Review #14

Caffeinated Alcoholic Drinks and Health.

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> *"If you set out to engineer a booze delivery system that is as cloying, deceptive and divorced from the usual smells, tastes and presentation of alcohol as possible, you'd be hard pressed to come up with something more impressive than Four Loko".*
>
> **Bruni (2010)**

> *"Thus, if you present alcohol in a manner divorced from the usual alcohol-associated stimuli, the effects of the alcohol are enhanced. That is, the drug-experienced individual does not display the expected tolerant response to the drug when it is administered in the presence of cues not previously associated with the drug. Rather, a large response to the drug, typically seen in the drug-inexperienced individual, is displayed. The phenomenon has been termed "the situational specificity of tolerance" (Siegel, 1976)".*
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> **Siegel (2011)**

Caffeine is a mild psycho stimulant, and despite basic and clinical evidence that caffeine is reinforcing (use leads to tolerance and mild withdrawal symptoms), it is rarely considered a drug of abuse (Franklin et al., 2013). However, mixing caffeine with alcohol is a public health concern (Norberg et al., 2021) with consumption of caffeine and alcohol together or in close approximation, associated with drinking for longer periods of time, consuming more alcoholic drinks, feeling more intoxicated, and experiencing more adverse alcohol-related consequences than when alcohol has been consumed on its own (see Norberg et al., 2021). Public health professionals in Western countries have long warned of the danger of mixing energy drinks with alcohol (e.g., Arria and O'Brien, 2011), believing that higher concentrations of alcohol can be consumed because of caffeine's masking of the sedative effects of alcohol.

It is thought that a lack of consideration or understanding of the consequences of drinking caffeinated alcoholic drinks can lead young drinkers to experience assaults, injury, and death, especially in the youngest age groups (Cleary et al., 2012). Alcohol and caffeine can be consumed together either in a pre-mixed context (manufactured products), or when mixed immediately before consumption. Pre-mixed caffeinated alcoholic beverages (such as 'Four Loko') were promoted for their ability to mask alcohol's effects and intensify intoxication. Their brightly coloured packaging, low cost, and retail placement meant that they are marketed like a sports or energy drink, appealing to a younger consumer (Cleary et al., 2012). Individuals who consume these drinks are more likely to engage in binge-drinking behaviours and report specific reasons for their doing so (Luneke et al., 2019), with

increasing concern over the risks associated with the consumption of caffeinated alcoholic beverages, especially given reports of associated fatalities (Roemer et al., 2019). These latter authors reported that following alcohol and caffeine use, the risk for injury was significantly greater among women than men, even after controlling for dose of alcohol and caffeine, with the authors suggesting a synergistic effect of alcohol and caffeine use on injury risk.

Specifically, College students who drank either pre-mixed or self-mixed drinks, were found to drink alcohol in greater quantities more frequently, compared to alcohol-only users (see Lau-Barraco & Linden, 2014). These authors found support for the predictive utility of both caffeine and alcohol expectancies in accounting for individual variability in caffeinated alcoholic drinks consumption and related harms. In a separate study, Lau-Barraco et al. (2014) reported that the majority of their sample of moderate to heavy College drinkers was classified into the Low Alcohol/Low caffeinated alcoholic beverage (CAB) group (65.87%) while 6.00% were classified into the High Alcohol/High CAB group. As could be expected, when compared with the High Alcohol/High CAB class, the Low Alcohol/Low CAB class reported significantly lower levels of caffeine withdrawal, caffeine dependence, frequency of heavy episodic drinking, and alcohol use problems.

Amid rising health concerns, the US Food and Drug Administration (FDA) described caffeine as an unsafe additive to alcoholic beverages (saying that consumption of caffeine-containing alcoholic beverages could lead to ‘‘hazardous and life-threatening situations’’) and issued warning letters to manufacturers which resulted in the removal of pre-mixed caffeinated alcoholic beverages from the US marketplace (FDA 2010a). The manufacturers were given 15 days to remove caffeine from their drinks, and they complied. These products (for example Four Loko) were reformulated shortly thereafter to remove caffeine, Guarine, and Tuarine (see Rossheim et al., 2018).

As one example, Four Loko, a fruit-flavoured, caffeinated alcoholic drink was the invention of students at Ohio State University in 2005. The ‘‘Four’’ referred to the four primary ingredients: alcohol, caffeine, taurine, and guarana (Siegel, 2011). At a time, there were reports of mass hospitalizations for alcohol intoxication following consumption of products like Four Loko (Siegel, 2011). Each beverage was sold in large 23.5-oz cans containing 12% alcohol, the equivalent of 3 to 4 beers and 156 mg of caffeine, the amount in 1½ cups of coffee, 1 tall serving of Starbucks coffee, or 2 servings of Red Bull (Cleary et al., 2011). According to the manufacturer, the caffeine content was comparable to that found in a cup of coffee (Siegel, 2011).

Despite the manufacturing ban, retail and internet supplies of the original formulation continued to exist. Esser and Siegel (2014) estimated Four Loko to contain the equivalent of 4.7 standard alcoholic drinks. In 2013, the Federal Trade Commission (FTC) filed a complaint against Phusion Projects, Four Loko manufacturers. The FTC stated that Phusion Projects’ marketing and packaging of Four Loko was misleading because it suggested that a 23.5-ounce can of Four Loko contained the alcohol content equivalent to 1 or 2 regular 12-ounce beers, when it actually contained the alcohol content of 4.7 regular beers (Federal Trade Commission, 2013a). Four Loko has been among the least expensive ready-to-drink alcohol available on the market and is sold in a broad range of stores throughout most states and is most commonly available at petrol stations and convenience stores (Rossheim et al., 2015; Rossheim et al., 2019).

Despite warnings to manufacturers and consumers (FDA 2010b), many individuals continue to combine alcohol and energy drinks (i.e., caffeinated, sweetened beverages marketed for their stimulant and recreational effects) or purchase mixed drinks of alcohol and energy drinks in bar settings (see Amlung et al., 2013; Sweeney at el., 2017). Among the major self-reported motivations for the mixing of alcohol and caffeinated drinks are the reduction of alcohols sedative effects, and the facilitation of increased alcohol consumption (see Sweeney at el., 2017). Consumption of caffeinated alcoholic beverages is also suggested to increase reports of happiness and euphoria, behavioural disinhibition, and physical vigour, relative to alcohol alone (see Franklin et al., 2013). However, caffeine does not affect the pharmacokinetics of alcohol, so that breath and blood alcohol concentrations are similar following ingestion of alcohol alone or caffeine and alcohol together (see Siegel, 2011). As with most substances of abuse, the interplay between abuse and socio-demographic factors (e.g., gender, age, culture, etc.) is complex.

Between 2010 and 2012, there were several reports of deaths among youth that were attributed to the consumption of Four Loko (Esser & Siegel, 2014). An internet-based survey (Siegel et al., 2013) was conducted to assess the consumption of 898 brands of alcoholic beverages – including 62 brands of flavoured alcoholic drinks. The findings indicated that in 2012, these types of drinks ranked as the second leading alcoholic beverage type consumed, accounting for over 16% of the alcohol consumption market share. Nearly half of youth drinkers reported consuming them in the past 30 days and four of the leading 25 brands consumed were flavoured alcoholic drinks, including Four Loko.

Production of caffeinated alcoholic drinks is not only a Western phenomenon. Cheng et al. (2012; Taiwan) reported on pre-mixed drinks containing 300mg of caffeine and 48g of alcohol (10%) per bottle of 600 ml, in addition to other additives such as amino acids, vitamin B and Chinese herb extracts. The Food and Drug Administration of Taiwan approved registration of these alcoholic energy drinks as ‘medicine’ because of their vitamin and caffeine ingredients. According to Taiwan’s Pharmacy Law, the sales of such drinks are restricted to pharmacies, and warning labels are required on containers and advertisement. However, in practice, these drinks were readily available on streets, and were sold at a lower price than most of the other alcohol beverages of similar alcohol strength, with alcohol dependence prevalent among those who consumed them (Cheng et al., 2012). Consumption of these was also found to be associated with a higher risk of work-related injury or disease after controlling for the presence of problem drinking and alcohol use frequency (Cheng et al., (2015).

Cleary et al. (2012) examined documented cases (Emergency Department visits) of those who had consumed caffeinated drinks, and of the eleven patients included, one had fallen onto subway tracks, three were found confused in public parks or on public transportation, and one was found unconscious in a building lobby, with another unconscious at school. The combined effects of caffeine with alcohol result in a decreased perception of intoxication by increasing alertness, leading to increased alcohol consumption and decreased awareness of physical impairment, commonly referred to as the “wide-awake drunk” (Cleary et al., 2012). Though individuals consuming these beverages may perceive themselves to be wide awake, simulated driving performance, attention/ reaction times, and test accuracy are not enhanced with the addition of caffeine relative to alcohol alone.

Four Loko remains on sale as what is known as a 'supersized alcopop' (Olson et al 2022). These products are characterized by both high alcohol content and sweet flavour that masks the taste of alcohol (Rossheim & Thombs, 2018). Research also indicates that supersized alcopops are popular among underage drinkers (Fortunato et al., 2014; Siegel et al., 2013). Four Loko has been reported as the most commonly consumed brand of supersized alcopop among underage drinkers (Fortunato et al., 2014). It is therefore not surprising that they are commonly consumed by underage drinkers. Several factors likely determine adolescents' preference for supersized alcopops, including their retail availability, the types of stores where they are sold, their high alcohol content, their low price per gram of alcohol, the sugary flavours that mask the taste of alcohol, and youth-oriented marketing including packaging (Rossheim et al., 2018). For young men and women of legal drinking age, consumption of just one can of beer over a 2-hour period could be expected to result in no detectable level of alcohol intoxication. In contrast, consumption of a single supersized alcopop would be expected to result in a BAC level beyond the legal driving limit (Rossheim & Thombs, 2018).

According to Rossheim et al. (2022) research conducted in the US in 2020 suggested that one-half of underage drinkers reported drinking alcopops in the past 30 days. Furthermore, "supersized" alcopops (e.g., Four Loko, Joose) contain up to 5.5 standard alcoholic drinks in a single can. Underage drinkers often consume supersized alcopops and, as a result, frequently experience negative consequences including blacking out and vomiting, as well as require Emergency Department and poison control centre services (see Rossheim et al., 2022). Rossheim & Thombs (2018) reported that in the USA in 2015, 17 state attorneys general sent a letter to the manufacturer of Four Loko, formally requesting that the alcohol concentration be voluntarily reduced to 8% abv on their 23.5 oz packages. Not only was the request ignored, but four new flavours with even greater alcohol content (14%) emerged, that contain the alcohol equivalent to 5.5 standard drinks. The authors pointed out that Drug Abuse Warning Network data indicated that in 2011 (the last year data were collected), there were nearly 5,500 emergency department visits involving Four Loko.

While combing caffeine with alcohol lowers subjective intoxication, corresponding behavioral impairments in reaction time, response inhibition, and driving performance may not be counteracted, although some contrary findings had also been reported (see Amlung et al., 2013). Based on the totality of the research, addictions researchers and health professionals have came down on the side of seeing the mixing of alcohol and caffeine as a significant public health concern (Amlung et al., 2013). Notably, the decrease in subjective feelings of being intoxicated may mistakenly make individuals believe that they are less intoxicated than they are and more capable of engaging in behaviours that require fine motor control such as driving a car (Brache & Stockwell, 2011). A 2011 study by Marczinski et al. found that while caffeinated alcoholic beverage consumption did not alter impairment when compared to alcohol alone, it did reduce subjective feelings of mental fatigue and increase feelings of stimulation.

The context of the alcohol provision is thought to be a factor in intoxication using these types of drinks. Drug tolerance partially results from an association between drug-paired stimuli and the drug effect (see Siegel, 2011). When these stimuli are altered, the drug-experienced individual does not display the expected tolerant response to the drug, rather, an enhanced (i.e., non-tolerant) response is seen. Four Loko and similar beverages may be

especially effective intoxicants because they provide a very novel flavour **context** for alcohol. In other words, the alcohol is provided in an atypical context (in a caffeinated or sweet-tasting medium).

When participants are asked to rate their level of intoxication, research has found that the addition of caffeine to alcohol may decrease, increase, or have no effect on subjective drunkenness (see Siegel, 2011). As an additional complication, when any effect of caffeine on alcohol-induced impairment is noted, it may be due not to the pharmacological interaction of the stimulant and depressive drugs, but rather to effects of expectancy (see Siegel, 2011). Referring back to the context of the drink, it has been known for many years that drugs in general, and alcohol in particular, have a greater effect if they are administered in the presence of unusual cues rather than in the presence of cues typically associated with the drug. This contributes to the "**situational specificity of tolerance**" in this regard (Siegel, 1976). In other words, that tolerance to the product is specific to the situation in which the product is consumed. Siegel (2011) somewhat ironically suggested that the phrase "situational specificity of tolerance" should be renamed the "Four Loko effect".

Research has also suggested that an overall lack of certainty about the alcohol content of some products may be an issue. Inaccuracies in self-estimated BAC observed in natural drinking environments (Rossheim et al., 2017) may be partially caused by lack of consistency in the amount of alcohol contained in each beverage. This clearly should not be the case with regard to pre-mixed beverages. It was suggested that rather than relying on the education of consumers about the alcohol content of each specific product and the computational capabilities of intoxicated individuals, there may be a need to restrict the amount of alcohol that can be sold in a single-serving product.

Thombs et al. (2011) questioned the exclusive focus on alcohol mixed with energy drinks, pointing out that several studies have documented the popularity of more "traditional" combinations of alcohol and caffeine, such as mixing alcohol with caffeinated soft drinks like cola (Rossheim & Thombs, 2011; Thombs et al., 2011). They suggested that there is evidence that consumption of cola-caffeinated alcoholic drinks leads to equivalent levels of intoxication among young people as the consumption of alcohol mixed with energy drinks (Thombs et al., 2011). Further, that for at least on-premises use, these 'traditional' caffeinated alcoholic drinks may be more popular than alcohol mixed with energy drinks (Rossheim & Thombs, 2011). In a study examining different forms of product consumption Kponee et al. (2014) defined non-traditional drinks as pre-packaged alcoholic energy drinks or self-mixed alcoholic beverages containing energy drinks, energy shots, or caffeine pills. They reported that adolescents who consumed both traditional and non-traditional forms were more likely to drink larger amounts of alcohol, to drink more days in a month, and to engage in binge-drinking behaviour, with results particularly striking among non-traditional users. They further reported that majority of caffeinated alcoholic drinking was attributable to self-mixing by the adolescents themselves, and that soda was the most commonly used caffeine additive to alcohol. They postulated that this may reflect the widespread availability of soda and the ability to hide the use of alcohol by making it look like a youth is consuming soda.

The search was run on 19th Sept 2023. Web of Science & CINAHL databases were searched for the term "Caffeinated alcohol*" in the title and abstract. This was supplemented with searches on Web of Science for specific caffeinated alcohol drinks in titles or abstracts: Four Loko, Dragon Soop, and Screaming Devil. This resulted in 893 potential papers fo inclusion, which were screened for relevance.

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