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, the risks associated with such mixtures, and the objective laboratory data examining how the effects of their consumption differ from consuming alcohol alone. The weight of the evidence reveals that consuming alcohol mixed with energy drinks is riskier than consuming alcohol alone and constitutes a public health concern. Consumption of these mixed beverages is frequent, especially in young and underage drinkers, and compared with alcohol alone, their use is associated with elevated rates of binge drinking, impaired driving, risky sexual behavior, and risk of alcohol dependence. Laboratory research (human and animal) has demonstrated that consuming alcohol mixed with energy drinks leads to altered subjective states including decreased perceived intoxication, enhanced stimulation, and increased desire to drink/increased drinking compared to consuming alcohol alone. Possible underlying mechanisms explaining these observations are highlighted in this review.

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. While energy drinks 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 Jägerbomb (a shot of the spirit Jägermeister placed in a pint glass filled with an energy drink). Up until November 2010, a variety of premixed caffeinated alcoholic beverages were available (with brand names including Four Loko, Moonshot, Sparks, B-to-the-E, and Joose). The risks of alcohol mixed with energy drinks 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 beverages’ safety. 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. 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. Elevated risks of alcohol poisoning, sexual assault, and impaired driving were also listed as potential concerns. Given the reviewed scientific evi-
dence and expert opinion, the FDA sent warning letters to the manufacturers of such premixed alcoholic beverages asking for their own scientific evidence that the addition of caffeine and other stimulants to alcohol was generally recognized as safe. Manufacturers of these products promptly responded to the warning letters by voluntarily removing caffeine and other stimulant ingredients from their alcoholic beverages.  

While the above history about the availability and then removal of premixed beverages containing alcohol and energy drinks from the marketplace might suggest that the issue of their safety 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, consequently, now drinking cocktails that are pharmacologically similar to what was previously available in one product package. Furthermore, the consumption of beverages containing alcohol mixed with energy drinks is becoming more widespread around the world. Concerns from scientists and physicians about the safety of combining energy drinks, particularly those containing caffeine, 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 United States, has been monitoring an increased incidence of negative medical outcomes associated with consumption of caffeine-containing energy drinks. From 2007 to 2011, emergency department visits in the United States involving individuals who had consumed energy drinks doubled, with a subset of these visits involving alcohol consumption as well. Second, concerns about alcohol mixed with energy drinks arise from recently published data of exposure to energy drinks 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 proportion of cases involving alcohol mixed with energy drinks among all calls involving energy drinks was 11%. The cases of alcohol mixed with energy drinks often involved underage drinkers (68.2% were younger than 20 years of age). Moreover, the incidence of moderate to major adverse effects of toxicity was 39.3% for alcohol mixed with energy drinks (as compared to 15.2% for energy drinks alone). The seriousness of the cases involving alcohol and energy drinks combined was also reflected in outcomes, with 76.7% of alcohol and energy drink-related phone calls to poison control centers resulting in a referral to a healthcare facility (as compared to 26.4% of phone calls pertaining to energy drinks alone). Given that there is continued concern about the risks associated with beverages containing both alcohol and energy drinks, the purpose of this review is to summarize what is known about the scope of use of these beverages, the risks associated with them, and the objective laboratory data examining why their consumption is riskier than consumption of alcohol alone. Certainly, the data from emergency room visits and calls to poison control centers justify taking a closer look at the effects of alcohol and energy drinks in combination.

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 alcohol mixed with energy drinks. As an overview, data regarding the scope of use of alcohol mixed with energy drinks indicates consumption of these beverages is common worldwide, particularly in underage and young adult drinkers. Second, their consumption is associated with elevated rates of binge drinking, impaired driving, need for medical treatment, risky sexual behavior, and risk of alcohol dependence when compared with alcohol alone. Finally, causal statements about how alcohol mixed with energy drinks can elevate the risks of alcohol consumption stem from data gathered from laboratory studies (human and animal). These laboratory studies indicate that alcohol mixed with energy drinks can alter the 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 alcohol mixed with energy drinks is riskier for the consumer than drinking alcohol alone. However, more research is clearly needed and some knowledge gaps that need to be addressed by scientists are discussed herein.

SCOPE OF USE OF ALCOHOL MIXED WITH ENERGY DRINKS

Consumption of beverages containing alcohol mixed with energy drinks might not present a major public health concern if it were a rare practice. However, the data gathered on the scope of use of such beverages suggest their 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 2010) indicated that about half of college students reported consumption of at least one caffeine-containing energy drink each month and 54% of these consumers
combined them with alcohol.\textsuperscript{15} Other survey data indicated that 25% of past-30-day alcohol drinkers consumed at least 1 beverage containing both alcohol and an energy drink in the past month.\textsuperscript{9} Survey data gathered around the same time period in a convenience sample of college students also found that consumption of alcohol mixed with energy drinks was common, with 1 in 10 college students reporting consumption of at least 1 such beverage in the past 2 weeks.\textsuperscript{16} Another probability sample of college students surveyed in 2010 revealed that prevalence rates for lifetime and past-year use of alcohol mixed with an energy drink were approximately 75% and 65%, respectively.\textsuperscript{17} Finally, athletes comprise a college population that is likely to engage in heavy episodic drinking. One sample of student-athletes revealed that 37% had consumed alcohol mixed with an energy drink in the past year.\textsuperscript{18}

The above studies reflect data collected either 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 alcohol mixed with energy drinks. The Monitoring the Future (MTF) survey examines licit and illicit drug use among 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 10\textsuperscript{th} graders, 26.4% of 12\textsuperscript{th} graders, 33.8% of college students, and 36.7% of young adults (ages 19–28 years) reported consuming a beverage containing both alcohol and an energy drink at least once in the past year.\textsuperscript{19,20} From the MTF data, one can conclude that use of such beverages is common, especially considering that these annual prevalence rates include data collected from individuals who may not legally consume alcohol.

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

Scope of use of alcohol mixed with energy drinks in other countries appears to be similar to that observed in the United States. 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 alcohol combined with an energy drink in the past year.\textsuperscript{24} A survey of Dutch college students ($n=6,002$) indicated that approximately 1 in 5 college students consumed such a beverage.\textsuperscript{25} Finally, a survey of Canadian college students revealed that almost 1 in 4 reported consuming alcohol mixed with an energy drink in the past 30 days.\textsuperscript{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 ALCOHOL MIXED WITH ENERGY DRINKS**

One common finding reported from epidemiological studies conducted in a variety of countries around the world is that consumers of alcohol mixed with energy drinks are more likely than consumers of alcohol alone to be heavy episodic (i.e., hazardous or binge) drinkers.\textsuperscript{17,18,21,24,26–29} In addition, results from one national survey from Taiwan ($n=22,085$) revealed that such consumers were more likely to be dependent on alcohol, when compared to consumers of alcohol alone.\textsuperscript{27} This observation bears some similarity to the finding from another study that weekly or daily use of energy drinks by US college students was associated with alcohol dependence.\textsuperscript{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 energy drinks or such products in combination with alcohol, whether energy drinks alone or in combination with alcohol increase hazardous drinking, or whether some combination of these mechanisms are interacting. However, other studies have more specifically reported that consumption of alcohol mixed with energy drinks is associated with a greater quantity of alcohol being consumed during a single episode when compared to episodes in which alcohol is consumed alone.\textsuperscript{23,28,31,32} Given these associations, it has been suggested that consumption of alcohol mixed with energy drinks leads to increased alcohol consumption when compared to alcohol alone. However, not all reports align with this observation. For example, one industry-supported survey of Dutch college students actually reported the reverse observation, as students reported consumption of fewer alcoholic drinks when consuming alcohol mixed with an energy drink compared with con-
sumption of alcohol alone. It is unclear why this Dutch report would differ from many other studies, but the price of the beverages containing both alcohol and energy drinks in that location or other cultural factors could be important and warrant further examination.

The observations from survey research that consumption of alcohol and energy drinks in combination 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, 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 one-third of the patients had blood alcohol levels greater than twice the legal limit.

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 alcohol with an energy drink were at a threefold increased risk of leaving the bar legally intoxicated (BrAC > 0.08 g%) and a fourfold risk of intending to drive home intoxicated, compared to other drinking patrons. 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 a caffeine-containing energy drink or cola mixer in combination with alcohol. Another field study conducted in 60 bars located in 4 European cities appeared to highlight the role that caffeine-containing energy drinks played in heightened patron intoxication. The researchers observed that promotion of caffeine-containing energy drink in a given location was associated with higher levels of customer intoxication.

Consistent with observations from field work, survey research has also found that consumption of alcohol in combination with an energy drink is associated with additional risky behaviors, beyond the association of such beverages with heavy episodic drinking. Individuals who reported consumption of alcohol mixed with an energy drink also reported engaging in a variety of risky behaviors and experiencing greater alcohol-related consequences, even after adjusting for the amount of alcohol consumed. After adjusting for demographic variables, drinking variables, and risk-taking propensity, it has been reported that users of alcohol mixed with energy drinks are more likely to be involved in high-risk traffic behaviors including driving after binge drinking. Note that this association is similar to that observed in one field study in which such consumers were more likely to report that they were going to drive home despite being intoxicated. Users of alcohol mixed with energy drinks are also more likely to need medical treatment or be hurt or injured when drinking when compared to consumers of alcohol alone. In addition, several studies have reported that use of alcohol in combination with energy drinks is associated with engaging in risky sexual behaviors when compared with alcohol alone. Such consumers have also been found to be more likely to use illicit drugs, including marijuana, cocaine, and ecstasy when compared with consumers of alcohol alone. All of the above studies controlled for the alcohol consumed (since alcohol use alone would elevate the risks for all of the risky behaviors noted above). Some, but not all, studies also controlled for risk-taking propensity and other demographic characteristics that are known predictors of risky behavior. Therefore, it appears that consumption of alcohol mixed with energy drinks increases a variety of health and safety risks that are 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 sessions involving alcohol in combination with an energy drink compared to those involving alcohol alone.

In sum, a variety of studies using different methodologies largely, although not universally, concur that consumption of alcohol in combination with energy drinks 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 did not randomly assign subjects to drink choices and then observe resulting behaviors. Consumption of alcohol mixed with energy drinks 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 alcohol mixed with an energy drink versus alcohol alone 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 alcohol in combination with energy drinks and risky behaviors is very useful for designing appropriate experiments to better understand the risks.

**LABORATORY STUDIES EXAMINING ALCOHOL MIXED WITH ENERGY DRINKS VERSUS ALCOHOL ALONE**

Laboratory research involving both human and animal participants has examined the combined effects of
alcohol and caffeine-containing energy drinks or the combined effects of alcohol and caffeine (the primary stimulant found in caffeine-containing energy drinks) when compared to alcohol alone. Interestingly, results from experimental studies are similar to the findings from survey and field studies. Double-blind, placebo-controlled experimental studies examining whether alcohol mixed with an energy drink differs from alcohol alone suggest that the former beverages are pharmacologically distinct from the latter and elevate the risks associated with alcohol consumption alone by altering the subjective state and increasing the desire to drink more alcohol.39–45

Human studies typically involve recruiting subjects to receive doses of alcohol, energy drinks, alcohol mixed with energy drinks, and placebo in a laboratory setting. Some studies incorporated within-subjects designs, whereby 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 based on body weight. After consuming the assigned 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 are assessed when blood alcohol concentration reaches a moderate to intoxicating level (0.05–0.08 g%), as assessed using a breathalyzer.

Across various human laboratory studies, there are important similarities and differences between alcohol mixed with energy drinks and alcohol alone. First, the similarities should be addressed. Blood alcohol concentrations do not differ when alcohol is administered with and without a caffeine-containing energy drink or caffeine alone, thus 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 alcohol mixed with an energy drink, with a few exceptions. Studies have found that alcohol mixed with an energy drink (or alcohol combined with caffeine) produces similar impairments to alcohol alone 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,7 coordinated responses,6,8,43 and information processing.43

However, caffeine-containing energy drinks or caffeine mixed with alcohol can sometimes antagonize some of the alcohol-induced impairment of behavioral responses.7,8,41–43,45 Such counteracting effects of caffeine-containing energy drinks 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 coadministrations 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 alcohol mixed with energy drink consumption. Other studies have found that alcohol mixed with energy drinks 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 impulsivity control.4 Such nonuniform counteraction of alcohol impairments from alcohol mixed with energy drinks could result in a dangerous combination. A consumer of alcohol alone is typically slow and impulsive. By contrast, a consumer of alcohol mixed with an energy drink is also impulsive but is able to react a little quicker. The consumer of alcohol in combination with energy drinks may consequently be more able to execute risky courses of action whereas a consumer of alcohol alone may be less able to execute all risky impulses due to the slowed ability to execute actions.

The second concern with consumption of alcohol mixed with energy drinks is revealed by examining the subjective responses from various questionnaires. Consumption of alcohol mixed with energy drinks (or alcohol and caffeine) results in several changes in subjective state that are riskier for the drinker when compared to alcohol alone including the following: 1) decreased perceived intoxication, 2) enhanced stimulation, and 3) increased desire to drink more alcohol. Decreased perceived intoxication for alcohol mixed with energy drinks versus alcohol alone has been demonstrated in at least two different laboratories.8,41 If a consumer of the former 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 alcohol mixed with energy drinks (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.8,47 The enhanced stimulation for alcohol combined with energy drinks (versus alcohol alone) has also been noted in surveys. For example, one online survey performed in Australia revealed that consumers reported a variety of side effects related to over-stimulation (including heart palpitations) when alcohol was consumed in combination with energy drinks com-
pared to alcohol use alone. Again, enhanced stimulation from the caffeine-containing energy drink 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 alcohol mixed with an energy drink versus alcohol alone has been compared, and desire for more alcohol (after an initial dose) is elevated for a longer period of time with consumption of alcohol mixed with energy drinks when compared with alcohol alone. This observation has been reported in studies from two laboratories and may account for the observation that consumers of the mixed beverages are more likely than consumers of alcohol alone to drink to intoxicating levels and to screen positive for alcohol dependence.

In sum, the laboratory studies highlight potential risks associated with antagonistic effects of caffeine-containing energy drinks and caffeine on alcohol impairment, increased stimulation from alcohol mixed with energy drink consumption, and the disconnect that occurs with subjective and objective state following such consumption. However, it is important to note that there is unclear consensus that subjective responses differ for alcohol mixed with energy drinks 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 caffeine-containing energy drink. As a result, the alcohol mixed with energy drink versus alcohol alone 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 the caffeine-containing energy drink), 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 alcohol mixed with energy drinks or not).

While questions remain, it is important to 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 alcohol mixed with energy drinks is compared to alcohol alone. While a mouse or a 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 caffeine-containing energy drinks are mixed with alcohol, locomotor activity is increased more than alcohol alone. 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 and humans.

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. The researchers then observed the response to alcohol mixed with an energy drink in the sensitized mice. Both groups had similar and high levels of locomotor stimulation in response to the alcohol and energy drink combination. This observation suggests that, in humans, the mixture of alcohol and energy drinks may be most problematic for lighter drinkers (who are less likely to abuse alcohol) as compared to heavier drinkers, although that would need to be empirically tested.

When assessing whether alcohol mixed with energy drinks 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. It 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. 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, which is similar to the caffeine doses contained in beverages comprised of alcohol and energy drinks.

With regard to laboratory research, there is consensus among the results of human and animal research on several findings for alcohol mixed with energy drinks versus alcohol alone. Alcohol mixed with energy drinks (or alcohol and caffeine) results in enhanced stimulation (in humans and animals), decreased perceived intoxication (in humans), and increased desire to drink or actual drinking (in humans and animals) when compared to alcohol alone. These observations suggest that the combination of alcohol and energy drinks is riskier than alcohol alone. Greater drinking may lead to immediate health and safety concerns during a single drinking episode. If consumption of alcohol mixed with energy drinks were observed in human studies.
drinks is repeated often, greater drinking across time could ultimately lead to serious problems with controlling alcohol intake and with alcohol dependence. Given that beverages containing alcohol and energy drinks in combination 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 these beverages in comparison with alcohol alone.

**POSSIBLE MECHANISMS**

The research on underlying neurotransmitter mechanisms explaining why beverages that combine alcohol with energy drinks 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. 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. 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. 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. Since, caffeine acts as an antagonist at the adenosine receptor, thus acting to block adenosine activity, dopamine activity will be increased when caffeine is on board and more dopamine will be released. Given what is known about effects at the cellular level, it seems unsurprising that beverages combining alcohol with energy drinks (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 an alcohol and energy drink mixture, it is important to note that adenosine signaling has been implicated in the development of alcohol use disorders.

When adenosine activity is diminished repeatedly, alcohol intake may become more excessive, to the point of dependence. This makes the repeated consumption of beverages combining alcohol and energy drinks more concerning than the repeated consumption of the same amount of alcohol alone.

**KNOWLEDGE GAPS**

An entire article could be devoted to the knowledge gaps that exist when examining risks associated with alcohol mixed with energy drinks compared to alcohol alone. While an exhaustive list is not within the scope of this paper, a few key unknowns are highlighted. However, it should first be noted that given the present authors’ expertise in laboratory research, the gaps in that area appear most salient. First, caffeine is a stimulant drug known to moderately increase blood pressure and heart rate. The acute effects of alcohol also increase blood pressure, especially at higher doses. It remains unknown how beverages combining alcohol with energy drinks impact blood pressure and heart rate, as compared to alcohol alone. Individuals with preexisting hypertension or other medical conditions for which elevated blood pressure is contraindicated should be cautious about consuming beverages containing alcohol and energy drinks combined and research on this topic is needed. Retrospective chart reviews of emergency department visits associated with AmED might be instructive for determining if cardiovascular complications and/or high levels of intoxication are resulting in these visits.

Another gap in knowledge concerns the ways in which the other ingredients of energy drinks (besides caffeine) may or may not have interactive effects with alcohol. While extrapolating from the literature on the combined effects of alcohol and caffeine can be instructive, it is unclear if caffeine-containing energy drinks 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 beverages containing alcohol and energy drinks combined, especially in underage drinkers, warrants explanation. Why, for example, have caffeine-containing energy drinks become the trendy mixer for alcohol in underage drinkers? Furthermore, what are the long-term implications of repeated use of alcohol mixed with energy drinks, particularly in underage drinkers, given the evidence that caffeine-containing energy drinks 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 caffeine-containing energy drinks, such as taurine, have any interactive effects with alcohol?

Finally, it is unclear if there are individual differences in the subjective response to alcohol mixed with energy drinks 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 either more or less locomotor activity (high versus low sensitization) in response to a given dose of alcohol, and it was the more sedated (low sensitization) mice that responded with a more robust stimulant effect to alcohol mixed with energy drinks 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 alcohol mixed with energy drinks 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 alcohol mixed with energy drinks 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 single piece of evidence can definitively determine whether consumption of alcohol mixed with energy drinks is riskier than drinking alcohol alone. However, the weight of evidence coming from scope-of-use data, associative data, and experimental studies provides compelling evidence that use of such mixed beverages is common and their consumption increases the risks associated with drinking alcohol. While any single piece of evidence may be imperfect, the weight of the evidence as a whole indicates the practice of mixing caffeine-containing energy drinks 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 in questionnaires. The risky behaviors that have been identified as being associated with use of alcohol mixed with energy drinks (e.g., impaired driving or risky sexual behavior) are difficult to study in laboratory settings. By contrast, the value of experimental studies is that causal associations can be determined and, if proven, statements can then be made about how consumption of alcohol mixed with energy drinks 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 use of alcohol combined with energy drinks is very common around the world, particularly in young individuals who are already prone to hazardous drinking. In sum, while more research is needed to better understand the nature and scope of the risks of mixing caffeine-containing energy drinks with alcohol, there is no doubt that consumption of such mixtures warrants closer examination by scientists and physicians who come from differing orientations.

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