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Binge drinking: Burden of liver disease and beyond

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Abstract

The consumption of alcoholic beverages is harmful to human health. In recent years, consumption patterns of alcoholic beverages have changed in our society, and

binge drinking has generalized. It is considered to be a socio-sanitary problem with few known consequences in terms of individual and third-party social impacts (in the form of violence or traffic accidents) and its organic impact (affects the liver and other organs and systems, such as the nervous and cardiovascular systems) and represents an important financial burden due to its increasing economic impact. This review provides a global approach to binge drinking and emphasizes its epidemiological character, the effect of this type of consumption and the possible management of a problem with an increasing tendency in our society.

Key words: Binge drinking; Binge drinking adolescent; Binge drinking brain; Binge drinking cardiovascular; Alcohol binge; Binge drinking liver

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Core tip: Binge drinking is an alcohol consumption conduct that is primarily performed during the weekend by 24% of teenagers and young adults. Although the consequences of this habit are not well known, they have a social and organic impact on individuals. Binge drinking is considered to be a public health issue that should be addressed with primary prevention programs and a comprehensive intervention of the problem.

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INTRODUCTION

The consumption of alcoholic beverages is harmful to human health. Excessive alcohol intake is a major global and public health challenge that has been

identified as one of the main determinants of a variety of noncommunicable diseases^[1]. The excessive consumption of alcohol is the leading global cause of preventable morbidity and mortality and a major problem in Western countries. According to the World Health Organization (WHO), it is the cause of 4.5% of the diseases in the world and 4% of the deaths in the world and is considered the main cause of death among men between 15 and 59 years of age, especially in Eastern Europe countries^[2,3]. In the United States, this excessive alcohol consumption causes 75000 deaths each year and is the third leading preventable cause of death^[4]. Alcohol is the main cause of cirrhosis and indication for liver transplants in Europe, and accounts for 1.8% of all deaths caused by liver disease^[5]. When the data are adjusted by age, alcohol is the main risk factor for impairment (*i.e.*, life-years lost at early ages) in young populations between 10-24 years of age^[6].

In recent years, consumption patterns of alcoholic beverages have changed in our society, and binge drinking has generalized. The reason for this change and its implications for the individual and the society are not well known. For this reason, we present this review using a comprehensive approach to the binge-drinking problem.

DEFINITION OF BINGE DRINKING

A unified definition of binge drinking is necessary to effectively approach this subject and to analyze the risk factors of binge drinking, its socio-sanitary implications and its relation to alcohol dependence. We review the controversial term of binge drinking, which lacks a consensus among the different studies. The controversy stems from the following items: (1) its inadequate definition; (2) the minimum amount of consumption that is considered to be a problem has not been established; (3) a standard drinking unit (SDU) that is common to all countries has not been established; and (4) the unspecified period of time that is considered to be "a single event".

Consequently, epidemiological studies describe important methodological problems; the prevalence of this type of consumption in young populations varies between 7% and 40% due to the lack of uniform cut-off points^[7]. This variability is attributed to the lack of consensus in determining the harmful consumption levels of alcohol and the differences in pure ethanol in an SDU for each country. Therefore, the cut-off points for the number of SDUs ingested in each event (*i.e.*, five alcoholic beverages and six alcoholic beverages) and the frequency intervals (*i.e.*, in the last week, 15 d, and 30 d) in which the episodes of heavy consumption occur vary in the different studies^[8]. Regarding the term binge drinking, several authors suggest that this definition traditionally refers to a pattern of consuming large amounts of alcohol in a few hours and primarily during weekend nights that is conducted by younger age groups without a differentiation of gender^[8]; they

primarily correlate it with clinical definitions of abuse or dependence^[9-11].

To prevent confusion, alternate terms have been suggested, such as heavy drinking^[12-16], heavy episodic drinking^[17-22], heavy sessional drinking, risky single-occasion drinking^[23], dangerous drinking^[24], or high-risk drinking^[25]. In Spain, the First Conference in Health Prevention and Promotion in the Clinical Practice in 2007 proposed the term heavy episodic drinking of alcohol.

Although binge drinking cannot be identified with the common criteria for the harmful consumption of alcohol, many authors have stressed its social and health consequences, which may exceed the social and health consequences of regular alcohol consumption^[26-29].

In the 1990s, the effect of alcohol consumption regarding the sex of the patient was determined in the Harvard School of Public Health College Alcohol Study^[30,31]. Wechsler's group employed a questionnaire to evaluate the habits of alcohol consumption. The group discovered that significant problems of alcohol consumption occur in men after the intake of five beverages in one event, whereas similar problems occur after the intake of four beverages by women. The term heavy alcohol consumption (HAC) evolved and was understood as the consumption of five or more drinks by men and four or more drinks by women in a single occasion, at least once in the last two weeks^[31].

Regarding the "single-event" discussion that is referenced in the binge drinking definition, several authors consider including the concentration of alcohol in the blood to determine the adequate threshold for the binge-drinking pattern. This threshold is explained by the difference in the effect of the intake of one alcoholic beverage in one hour during five continuous hours in an adult with an average body weight and the intake of the same amount of alcohol (five beverages) over a shorter period, for example, two hours.

Accordingly, the National Institute on Alcohol Abuse and Alcoholism (NIAAA)^[32] redefined the term HAC by considering the level of concentration of alcohol in the blood. HAC considers minimum levels of 0.08 g/L of alcohol in the blood when determining the pattern of alcohol consumption. In adults, this level would correspond to the intake of five or more beverages by men and four or more beverages by women in approximately two hours. The NIAAA considers duration (two hours) in the HAC definition.

To consolidate a definition that includes alcohol levels in the blood, several studies have employed different variants of Widmark's formula, which was developed in the 1930s and has proven adequate reliability^[33]. This equation establishes that the maximum concentration of alcohol in the blood is $A/(p \times r)$, where A = amount of alcohol consumed (in grams); p = body weight and r = fat/water ratio (0.7 for men and 0.6 for women).

Recently, another study^[34] determined that the definition by Wechsler's group^[30,31] and the NIAAA proposal^[33] are strongly correlated with a similar pattern of association among the variables of sex, race and

Table 1 Prevalence of binge drinking

Ref.	Prevalence
Galán <i>et al</i> ^[41]	13.35%
Slutske <i>et al</i> ^[150]	19.50%
Bartoli <i>et al</i> ^[42]	37.85%
Delegación del Gobierno para el Plan Nacional sobre Drogas ^[40]	18%
CDC ^[44]	17.10%
Grucza <i>et al</i> ^[45]	50%
Hanewinkel <i>et al</i> ^[151]	27.00%
Lee <i>et al</i> ^[152]	46.30%

Table 2 Factors associated with binge drinking^[42]

	OR (95%CI)
Female gender	1.57
Living with parents	0.57
High financial availability for each weekend	1.33
Cannabis use	1.61
Smoking e-cigarettes	2.49
Positive alcohol expectancies	1.11
Peer influence	2.4
Interest for discos and parties	1.53
High educational level	3.63

age and the initiation of consumption. These authors believe that quantity and duration should be considered, as suggested by the NIAAA, because the sole inclusion of the quantity variable underestimates the HAC prevalence and is insufficiently sensitive in discriminating between problematic and nonproblematic patterns of consumption.

An additional and more adequate definition for the clinical environment may be the consumption of six or more alcoholic beverages by men (60 g) and five or more alcoholic beverages by women (50 g) in a single occasion (in a two-hour period) at least once in the last 30 d. This definition is similar to the approach by the NIAAA^[32] and Wechsler's group^[30,31] and gathers all proven relevant variables of quantity and frequency but requires customization to the country in which the research will be conducted.

EPIDEMIOLOGY

Since Strauss and Bacon's epidemiological study, which was performed in the United States during the 1950s^[30], several authors have reported an alarming increase in alcohol consumption among young global populations and consider it to be a risk pattern of consumption in this population (Table 1)^[35-38]. At the European level (Eurobarometer, 2007), approximately 80 million Europeans who are aged 15 years or older [over one-fifth of the adult European Union (EU) population] reported binge drinking at least once a week in 2006; this proportion has increased since 2003 in the adult population of the EU 15 (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy,

Luxembourg, The Netherlands, Portugal, Spain, Sweden, and the United Kingdom). Binge drinking is not the prerogative of the young. Eighteen percent of persons aged 55 years of age and older reported binge drinking at least once a week in 2006 compared with 24% of persons aged between 15 and 24 years. Eastern Europe had the highest pattern of drinking score of 4.9, which indicated that people in this region frequently consumed large quantities of alcohol and frequently drank to intoxication, engaged in prolonged binges, and primarily consumed alcohol outside of mealtime^[39]. Traditionally, alcohol consumption in Spain has been associated with the adult population; its regular consumption was primarily linked with gastronomy and social events. In the last 20 years in the remaining Mediterranean countries, important changes have occurred regarding the quantity, patterns and meaning of consumption that are similar to the increased binge drinking in the rest of the world^[8]. One of the most recent household surveys on alcohol and drug use in Spain showed that 18% of the population between 15 and 34 years of age (with a mean age of first contact with alcohol at the age of 16.8 years) indicated that they consumed five or more alcoholic beverages in one single occasion (occasion refers to the intake of several glasses in a couple of hours) in the last 30 d^[40]. A cross-sectional study^[41] with a significant number of participants ($n = 20608$) of 15 years of age and older that employed the 2011-2012 National Health Survey as a source of information (Servicio Nacional de Salud, by its initials in Spanish) considered the intake of ≥ 40 g/d of alcohol in men or ≥ 24 g/d in women to be high-risk consumption. Binge drinking was defined as the consumption of ≥ 6 (men) and ≥ 5 (women) standard beverages of alcohol in 4-6 h in the last 12 mo. A total of 1.3% of the surveyed subjects were average high-risk drinkers; 19.6% of the men and 7.1% of the women had performed binge drinking in the last year. This pattern decreased with age but increased with educational level in both sexes, with beer as the most-consumed beverage. A study in Italy^[42] of 654 individuals with a mean age of 20.6 years showed that 38% of the subjects had recently engaged in binge drinking. By performing a multivariate analysis, a relation was observed between this type of consumption and higher educational expectations, a larger amount of money available to spend during the weekends, interests in parties and discos, a higher prevalence in women (despite the reports from Anglo-Saxon countries), the use of cannabis, a greater influence of friends and the use of electronic cigarettes. Conversely, living with parents produced a protective factor (Table 2). In another Italian study based on the CAGE questionnaire or Alcohol Use Disorders Identification Test showed that 19.5% of the 1520 patients who attended an emergency service during the five months of the study had problems with alcoholism; the most frequent attendees were young males (18-20 years of age), divorced or single patients, and unemployed, homeless or immigrant patients^[43].

In the United States, approximately 38 million adults binge drink, according to a 2010 survey by the Centers for Disease Control. The total prevalence of binge drinking among adults in the 48 states and the District of Columbia was 17.1%^[44]. Epidemiological studies have identified that binge drinking is prevalent on college campuses; some studies indicate that approximately 50% of students reported binge drinking in recent weeks^[45]. A recent study noted that approximately 500000 college students are injured and 1700 college students die each year from alcohol-related injuries^[46].

Binge drinkers have a greater risk for developing alcohol dependence^[47]. In addition, binge drinking has been associated with unplanned and unsafe sexual activity, assaults, falls, injuries, criminal violations, automobile crashes, and total poor neuropsychological functioning^[48]. Each year, two thousand homicides are registered in Europe due to excessive alcohol consumption.

The importance of this problem translates to high healthcare costs. In the United States, the estimated annual expenditure for binge drinking is 168 billion dollars^[44]. The estimated cost of binge drinking for the English Public Health System was £1.7 billion in 2003, which reflects the physical and psychological health problems that are associated with this type of excessive drinking^[49].

ALCOHOL AND TOBACCO

Similar to alcohol, tobacco is considered to be a major cause of morbidity and mortality^[50,51]. Tobacco has been directly responsible for 100 million deaths in the XX century^[50,51]. Cigarette smoking is strongly associated with alcohol consumption^[52-58]. Conversely, drinkers, especially binge drinkers, are more likely to smoke than nondrinkers^[52,55]. This tobacco-alcohol relationship involves the pleasure-reward dopamine brain systems, as evidenced in murine models. In a recent study of mice, the rodents that were exposed to nicotine tended to ingest alcohol more frequently than rodents that were not administered nicotine due to a reduction in the dopamine response of the reward-response system in the brain, which decreased the pleasurable response to alcohol^[59].

Young adults perceive an increased enjoyment of and desire for cigarettes while drinking alcohol^[53,60], which may explain why smokers smoke more cigarettes while under the influence of alcohol^[53,61-63], especially during binge drinking episodes^[53,61]. If the frequency of alcohol consumption, binge drinking and being a smoker are associated, we are experiencing a global health issue with an early beginning in adolescence because both substances synergically increase the future risk to a level that exceeds the usual risk for liver, cardiovascular and neoplastic diseases posed by the individual use of either of these substances^[64]. Young adults smoke cigarettes at rates that are higher than any other age group. According to the 2010 National Survey on Drug Use and Health survey, 34.2% of young adults aged 18 to 26

are current smokers, compared with 22.8% of adults aged 26 or older. In a recent study^[65], teenagers who attend bars and discos showed a higher rate of tobacco consumption; this consumption was highly associated with the intake of alcoholic beverages.

TOXICITY OF ALCOHOL

The factors that affect the susceptibility to alcohol toxicity include genetics, gender, lifestyle/nutrition, exposure to environmental chemicals and drugs, and comorbidities. Toxic and other adverse effects of alcohol on organs and tissues in humans are a consequence of its metabolism to acetaldehyde, the associated formation of reactive oxygen and nitrogen species, the depletion of co-factors (e.g., NAD+), and the impairment in energy homeostasis^[66]. Due to the considerable redundancy in the oxidative enzymatic pathways (alcohol dehydrogenases, CYP2E1 and catalase) that can convert alcohol to acetaldehyde, the majority of tissues are capable of alcohol metabolism even though the liver is the primary site. Similarly, acetaldehyde dehydrogenases are ubiquitous in mitochondria. A minor and non-oxidative pathway of alcohol metabolism is *via* fatty acid ethyl ester (*via* fatty acid ethyl ester synthase) and phosphatidyl ethanol (*via* phospholipase D). Alcohol impacts the integrity of the gastrointestinal mucosal barrier, resulting in the translocation of the gut bacteria-derived lipopolysaccharide (endotoxin) and other molecules to the liver *via* the portal blood flow and the activation of the innate immune response. The molecular and cellular sequelae of the toxic mediators of alcoholic injury assume many forms. Acetaldehyde and oxidants are highly reactive molecules that can damage deoxyribonucleic acid (DNA), proteins and lipids. Changes in hepatic respiration and lipid metabolism can cause tissue hypoxia and impairment in the mitochondrial function. Secondary effects include the disruption of signaling pathways and ion channel function, the unfolded-protein response and oxidative stress as well as the activation of adaptive immune response that is significantly triggered by acetaldehyde protein adducts. Cell death triggers additional innate immune response, activation of fibrogenesis, and tissue repair. In addition to pro-inflammatory mediators, other signaling molecules, such as neurotransmitters, are affected by alcohol. Depending on the affected tissue, gross pathological changes that are associated with alcohol drinking include most or all of the following conditions: Fat accumulation (steatosis), inflammation, necrosis and fibrosis and functional deterioration^[67]. Alcohol *via* acetaldehyde also favors carcinogenesis and has been considered to be a class 1 carcinogen by the WHO^[68].

CONSEQUENCES

Compared with nonbinge drinkers, frequent binge drinkers were more likely to report fair or poor health and experience a greater number of sick days. These findings appear to reflect the generally negative consequences

Table 3 Summary of the organic effects of alcohol-binge drinking

Hepatic	Neurocognitive	Renal
Steatosis	Impaired verbal memory	Glomerulonephritis
Steatohepatitis	Impaired episodic memory	Acute nephropathy
Fibrosis	Deficits language and attentional tasks	Kidney graft failure
Cirrhosis	Prospective memory	
Hepatocellular carcinoma	Executive functions	
Oncogenic	Cardiovascular	Others
Oral cavity	Hypertension	Acute pancreatitis
Pharynx	Ischemic heart disease	Chronic pancreatitis
Larynx	Stroke	Major depression
Esophagus	Cardiomyopathy	Impaired fertility
Colorectum	Myocarditis	Premature and low weigh births
Breast	Arrhythmias	Fetal alcohol syndrome
Pancreas	Atherosclerosis	

of alcohol abuse but at an earlier stage in poor health development^[69]. Binge drinking is associated with the deterioration of work performance, brain damage, alcohol dependence, stroke, heart rhythm disturbances, coronary disease, sexually transmitted diseases and premature death^[35]. Table 3 summarized the organic effects of binge drinking on different organs and systems.

Effect on the liver

The epidemiological evidence demonstrates that binge drinking in chronic alcoholics augments liver injury^[70]. A recent study showed that frequent consumers (5-7 d/wk) have a higher mortality rate compared with persons with lower rates of consumption (1-4 d/wk)^[71]. A heavy binge drinking episode in patients who chronically consume alcohol is the most common trigger for the admission of patients with steatohepatitis^[72]. A study of a large cohort of drinkers with consecutive biopsies suggested the concept of multiple hits of alcoholic hepatitis in the same patients as the prime determinant in the progression of alcoholic liver injury^[73]. Mathews *et al*^[74] have recently developed a chronic plus binge alcohol feeding model in mice, which is similar to the drinking patterns of many alcoholic hepatitis patients: A history of chronic drinking and recent excessive alcohol consumption have begun to identify novel mechanisms that participate in the pathogenesis of alcoholic liver injury. Chronic binge ethanol feeding induces higher levels of steatosis, serum alanine transaminase, and liver inflammation^[74]. Binge alcohol consumption aggravates oxidative stress and promotes the pathogenesis of nonalcoholic steatohepatitis from obesity-induced simple steatosis. Alcohol and high fat diets synergistically induce nitrosative, endoplasmic reticulum, and mitochondrial stress and an up-regulation of hepatic toll-like receptor 4 (TLR4), thereby contributing to steatohepatitis^[75,76]. Additionally, high fat diet plus binge ethanol synergistically exacerbates acute steatohepatitis through the induction of CXCL1 and subsequent hepatic neutrophil infiltration^[77]. Moderate ethanol binges induce significant liver damage

(hepatocyte apoptosis) in genetically obese (*ob/ob*) mice by increasing tumor necrosis factor α and decreasing nuclear factor κ B activity^[78]. Individuals with fatty liver are predisposed to increased liver injury by chronic binge alcohol drinking. This finding has been proven in studies involving rats, where repeated alcohol binges in the context of mild steatosis may promote the activation of stellate cells and contribute to liver injury^[79].

Despite these findings, note that the majority of experimental data concerning the impact of binge drinking on the pathogenesis of a liver injury may not be completely extrapolated to humans because the majority of the studies are based on animal models that do not completely mimic liver injury in humans. Note that ethanol sensitivity in human, rat, mice, and other animal models (*e.g.*, drosophila, zebrafish) can also vary due to differences in populations, species, and strains. In animal models, several approaches have been considered to examine the effect of binge ethanol, including the single binge, the intermittent repeat binge, and chronic ethanol exposure followed by episodes of binging. Evidence from these animal studies provide mechanistic information on the binge ethanol effect relevant to alcoholic liver disease. For example, the cellular effects of ethanol are increasingly attributed to the modulation of immunological, metabolic, signaling, and epigenetic pathways^[80-82]. Binge alcohol alters the levels of several cellular components and dramatically amplifies liver injury in chronically alcohol exposed liver. Evidence exists that acute alcohol exposure inhibits hepatic mitochondrial DNA synthesis and also impairs mitochondrial metabolism and dynamics. Alcohol intoxication inhibits the inflammatory response by inhibiting signaling through TLRs when a potent external TLR stimulus is provided during alcohol intoxication^[83]. As previously reported, binge drinking promotes the activation of stellate cells and contributes to liver injury *via* a pro-fibrogenic response^[79].

Other factors involved in the toxicity of alcohol to the liver are obesity, resistance to insulin, chronic infection with hepatitis C virus, being female, and tobacco consumption^[84]. A priori, tobacco appeared to have a minor role in fibrosis and chronic liver disease; however, additional studies have suggested its deleterious role in the course of chronic liver disease. Tobacco and alcohol may have a synergic and deleterious impact on chronic liver disease^[85]. Tobacco may accelerate the progression to cirrhosis in patients with alcoholic chronic liver disease and increase liver decompensations in individuals with established cirrhosis^[86]. Approximately 90% of the patients with advanced alcoholic chronic liver disease are smokers^[87]. Tobacco seems to be involved in the risk of developing hepatocarcinoma^[88] by increasing aflatoxin B1, which is a known hepatic carcinogen^[89].

The mechanisms by which smoking promotes the progression of chronic diseases are substantially unknown. Smoking may accelerate the progression of "fibrogenic" conditions, such as chronic renal, cardiac or pancreatic diseases^[90,91]. Cigarette smoke induces an

array of pathogenic effects that are potentially involved in tissue fibrogenesis, including systemic inflammation, thrombogenesis and oxidative stress^[92]. Smoking exerts powerful immunoregulatory actions that can produce an impaired wound healing response to injury. These effects may be more pronounced in susceptible individuals as suggested by genetic epidemiological studies^[93]. The strongest evidence to support a fibrogenic effect of smoking is the fact that smoking cessation has beneficial effects on the progression of chronic renal diseases^[94,95].

Smoking increases the production of pro-inflammatory cytokines (interleukin 1, 6 and 13) and tumor necrosis factor α , angiogenic factors (vascular endothelial growth factor-A) and fibrogenic mediators (leptin, transforming growth factor β 1 and angiotensin II) also induces oxidative stress by stimulating nicotinamide adenine dinucleotide phosphate oxidase and decreasing antioxidant defenses, which cause lipid peroxidation^[92]. These effects can cause an increase in hepatocellular damage and the subsequent activation of resident hepatic stellate cells, which comprise a major fibrogenic cell type. Another potential mechanism by which smoking causes liver fibrogenesis may be iron deposition. Smoking also induces profound changes in the microvasculature, such as endothelial dysfunction, smooth muscle cell proliferation and vasoconstriction, which cause impaired delivery of nitric oxide and tissue hypoxia^[96]. These events are potentially implicated in the wound healing response of the liver to chronic injury. Heavy smokers commonly exhibit several features of the insulin resistance syndrome and develop an increased risk for type 2 diabetes^[97]. Because insulin resistance promotes liver fibrogenesis, it can participate in the fibrogenic effect of tobacco in the liver. Therefore, we can conclude that the interaction between alcohol and tobacco synergistically elevates the disease risk to a level above the risk posed by the individual use of either of these substances^[64].

Oncogenic effects

Alcoholic beverages and ethanol in alcoholic beverages are classified by the WHO International Agency for Research on Cancer as "carcinogenic to humans" (group 1)^[68]. Probable mechanisms for the association between alcohol drinking and upper digestive tract cancer have been presented in several studies^[98,99]. The carcinogen of esophageal cancer, with regard to alcohol consumption, is acetaldehyde^[100,101], which is a highly reactive and toxic alcohol metabolite. Acetaldehyde interferes with DNA repair machinery and directly inhibits O6 methylguanyltransferase, which is an enzyme that is deemed important for the repair^[102]. The inhalation of acetaldehyde has been known to cause bronchial cancer and esophageal cancer. Several studies have reported the hazards of binge drinking using experiments. After *in vivo* administration of ethanol in the stomach of rats, which is analogous to the binge drinking condition, histone H3 modification, which primarily affects histone methylation in the liver, lung and spleen, was detected in

the histone of rat tissues^[103]. A study in a South Korean population that included 2677 men of 55 years of age, with a follow-up of 20.8 years, associated severe binge drinking and its frequency with mortality due to oral and esophageal cancer. A higher mortality was observed in these cancers for patients with a daily binge drinking habit compared with nondrinkers. The alcohol dose and mortality due to esophageal cancer and the mortality and the frequency of alcohol consumption are highly associated, whereas the volume of consumed alcohol is not highly associated. Note that tobacco consumption was an important confounding factor in this study^[104]. Binge alcohol consumption seems to be a risk factor for pancreatic cancer. After adjusting for sex and age in a case-control population study^[105] in San Francisco (United States) with 532 cases and 1701 controls, the risk of pancreatic cancer was determined to be higher in binge drinking patients when a higher amount of units were consumed and a longer consumption had occurred. This finding supports the notion that a high consumption of alcohol, including binge drinking, is a risk factor for the development of pancreatic cancer. Alcohol is also involved in the development of a hepatocarcinoma. Acetaldehyde, a reactive metabolite of ethanol, binds to nucleic acids, proteins such as enzymes, microsomal proteins and microtubules. The generated reactive oxygen species can also activate or repress the epigenetic elements such as chromatin remodeling, non-coding RNAs (micro-RNAs), DNA (de) methylation and histone modification that affect gene expression, hence leading to hepatocarcinoma^[106].

We should consider that smoking is a known risk factor for upper digestive tract cancer, including oral cavity, pharynx and esophagus cancers. Therefore, the interaction of alcohol and tobacco synergistically elevates the disease risk to a level above the risk posed by the individual use of either of these substances.

Neurocognitive effects

The consequences on the memory of alcoholic beverage binge drinking have been explored in animal models. The results show that binge doses of alcohol cause a disruption in the growth of new brain cells; this lack of new growth may cause the long-term deficits detected in key areas of the brain (such as hippocampal structure and function) that are induced by binge drinking^[107,108]. The increasing interest in performing studies to analyze the neurotoxic effect of alcohol due to the increased practice of binge drinking in adolescence is not surprising. A "safe" alcohol dose for the developing brain of an adolescent is unknown. The prefrontal cortex and limbic system, which includes the hippocampus, undergoes prominent reorganization during the late teenage years^[109,110]; these cognitive processes, which are dependent on these areas of the brain, such as memorial processes, are very sensitive to any damage caused by excessive alcohol ingestion. Different studies have reported poorer performance in neurocognitive tests with the worst verbal memory and poorer episodic memory^[111]. Binge

drinking affects the executive functions and the working memory from the Brodmann areas 46 and 9 of the dorsomedial prefrontal cortex. Studies of neurocognitive function in teenagers aged 15-19 years with a history of alcohol abuse have revealed deficits for a range of language and attentional tasks, verbal and non-verbal memory tasks, and specific working memory impairments^[112,113]. Compared with nonalcohol drinkers, binge drinkers evinced cognitive impairments in the Paced Auditory Serial Addition Test regarding executive planning function and episodic memory tasks—these findings were similar to frontal function deficits observed in Korsakoff alcoholics^[105]. Using magnetic resonance, several studies^[114] have correlated binge drinking in post-adolescence and early adulthood with brain structural alterations. These results showed a greater decrease in the gray matter of the dorsomedial prefrontal cortex in binge drinking subjects compared with the control subjects. A positive correlation between the increased gray matter in binge drinkers and the results from the Self-Ordered Pointing Test (SOPT), which is an error test, was observed^[109]. The measure of the prefrontal cortex was also correlated with the volume and the rate of alcohol intake^[109].

A Spanish cohort study^[115] evaluated the binge drinking habits of 89 university students with a two-year follow-up. The neuropsychological performance was measured using several scales; binge drinkers yielded the worst scores in the Wechsler Memory Scale-III and the SOPT and demonstrated a worse verbal memory compared with nonbinge drinkers. Another study, with a longer follow-up of ten years, of adolescents with abusive alcohol consumption revealed that verbal memory deteriorated with time for adolescents who presented the habit to a young adult age^[116]. At a neuropsychological level, binge drinking subjects show deficiencies in the assessment tests for the frontal executing functions of attention, planning, cognitive flexibility, work memory, decision-making, verbal fluency, decision-changing and inhibitory control tasks^[117].

Regarding the effect of prospective memory, a study^[118] showed similar results on the Prospective and Retrospective Memory Questionnaire test for binge drinkers and nonbinge drinkers. These findings contrast with another study by the same author^[119]. A higher number of short- and long-term prospective memory lapses were observed in this group. This study excluded consumers of other substances and lacked the control of the age, type of alcohol consumption, hours after the last intake or period of consumption. However, a lower score in the prospective remembering video procedure (PRVP) was observed in binge drinkers, which revealed differences when consumers of other substances and consumers who had drunk alcohol in the last 48 h were excluded. Nonsignificant differences were observed between the groups regarding age, anxiety or depression levels, and years of alcohol consumption. Subjects with a higher intake of alcohol units per week demonstrated lower results in the PRVP test.

Effect on the cardiovascular system

Approximately 10% of cardiovascular disease-related deaths are attributable to alcohol^[120]. The probability of coronary heart disease and cardiovascular mortality increases with heavy consumption^[121]. Studies suggest that a binge pattern of drinking may precipitate myocardial ischemia or infarction^[122], and evidence of an association between binge alcohol consumption and a two-fold greater mortality after acute myocardial infarction also exists^[123]. In addition to the volume of consumption, the *pattern* of drinking must be considered. Recently, Liu *et al.*^[124] demonstrated that binge patterns in mice increase the development of atherosclerosis compared with no alcohol controls. The results from retrospective studies of adults who range in age between 40 and 60 years have indicated that binge drinking is associated with a heightened risk of cardiovascular (CV) events, such as stroke, sudden death, myocardial infarction, and increased mortality after myocardial infarction^[123,125-127]. In addition, an alcohol binge drinking pattern is associated with the progression of carotid atherosclerosis^[128]. Endothelial dysfunction is an early indicator of blood vessel damage and atherosclerosis and a strong prognostic factor for future CV events^[129-131]. In binge drinkers, cardioprotective changes in high density lipoproteins are not observed, and adverse changes in low-density lipoproteins are acquired. Binge drinking seems capable of predisposing the heart to arrhythmia by reducing the threshold for ventricular fibrillation and by causing scarring of the myocardium. The myocardium may be especially sensitive during withdrawal, as will occur after weekend binges. In addition, irregular drinking is associated with an increased risk of thrombosis, which is most likely to occur after heavy drinking stops. These physiological mechanisms may explain the observed increase in cardiovascular events during the weekend and on Mondays. In countries with known weekend binge drinking, the Monday peak is pronounced and is accompanied by slight increases in mortality on Saturdays and Sundays. This finding has been observed in countries of the former Soviet Union and in Scotland^[132-134]. Chenet *et al.*^[135] hypothesize that alcohol, particularly when drunk in binges, serves as a catalyst in acute ischemic heart diseases by being synergetic to other triggering factors.

In an experimental animal model in which binge alcohol was administered after chronic alcohol treatment, binges caused a decrease in the messenger ribonucleic acid (mRNA) of low-density lipoprotein-receptor (LDL-R) and increased mRNA levels of the angiotensinogen gene in the liver. Binge ethanol intake in chronically exposed rat liver decreased LDL-R and increased angiotensinogen gene expression^[136]. Note that increases in plasma LDL cholesterol and angiotensin are cardiovascular risk factors in human alcoholics. In a recent study performed in ApoE KO mice, the arterial lumen was reduced and the deposits of macrophages were more evident, which confirms the atherogenic capacity of alcohol binge drinking^[124]. These results imply that binge alcohol-

induced alterations in liver have consequences on the cardiovascular system. Thus, binge drinking affects interorgan cross-talk. This finding is further supported by increases in the plasminogen activator inhibitor (PAI). PAI-1 serves a major role in fibrin metabolism by blocking fibrinolysis. The role of PAI-1 in fibrin accumulation in vascular disease is well understood to contribute to endothelial dysfunction and inflammation.

Thus, these findings provide strong evidence to support a health message that discourages binge drinking. The provision to healthcare professionals of scientific evidence that binge drinking can accelerate atherosclerosis may encourage them to perform brief interventions for individuals with at-risk drinking behaviors.

Other effects

The effect of alcohol on other organs and systems varies. Binge drinking is one of the main causes of pancreatitis^[137] and is involved in a higher mortality from a duodenal ulcer^[138]. It is also the cause of neuropsychiatric conditions, such as depression^[139]. In the kidney^[140], binge drinking has been correlated with glomerulonephritis, acute nephropathies, and the loss of kidney transplants. It is the cause of fertility disorders, prematurity, low weight and newborn alcoholic syndrome^[141].

APPROACHING THE PROBLEM

Numerous social and political interventions are available to decrease this type of consumption, such as laws against driving under the effect of alcohol, increased taxes, restriction of access and availability of alcohol, and brief interventions, such as medical advice and control *via* publicity.

Our main weapon against this problem is primary prevention, which is difficult to develop due to established alcohol consumption among different cultures, which is primarily associated with social events. In this manner, the WHO has developed a strategic plan to approach the harmful consumption of alcohol, based on preventive interventions^[142,143] with the help of health services, to reduce access to alcoholic beverages and prohibit its marketing and by increasing prices.

A substantial amount of evidence across different countries to support making alcohol more expensive, primarily *via* taxation, and to reduce the extensive range of harm due to intoxication and binge drinking, including road traffic accidents and fatalities, intentional and unintentional injuries, rapes and robberies, homicides, crime, and violence^[144]. Another issue in this plan is the marketing control of the illicit production of beverages with regulation systems.

Similarly, a substantial amount of evidence to support raising the minimum purchasing age to reduce alcohol-related road traffic accidents and to reduce the density of alcohol outlets to reduce drunkenness, assaults, and road traffic fatalities. However, these strategies will only be effective if it is not backed up

with a credible threat to remove the licenses of outlets that repeatedly sell to under-aged customers. These strategies are also more effective when supported by community-based prevention programs. Some of these measures are effective in decreasing the damage caused by alcohol but are also cost-effective from a revenue point of view due to increases in the price and taxes of alcoholic beverages^[143,145].

Preliminary data support the intriguing possibility that integrated intervention may enhance smoking cessation and reduce binge drinking^[146].

Decreased smoking and improved maintenance of abstinence may result from a behavioral intervention to reduce binge drinking. This hypothesis is supported by several lines of evidence, including conditioning mechanisms in which the craving to smoke is elicited by higher levels of alcohol consumption^[147,148], and environmental factors, such as parental and peer influence for concurrent use of cigarettes while engaging in binge drinking^[149].

Smoke-free bar policies may not be sufficient to influence the association between smoking and drinking, particularly if tobacco marketing continues in these venues or in the absence of programs that specifically address the co-use of tobacco and alcohol. Tobacco interventions should prioritize bars and other social venues that are popular among young adults to reach persons who are at greatest risk. The strong and consistent association between smoking and drinking indicates that public health efforts and clinical cessation programs need to address the paired use of tobacco and alcohol among the young adult bar-going population.

CONCLUSION

Binge drinking is an increasing public health issue that affects teenagers and young adults. Although its consequences are not well known, relevant hepatic, cardiovascular, neurocognitive and oncogenic effects may be present. Binge drinking also has a significant social and economic impact. Interventions should be globally approached to address the consumption of alcohol and tobacco.

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