stimulation is associated with rewarding effects. Drug users often perceive drug-induced stimulation as positive, sought-after effects from drugs.[47] The enhanced stimulation for AmED (versus alcohol alone) has also been noted in surveys. For example, one online survey of Australians revealed that consumers reported a variety of side effects related to overstimulation (including heart palpitations) on AmED sessions compared to alcohol alone sessions.[39] Again, enhanced stimulation from the CCED mixer could potentially increase the risks of drinking. Sedation is considered to be a protective interoceptive cue that ends a drinking episode. Without the

cue of sedation, a consumer may continue drinking more alcohol. This coincides with the third observation coming from laboratory studies when examining motivation to drink more alcohol.

The desire to drink more alcohol following AmED versus alcohol alone has been compared, and desire for more alcohol (after an initial dose) is elevated for a longer period of time with AmED when compared with alcohol alone. This observation has been reported in studies from two laboratories[41,44] and may account for the observation that AmED consumers are more likely than alcohol alone consumers to drink to intoxicating levels and to screen positive for alcohol dependence.[27]

In sum, the laboratory studies highlight potential risks associated with antagonistic effects of CCEDs and caffeine on alcohol impairment, increased stimulation from AmED consumption, and the disconnect that occurs with subjective and objective state following AmED consumption. However, it is important to note that there is unclear consensus that subjective responses differ for AmED versus alcohol alone. Null observations may be a function of research design. For example, in one study all of the subjects received alcohol or placebo, yet only half received the CCED.[48] As a result, the AmED versus alcohol comparison was a between-subjects comparison that likely lacked statistical power with only 10 subjects per condition. However, variability in subjective response data also may occur in studies based on other factors including the doses chosen (for both the alcohol and CCED), the timing of the subjective assessment (during the blood alcohol curve), the choice of subjective assessment, and the background characteristics of the subjects (light versus heavy drinkers or experienced consumers of AmED or not). While questions remain, it is important to next highlight how animal research on this topic is remarkably similar to what is being observed in human studies.

In the human laboratory studies, reduced perceived intoxication, enhanced feelings of stimulation, and increased desire to drink are the most frequently observed subjective outcomes that occur when AmED is compared to alcohol alone. While a mouse or rat cannot be asked how intoxicated it feels, assessments of stimulation and actual alcohol consumption can be examined using animal models. Locomotor activity provides a means to assess stimulation in mice. Alcohol alone will increase locomotor activity (at least in doses that are not too high thus inducing behavioral sedation). When caffeine or CCEDs are mixed with alcohol, locomotor activity is increased more than alcohol alone.[49,50] These results obtained from two different laboratories are important because the repeated exposure to alcohol alone progressively increases psychomotor stimulant effects (known as behavioral sensitization) and is considered to be a phenotypic marker for the abuse potential of alcohol in both animals[51,52] and humans.[47]

Interestingly, mice differ in alcohol-induced locomotor stimulation. One study divided mice based on whether they were low or high sensitized mice in response to alcohol alone.[49] The researchers then observed the response to AmED in low and high sensitized mice. Both groups had similar and high levels of locomotor stimulation in response to AmED. This observation suggests that AmED in humans may be most problematic for lighter human

drinkers (who are less likely to abuse alcohol) as compared to heavier drinkers, although that would need to be empirically tested.

When assessing whether AmED increases drinking as compared to alcohol alone, three different laboratories have now demonstrated that 5 mg/kg doses of caffeine (similar to human consumption) increases alcohol consumption in ad lib alcohol administration models using rats.[53-55] Is should be noted that this dose effect for caffeine is biphasic with caffeine doses of 10 mg/kg or higher resulting in decreased alcohol intake.[54-55] Although it is challenging to compare animal and human doses of drugs (since rat metabolism is faster than human metabolism), it is notable that most human studies that combine alcohol and caffeine use caffeine doses in the range of 2 mg/kg to 4 mg/kg[7-8,41] which is similar to the caffeine doses being consumed in AmED beverages.

To conclude this section on laboratory research, there is consensus from results of human and animal research on several findings for AmED versus alcohol alone. AmED (or alcohol and caffeine) results in enhanced stimulation (in humans and animals), decreased perceived intoxication (in humans), and increased desire to drink/actual drinking (in humans and animals) when compared to alcohol alone. These observations suggest that AmED is riskier than alcohol alone. Greater drinking may lead to immediate health and safety concerns during a single drinking episode. If AmED consumption is repeated often, greater drinking across time could ultimately lead to serious problems controlling alcohol intake and an alcohol dependence problem. Given that AmED beverages appeal to underage and young adult drinkers, it should be noted that there is no laboratory research that has examined if adolescents respond differently to AmED or alcohol alone.

Possible Mechanisms

The research on underlying neurotransmitter mechanisms explaining why AmED beverages are riskier than alcohol alone has yet to be specifically elucidated. However, there is some research available providing insight into how alcohol and caffeine in combination have effects in the brain. The work has focused on the two neurotransmitters of adenosine and dopamine. Adenosine is an inhibitory neurotransmitter in the brain that is involved in sedation. Over the course of the day in all animals, rising adenosine levels suppress arousal and eventually promote sleep. When alcohol is consumed, alcohol blocks the reuptake of adenosine thus elevating adenosine activity.[56,57] In humans and animals, elevated adenosine activity after alcohol is consumed results in behavioral sedation and feelings of sleepiness. Caffeine has the opposite action on adenosine activity. Caffeine is an adenosine antagonist. By blocking adenosine receptors, caffeine prevents the action of adenosine which decreases sedation and increases stimulation. Caffeine is most effective as a drug when adenosine activity is high and the human/animal feels most sedated.[58,59] Whether elevated adenosine activity in the brain originates from lack of sleep or the acute effects of alcohol may not matter; caffeine will block the action of adenosine and the human or animal will feel and act more stimulated.

Through changes to adenosine, both alcohol and caffeine will also enact changes in dopamine activity (the neurotransmitter that plays a key role in the abuse potential of most

drugs). Activation of adenosine A2A receptors inhibits dopamine transmission.[60] Elevated dopamine activity is involved in the reinforcing properties of alcohol, so elevated adenosine activity regulates alcohol consumption and would keep consumption at a lower level.[61,62] Since, caffeine acts as an antagonist at the adenosine receptor, thus acting to block adenosine activity,[56,62] dopamine activity will be increased when caffeine is on board and more dopamine will be released.[60,63,64] Given what is known at the cellular level, it seems unsurprising that AmED beverages (or alcohol and caffeine) would lead to greater desire to drink or greater drinking than alcohol alone. Adding caffeine to alcohol increases the reinforcing properties of alcohol. While these changes would occur after one dose of AmED, it is important to note that adenosine signaling has been implicated in the development of alcohol use disorders.[65-66] When adenosine activity is diminished repeatedly, alcohol intake may become more excessive to the point of dependence. This makes the repeated consumption of AmED beverages more concerning than the repeated consumption of the same amount of alcohol alone.

Knowledge Gaps

An entire paper could be devoted to the knowledge gaps that exist when examining risks associated with AmED compared to alcohol alone. While an exhaustive list is not possible within the scope of this paper, a few key unknowns should be highlighted. However, it should be noted that our expertise is in laboratory research and so those gaps appear most salient to us. First, caffeine is a stimulant drug known to moderately increase blood pressure and heart rate.[67] The acute effects of alcohol also increase blood pressure especially at higher doses.[68-70] It remains unknown how AmED beverages impact blood pressure and heart rate as compared to alcohol alone. Individuals with preexisting hypertension or other medical conditions where elevated blood pressure is contraindicated should be cautious about consumption of AmED beverages and research on this topic is needed. Retrospective chart reviews of emergency department visits associated with AmED might be instructive in determining if cardiovascular complications and/or high levels of intoxication are resulting in these visits.[71]

Another knowledge gap concerns the lack of knowledge regarding how the other CCED ingredients (besides caffeine) may or may not have interactive effects with alcohol. While extrapolating from literature on the combined effects of alcohol and caffeine can be instructive, it is unclear if CCED are similar to caffeine alone when mixed with alcohol. It is interesting to observe that while caffeine has been combined with alcohol in the past (e.g., rum and coke or Irish coffee), the rapid escalation in the use of AmED beverages, especially in underage drinkers warrants explanation. Why are CCEDs now the trendy mixer for alcohol in underage drinkers? Furthermore, what are the long-term implications of repeated use of AmED, particularly in underage drinkers, given the evidence that CCEDs could increase the abuse potential of alcohol and that adenosine signaling has been implicated in the development of alcohol use disorders? Do the other ingredients in CCED, such as taurine, have any interactive effects with alcohol?

Finally, it is unclear if there are individual differences in the subjective response to AmED versus alcohol alone. In humans and animals, the acute subjective response to alcohol alone

is known to be a phenotypic marker for the development of alcohol-use disorders (AUD) or heavy drinking. In humans, heavier drinkers (who are more likely to develop AUD) report greater stimulation when drinking alcohol.[72-76] Moreover, stimulant alcohol effects are more reinforcing and predict within session drinking behavior.[77] As described earlier, mice exhibit more or less locomotor activity (high versus low sensitization) in response to a given dose of alcohol. It is the more sedated (low sensitization) mice that responded with a more robust stimulant effect to AmED when compared with highly sensitized mice.[49] Combining all of these observations, it seems likely that the protective effects of alcohol-induced sedation in lighter drinkers may make consumption of AmED an exogenous factor that could lead to AUD in a group that really was never at risk for developing an AUD. By contrast, heavier or dependent drinkers might be less responsive to subtle differences in subjective response to AmED or alcohol alone although this needs to be empirically tested. All of the above research gaps require much closer examination from both human and animal laboratories.

Conclusion

No one piece of evidence can definitively determine whether AmED is riskier than alcohol alone. However, the weight of evidence coming from scope of use data, associative data, and experimental studies provides compelling evidence that AmED use is common and AmED consumption increases the risks of drinking alcohol. While any one piece of evidence may be imperfect, the weight of the evidence as a whole is clearly telling us that the practice of mixing CCEDs with alcohol is unwise. Certainly, the value of survey and field research is clear. It would be unsafe to administer alcohol doses to human subjects that are being observed in the field or being reported on questionnaires. The risky behaviors that have been identified to be associated with AmED use (impaired driving or risky sexual behavior) are difficult to study in laboratory settings. By contrast, the value of experimental studies is that causal statements can be made about how AmED consumption can lead to altered subjective states and increased motivation to drink. The consistency across human and animal studies is remarkable. The cellular work examining how alcohol and caffeine alter both adenosine and dopamine neurotransmitter activity is invaluable. Finally, it would be imprudent to emphasize this area of research if it were not a public health concern. However, the scope of use studies reveal that AmED use is very common around the world, particularly in young individuals who are already prone to hazardous drinking. In sum, while we concur that more research is needed to better understand the nature and scope of the risks of mixing CCEDs with alcohol, there is no doubt that AmED consumption warrants closer examination by scientists and physicians who come from differing orientations.

Acknowledgments

Sources of Funding: Support from National Institute of Health grants R15AA019795 and P20GM12345 awarded to CAM is gratefully acknowledged. The sponsor played no role in the preparation of this manuscript.

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