Alcohol: Gastrointestinal and Other Toxicities

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This article will focus on the two areas of alcohol injury: first, the gastrointestinal system, primarily liver toxicity and cirrhosis, and second, the human toll in injury, examining injury epidemiology information that estimates alcohol's involvement in trauma. Any pharmacist consulting in any capacity, especially related to gastrointestinal disorders, will need to understand the significant sociological, pathological, pharmacological, and psychological impact of alcohol. Pharmacists providing care, including dispensing many different drugs to patients, should be cognizant of the interacting effects of alcohol and the need to warn patients. Finally, the reader will learn of a case in which a pharmacist was sued for not warning about the use of alcohol with a central nervous system depressant, and the resultant litigation after that lawsuit.

THE SCIENTIFIC LITERATURE for the past 60 years is abundant with reports, descriptions, studies, and analyses describing the toxic effects of chronic and excessive alcohol intake. These effects include the following:

1. GI: cirrhosis of the liver, pancreatitis, gastritis, and vitamin deficiency.
2. Cardiovascular: hypertension, cardiomyopathy, dysrhythmia, and hemorrhagic stroke.
3. Neoplasm: cancers of the mouth, pharynx, larynx, esophagus, and liver.
4. Neurological: direct neurotoxic effects (peripheral and central), brain damage secondary to vitamin deficiency, cerebral and cerebellar degeneration, organic brain syndromes, permanently diminished intellectual function, and amnesia.
5. Psychiatric: alienation, aggression, rage, violence, disinhibition, defense mechanisms of denial, reversal and externalization, self-directed aggression, confusion, and severe family psychopathology.
6. Hormonal and dermatologic disease.

For a review of ethanol's toxicity, the reader is referred to other excellent papers.[1-6] This article will focus on the two areas of alcohol injury: first, the adverse gastrointestinal effects, primarily cirrhosis; and second, an epidemiological study of the human toll. Consulting pharmacists need to understand the significant sociological, pathological, pharmacological, and psychological impact of alcohol. Finally, the reader will learn of a case in which a pharmacist was cautioned for not warning about the use of alcohol with a central nervous system depressant, and the litigation that ensued.

T.G. Coffey's description of the gin epidemic in 18th century Britain is a semi-analytic account of the decay of society due to alcoholism[7]:

> A rural to urban migration, the politics of urban renewal following the great London fire of 1666, rural domination of Parliament, poverty and disorganization, the introduction of Dutch gin into England by soldiers returning from wars, led, between 1720 and 1750, to the despair evident in Hogarth's Gin Street, to high mortality from alcohol-related disease, to rampantly excessive infant mortality, and to general chaos in the streets. Prohibition of gin failed, and the eventual decline of consumption seemed directly related to high gin taxes, legislation forbidding alcohol consumption on the street and confining it to selected and dispersed taverns, the appearance of coffee shops for recreation, and—crucially—John Wesley's Methodism, directed to the poor and their customs, and evangelically enlisting them in alternatives to alcohol intoxication. While coffee and, later, tea (witches' brew), were also blamed for the moral deterioration of the poor, social reformers such as Henry Fielding and William Hogarth, who battled against both gin and beer, did not oppose these lighter beverages. Wesley even countenanced beer, the consumption of which markedly increased in the latter half of the seventeenth century. The marked decrease in gin consumption, achieved by the late eighteenth century, was thus related in part to legal, economic, and trafficking regulations, urban power, and alternatives, including a religious cause.

ALCOHOLIC LIVER DISEASE

Alcoholic liver disease remains the major cause of clinically significant chronic liver disease in the United States.[8] The hepatotoxicity of alcohol has been suspected for centuries. Large epidemiological surveys confirmed this association between liver disease and alcoholism. For example, in the United States, deaths

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from cirrhosis were found to decline during Prohibition (1920s). Conversely, in many countries, deaths from cirrhosis have been noted to correlate with per capita consumption of alcohol.[9,10]

Alcohol Metabolism

Only 2% to 10% of the ethanol absorbed is eliminated unchanged by the kidneys and lungs. The vast majority of ingested ethanol must be oxidized in the body, chiefly in the liver, which contains the bulk of the body's metabolizing enzymes. Extensive uptake of ethanol by the liver probably explains why ethanol oxidation produces striking metabolic imbalances in the liver. When ethanol is present, it becomes the preferred fuel for the liver, effectively displacing up to 90% of all other substrates normally used by the liver.[11] Hepatic metabolism results in the production of hydrogen and acetaldehyde. Each of these two products is directly responsible for a variety of metabolic alterations that play a role in the development of liver injury. All known oxidative pathways of ethanol metabolism result in the production of acetaldehyde.[11,12]

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Once in the cell, alcohol is efficiently oxidized by several enzyme systems to form potentially toxic intermediates. In nonalcoholic subjects, most ethanol oxidation is accomplished by the cytosolic alcohol dehydrogenase-aldehyde dehydrogenase system. However, chronic consumption of alcohol also induces certain microsomal cytochrome P-450 isozymes; hence, this pathway provides a supplemental route for ethanol disposal in alcoholic individuals.

Alcohol dehydrogenase-catalyzed oxidation of ethanol to acetaldehyde and eventually to acetate generates excessive reducing equivalents. This, in turn, upsets the normal cellular oxidation-reduction (redox) balance and interferes with the intermediary metabolism of many nutrients. Induction of microsomal enzyme oxidation system (MEOS) activity by ethanol and other inducers increases the probability of generating metabolites, some of which are hepatotoxic. Liver toxicity (cirrhosis) seems to occur in only a minority of humans and animals that chronically consume the alcohol. Only about one fifth of men will develop cirrhosis after drinking the equivalent of two six-packs of beer daily for more than a decade.[13,14]

Although acute ethanol ingestion can inhibit the MEOS, chronic consumption of ethanol induces the activity of several microsomal enzymes and hence potentiates the metabolism of drugs that normally serve as substrates for these enzymes. The potential importance of hepatocellular injury from other drugs to the development of liver disease in alcoholic patients is also a factor.

Acetaminophen is a widely used and generally safe analgesic that is metabolized by ethanol-inducible P-450 enzymes. Indeed, the principal isoenzyme induced by ethanol (p4592EI) has been shown to be the one primarily involved in the metabolism of acetaminophen.[15] As a result, the threshold for acetaminophen-induced hepatocyte necrosis is significantly lowered by chronic alcohol use, and, in alcoholic individuals, lethal hepatotoxicity has been reported to follow the ingestion of doses that are typically well-tolerated in subjects devoid of ethanol-induced liver damage.[16] These observations prompt serious concern about the possibility of occult, drug-induced liver injury in any individual who habitually consumes excessive quantities of alcohol.

The Extent of the Problem

There are up to 15 million alcoholics in the United States. In addition, approximately two-thirds of the adult population use alcohol on occasion, and about 12% can be defined as "heavy drinkers." Calabrese[17] describes alcohol as "the most significant drug of abuse in the United States." Despite the high visibility that alcohol abuse has within society, the critical role alcohol consumption plays in affecting susceptibility to a wide range of environmental and industrial contaminants has not been generally

acknowledged by society. Calabrese describes a general myth that only heavy drinkers need be concerned with the interaction of ethanol and pollutants, and cites an example that as little as a single beer can alter the metabolism of highly carcinogenic nitrosamines and enhance cancer risk.[17] (Editor note: One reviewer questioned whether the risk was from the alcohol or any of the other ingredients in beer!)

Among the medical problems associated with alcoholism, hepatic disorders are at the forefront. The spectrum of alcoholic liver injury involves hepatic steatosis (fatty liver), early fibrosis (perivenular and perisinusoidal fibrosis), alcoholic hepatitis, and cirrhosis. Of all medical deaths attributable to alcoholism, 75% are the result of cirrhosis of the liver. In the United States, cirrhosis has overtaken diabetes as the fifth most common cause of death; in large urban areas, it has become the fourth cause of all deaths in the active group of people of 25 to 65 years.[18] Early recognition of the contribution alcohol makes to the nature of many patients' complaints may lead to intervention at the initial stages of the disease, prior to the medical or social disintegration of the patient, and prior to the development of irreversible cirrhosis.[19]

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Alcohol and Nutrition

Classically, malnutrition has been recognized as an important compounding factor in the progression of alcoholic liver disease. Chronic consumption as a substitute for food impairs the intake, digestion, absorption, utilization and storage of many macronutrients and micronutrients.[20] Alcohol is both a food and a drug. Alcohol is rich in energy, and in many societies alcoholic beverages are considered part of the basic food supply. Alcohol is also consumed for its mood-altering effects. Under both circumstances, a large intake of ethanol may be the cause of primary malnutrition by displacing other nutrients in the diet because of preference for ethanol over food or because of associated socioeconomic and medical disorders. Until two decades ago, primary malnutrition (due to dietary deficiencies) was considered the main cause of liver disease in alcoholics. As the overall nutrition of the population improved, more emphasis was placed on secondary malnutrition.

Secondary malnutrition may result from either malabsorption or impaired utilization of nutrients caused by GI complications associated with alcoholism. Such primary and secondary malnutrition can affect virtually all nutrients.[21] Some metabolic nutritional effects of alcohol, include hyperlipemia, hyperuricemia, and ketoacidosis.[22]

CIRRHOSIS

Cirrhosis, considered the final stage of alcohol-induced hepatic pathology, results after recurrent bouts of alcoholic hepatitis. Hepatocellular injury and perhaps direct actions of acetaldehyde on collagen-forming nonparenchymal cells induce a fibrogenic response in hepatocytes. Because chronic excessive alcohol consumption impairs the hepatic regenerative response to injury,[23] the regenerative nodules in alcoholic cirrhosis are typically small (micronodules).

Although studies suggest that the risk of alcohol-induced hepatic disease increases progressively when habitual intake exceeds 80 g/d of ethanol (5 to 6 drinks) in men and 20 g/d (less than 2 drinks) in women, significant liver disease occurs only in a minority of individuals who drink two to three times these amounts.[24,25] Nonetheless, alcohol should be considered a potential contributor to liver disease in all individuals, regardless of how little they consume.

The outcome for patients who survive hospitalization for alcoholic liver disease is also variable and is related to the severity of the residual end-organ damage and subsequent drinking habits. Two studies indicated that approximately 10% of patients hospitalized with alcoholic hepatitis can regain normal hepatic

histology and function. Such "cures" requires complete discontinuation of alcohol use. However, abstinence does not always guarantee resolution of liver disease. Almost half the patients hospitalized with pre-cirrhotic alcoholic hepatitis will go on to develop cirrhosis. The risk of progression to cirrhosis increases with increasing histopathological severity of the alcoholic hepatitis. Women are at greater risk than men for disease progression. Cirrhosis is likely to develop in women hospitalized with alcoholic hepatitis even if they had relatively mild disease initially and even if they become abstinent.[26,27] Recent identification of a gender-sensitive, gastric form of alcohol dehydrogenase (ADH) may help explain increased female susceptibility to alcohol toxicity. Gastric ADH activity seems to be lower in women than in men. Hence, women detoxify less ethanol intragastrically, and a relatively greater fraction of ingested alcohol in each drink is absorbed "intact" into the portal circulation to be metabolized by the liver.[28] This phenomenon explains the seeming vulnerability of women to low doses of alcohol.

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Alcohol consumption continues to influence prognosis even after cirrhosis has developed. The 5-year survival rate of patients with clinically compensated cirrhosis approaches 90% if they abstain from alcohol, but decreases to 60% if they continue to drink. Abstinent patients with decompensated cirrhosis can expect a 60% 5-year survival rate, whereas similar patients who continue to drink have, at best, a 30% chance of living 5 years.[26]

Treatment

Optimal treatment for most patients with alcoholic liver disease revolves around the resumption of a nutritious diet and abstinence from alcohol. The decision to intervene with corticosteroid therapy aimed at the underlying alcoholic liver disease should be based on the anticipated risks of morbidity and mortality. Several meta-analyses and two randomized, controlled prospective clinical trials have indicated that, once infections and gastrointestinal bleeding have been controlled, severely ill, recently drinking patients with alcoholic liver disease benefit from treatment with corticosteroids.[29-31]

ALCOHOL AND DENTAL DISEASE

The impact of alcohol and nutritional deficiencies on dental disease is significant. The problem of severe dental disease has been reported to be frequently neglected during the routine clinical examination of patients hospitalized on an internal medicine service.[32] This oversight is reflected by the paucity of medical reports focused on dental disease and its medical consequences. Recently, however, the US Preventive Services Task Force prepared recommendations for physicians and other health professionals to integrate preventive dentistry in needy patients.[33,34]

Specific attention to dental disease among alcohol abusers is important because these individuals have higher tooth mortality and lower use of dental care than do nonalcoholic individuals.[35,36] The deleterious effects of alcohol abuse on dental health include increased rates of periodontal disease, coronal and root caries, dental mortality, bruxism, and trauma. It is also hard to eat a balanced diet without teeth![37-39]

ALCOHOL AND TRAUMA

Risk Factor Surveillance

Alcohol is a major factor in the causation of all types of accidental trauma. Approximately 158 million persons are licensed to drive vehicles in the United States. Based on the estimated 19.3 million crashes with injuries or property damage that occur annually, more than 10% of drivers will experience a crash during the year.[40] Of course, driving more hours, abusing alcohol, being a young male, and other host and environmental factors can increase those odds.

Using autopsy records and other data, it was determined that, of 1,026 drivers who died within 15 minutes of single-vehicle crashes in

California, 155 (15%) died as a result of medical conditions and not traumatic injuries. The 1,026 crashes represented about 12% of all fatal crashes in the state during the 3-year period of the study. Of the 155 drivers, 19% had a blood alcohol concentration (BAC) greater than 100 mg%, which under the laws of most states, represents a statutory level of intoxication.[41]

Spanning the 8-year period from 1980 to 1987, a review of almost 200,000 vehicular crash-related fatalities in the United States indicated that an active participant in the crash (driver, pedestrian, bicyclist) had consumed alcohol. This figure represents more than 50% of the cases of fatal injury. A further study from the Centers of Disease Control (CDC) indicated that close to 12% of the years of potential life lost in the United States in 1986 were the result of injuries sustained in vehicular crashes. Again, alcohol consumption was present in more than 40% of these crashes.[42]

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Impairment and Intoxication by Alcohol

Although the effect of alcohol is usually described as impairment, there are several aspects of the relationship between alcohol and injuries that suggest a more complex causal pattern. Table 1 correlates blood alcohol levels with impairments of neurological, cognitive, and physical functions.

Table 2 describes the effects of acute alcoholic intoxication in intolerant individuals. These effects range from slight changes detectable by special tests, to coma and death by respiratory paralysis.[44]

Motor Vehicles

Alcohol use in drivers in motor vehicle crashes is more highly correlated with injury severity than incidence. Virtually all of the attempts to reduce alcohol-related injuries are directed at driving while intoxicated (DWI). However, driving a vehicle is not the only activity that is made more dangerous by alcohol. There seems to have been little notice that drunk walking, drunk arguing, or even drunk sleeping, given fire/smoke hazards, are also dangerous. Alcohol is found more often in the perpetrators of victims of assault and homicide than in drivers killed in motor vehicle crashes. If the anti–alcohol-driving programs were successful in reducing driving while intoxicated without reducing general ethanol ingestion, there is no guarantee that the overall severe injury rate would be reduced, given the possibility that intoxicated persons would engage in other activities in which the risk of injury is increased by intoxication.

A decline in the proportion of fatally injured drivers with illegal blood alcohol levels was observed during the 1980s in the United States, which was partly due to the reinstitution of the laws for 21 years as the legal drinking age in several states and partly due to other laws and enforcement.[45] Increased public attention to dieting and the marketing of beverages with lower alcohol content may have also contrib-

Table 1. Impairing Effects of Alcohol

Sign or Symptom	Approximate Blood Alcohol Level
Alcohol and perception	
Dynamic visual acuity	ca. 0.02%
Light-dark adaptation	0.09%
Peripheral vision (multi-tasking)	0.05%
Tasking of great difficulty	0.017%
Above 0.08% peripheral events ignored	
Eye blink frequency and blink closure	0.07%
Color discrimination	Very variable
Oculomotor function	
Depth perception	0.015%-0.04%
Sacchadic eye movements	0.05%-0.10%
Nystagmus of various types	0.03%-0.09%
Tracking tasks	
With angular acceleration	0.07%
added multi-tasking,	0.03%-0.06%
about 90% of subjects affected	0.10%
Division of attention	
Vigilance (multi-tasking)	0.015%
Fixation time (foveal focusing)	0.10%
Mood and emotions	
Increased drowiness and decreased clear-headedness (attentiveness)	0.03%
Memory	
Short-term input and/or recall spans	0.05%-0.10%[43]

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Table 2. Stages of Acute Alcoholic Influence / Intoxication in Nontolerant Individuals

Blood Alcohol Concentration (% w/v)	Stage of Alcohol Influence	Clinical Sign/Symptom
0.01-0.05	Sobriety	No apparent influence
		Behavior nearly normal by ordinary observation
		Slight changes detectable by special tests
0.03-0.12	Euphoria	Mild euphoria, sociability, talkativeness
		Increased self-confidence; decreased inhibitions
		Diminution of attention, judgment, and control
		Loss of efficiency in finer performance tests
0.09-0.25	Excitement	Emotional instability; decreased inhibitions
		Loss of critical judgment
		Impairment of memory and comprehension
		Decreased sensory response; increased reaction time
		Some muscular incoordination
0.18-0.30	Confusion	Disorientation, mental confusion; dizziness
		Exaggerated emotional states (fear, anger, grief, *etc*)
		Disturbance of sensation (diplopia, *etc*) and of perception of color, form, motion, dimensions
		Decreased pain sense
		Impaired balance; muscular incoordination; staggering gait, slurred speech
0.27-0.40	Stupor	Apathy; general inertia, approaching paralysis
		Markedly decreased response to stimuli
		Marked muscular incoordination; inability to stand or walk
		Vomiting; incontinence of urine and feces
		Impaired consciousness; sleep or stupor
0.35-0.50	Coma	Complete unconsciousness; coma; anesthesia
		Depressed or abolished reflexes
		Subnormal temperature
		Incontinence of urine and feces
		Embarrassment of circulation and respiration
		Possible death
0.45+	Death	Death from respiratory paralysis

uted to the reduction; however, evaluation of these factors is difficult because of the lack of specific comparative data regarding the factors in drivers in crashes, relative to drivers exposed to similar driving conditions.

Aquatic Injuries and Alcohol

Each year, more than 60 million Americans board 13 million boats eager to do everything from fishing and sailing to hunting and waterskiing. Boating attracts a diverse group of enthusiasts, practically of all ages and cultural backgrounds. Unfortunately, in the minds of many, recreational boating is automatically associated with alcohol. People who would never consider drinking and driving think nothing of stowing alcoholic beverages for an afternoon outing on the water. However, boating presents special circumstances requiring decisions and judgments motorists never face. For instance, such stress factors as the boat's motion and extreme glare from the water can actually intensify the effects of alcohol. Yet, few boaters are aware that drinking or other drug use at the helm of a boat is at least as dangerous as drinking and driving. The hard statistics show that boating fatalities make waterways second only to highways as the scene of accidental deaths in the United States.

In fact, the National Transportation Safety Board has concluded that alcohol is involved in as many as 400 to 800 recreational boating fatalities annually. In addition, the Safety Board has estimated that as many as 35% to 38% of fatal recreational boating accidents may involve persons "legally drunk" at the widely accepted blood alcohol concentration (BAC) of 0.10%. Information provided by the Centers for Dis-

ease Control, the National Council on Alcoholism, and several state agencies suggests that as many as 70% of all recreational boating fatalities may involve the use of alcohol.[46]

The contrast between male and female drowning rates after age 10 is believed to reflect differences between the sexes in exposure to hazardous activities including cultural expectations, alcohol and drug use, and biological make-up. Approximately 90% of recreational boating deaths result from drownings. In 1980, approximately 1,200 drownings involved recreational boats, and alcohol use was a prominent factor in many of the teen and young adult drownings. Drowning accidents while fishing are not uncommon and frequently involve the combination of alcohol imbibing and an open motor-boat. The story of the fisherman who has been drinking beer, stands up in the boat to urinate overboard, falls out of the boat, and drowns is well known among coroners.

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It is estimated that there are 700 to 800 diving injuries per year. Most of the victims are adolescent or young adult males. In 40% to 50% of cases, consumption of alcoholic beverages, primarily beer, has been involved.[47] The diver is required to make a series of decisions before and during a dive. These include the individual's appraisal of the elements of the environment and a conscious evaluation of the specific behavior that is being planned. It is clear that the ability to process this information is degraded by even small amounts of alcohol. Additionally, any sensory inputs that would require divided attention would be expected to further interfere with the execution of the intended dive. Interference with judgment involved in the diving process has been measured at blood alcohol levels of 0.015% (15 mg% = less than one beer). Also, 0.1 g/dL is the legal limit for presumptive intoxication in most states.[48]

Burn Injuries

Fires are the third leading cause of unintentional injury/death in the United States. Each year, residential fires are responsible for about 5,000 deaths, 19,000 injuries, and $3.4 billion in property damage. Predisposition to burn injury includes such factors as alcoholism, drugs, senility, neuropathies, psychiatric disorders, suicide attempts, and prior immobilizing physical injury.[49]

The presence of an alcohol-impaired person was the strongest independent risk factor for death due to fire, odds ratio, 7.5; (95% confidence interval, 4.4 to 12.7).

Thirty-two studies published between 1947 and 1986 on alcohol and injuries and deaths attributed to fires and burns were analyzed in detail.[50] Eight of the nine best descriptive studies indicated that alcohol exposure was more likely among those who died in fires started by cigarettes than in those attributable to other causes. There is substantial, although not definitive, evidence that alcohol plays a contributing role in the etiology of fires and burn-related injuries and deaths.

Behavioral risk factors also contribute to residential fires. These include the combination of cigarette smoking and alcohol use. Cigarettes were involved in half of the deaths caused by house fires. These fires typically occurred at night when people fell asleep while smoking in bed. Alcohol intoxication could hamper the chances of escape during a fire, and several investigations have indicated that approximately 40% of victims of residential fires who were tested for alcohol were legally intoxicated (blood alcohol concentration of ≥ 0.1 mg/dL).[51]

Alcohol Abuse in Psychiatric Patients

Substance abuse, including alcohol, by psychiatric patients is generally recognized as a frequent and significant problem. Most studies have indicated that the prevalence of substance abuse by mentally ill patients is quite high (60% to 85%), though physical dependence on drugs and alcohol occurs less commonly (15% to 35%). Recent studies have found high preva-

lence rates (up to 48%) for alcohol abuse in groups of patients with mixed diagnoses.

Alcohol and substance abuse complicate the course and outcome of psychiatric illness. Among those who are chronically mentally ill, substance abuse has been associated with exacerbations of illness, with a more severe course of illness, poorer outcome, problems with housing, and disruptive behavior. Undetected alcohol and drug abuse in this population has led to inappropriate diagnoses and treatment, less effective results, and noncompliance with treatment.

Detection of alcohol abuse in acutely ill psychiatric patients is essential, but often difficult because of disturbances in the patients' mental status, or because they are unable or unwilling to cooperate with an interview. Psychiatric patients who abuse alcohol and drugs often cannot be differentiated from nonusers solely on the basis of age, race, and gender. Routine psychological screening of all hospitalized young adult chronic patients for drug and alcohol exposure, as well as interviews with family and friends for obtaining information about substance use, may be helpful. Screening instruments to identify alcohol abuse in the general population have been developed, such as the Michigan Alcoholism Screening Test (MAST), and some have been used successfully in stable psychiatric populations as well. The Self-Administered Alcoholism Screening Test (SAAST) is a 34-item questionnaire with a yes-no format. A score of 10 or greater denotes "probable alcoholism," a score of 8 to 9 indicates "possible alcoholism," and a score of 7 or less denotes no likely problem with alcoholism. The SAAST has been evaluated in general medical patients and found to be a useful adjunct to the physician interview and examination for detecting alcoholism. More recently, the SAAST was found to be helpful for identifying alcohol abuse among stable psychiatric inpatients.[52]

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Is Alcohol Good for Your Health?

In speaking about the role of alcohol in society, Abraham Lincoln observed, "None seemed to think the injury arose from the use of a bad thing but from the abuse of a very good thing." Gaziano et al again raise the question of whether moderate consumption of alcohol (usually defined as up to two standard drinks per day), is a good thing.[53] Previous studies have suggested that moderate alcohol intake exerts a protective effect against coronary heart disease. Increases in HDL cholesterol levels represent one plausible mechanism of this apparent protective effect.

There now seems little doubt that alcohol exerts a protective effect against coronary heart disease. Most large-scale studies have shown that people who consume one or two drinks a day have fewer coronary events than abstainers. The well-known U-shaped curve, in which increasing consumption well beyond two drinks per day is associated with an increasing occurrence of coronary heart disease, derives primarily from studies of mortality incidence. In addition to confirming the inverse association, Gaziano et al[53] have contributed importantly to our understanding of the mechanism by showing a convincing relation between alcohol intake and the level of protective high-density lipoprotein cholesterol (HDL), including both its HDL2 and HDL3 subfractions. The level of each subfraction was inversely related to the risk of a first myocardial infarction, and each explained some of the protective effect of alcohol.

Some (but not all) previous studies suggested that alcohol increased primarily the HDL3 subfraction, whereas protection against coronary disease came primarily from HDL2. Because the evidence of the association is observational rather than experimental, some other factor may still have to be determined. Yet none has become evident in two decades of active investigation. Two established risk factors for coronary disease are known to correlate with alcohol intake. Cigarette smoking is one. It would tend to put drinkers at higher risk and must therefore

be accounted for in order to obtain an accurate view of the effects of alcohol. Second, an alcohol intake of three or more drinks per day can raise blood pressure, thus putting heavier drinkers at greater risk.

In deciding whether moderate alcohol consumption is food for one's health, the prevention of gallstones may be another benefit to consider. However, evidence is accumulating that a moderate intake of alcohol increases the risk of cancer of the breast and large bowel.[54,55] Though a causal relation has not yet been established,[56] these are two of the most common cancers, and it is prudent to consider them in assessing the potential effects of alcohol on health.

In summary, the daily consumption of relatively large amounts of alcohol (three or more drinks per day) is undesirable from the standpoint of health for almost all people. Consumption of 1 to 2 drinks per day, however, can be desirable depending on individual characteristics. Health care workers have not yet started to advise people to drink daily; however, for those who chose, moderation to two drinks per day may have a protective effect.

Pharmacists are advised to caution patients who consume ethanol chronically and in excess about this acetaminophen interaction.

PHARMACEUTICAL CARE CONCERNS

Drug Interactions

How does the pharmacist respond to the patient who asks, "Is it okay to drink with this prescription? I'm going to a wedding." When should the pharmacist affix an auxiliary label? What should the auxiliary label say? A review of general Physicians Desk Reference entries cautions about the concomitant consumption of alcohol and central nervous system depressants. Common drug interaction references, such as Drug Interaction Facts,[57] list no less than 68 *significant* interactions, and a few suspicious interactions in the index. Mechanisms such as the additive CNS depression with barbiturates, phenothiazines, and benzodiazepines, are clear. Less well-known, but increasing in awareness is the chronic consumption of ethanol elevating the risk of acetaminophen-induced liver damage. Pharmacists are advised to caution patients who consume ethanol chronically and in excess about this acetaminophen interaction and advise them to avoid regular and excessive acetaminophen use or avoid chronic use of ethanol.

Three effects of ethanol have been identified with sulfonylureas: Prolongation but not augmentation of glipizide-induced reductions in blood glucose[58]; chronic use of ethanol may decrease the half-life of tolbutamide[59]; and ethanol ingestion by patients taking chlorpropamide may result in a disulfiram-like reaction.[60] Another disulfiram-like reaction,[61] manifested by flushing, tachycardia, bronchospasm, sweating, nausea, and vomiting, is reported as occurring when ethanol is ingested after a patient has taken a cephalosporin with the methy-tetrazolethiol moiety (eg, cefamandole, cefoperazone, ceforanide, cefonicic, cefotetan, moxalactam).[62] Other cephalosporins (eg, Cephalothin, cephadrine, cefoxitin, cefazolin, cefotaxime, and ceftizoxime) do not illustrate this reaction; they also do not possess the characteristic moiety.[63]

The disulfiram-like reaction is associated with metronidazole.[64] Ethanol potentiates aspirin-induced GI blood loss and hemorrhagic episodes. The latter may occur up to 36 hours after aspirin administration. Clinically significant bleeding is possible in predisposed patients. Aspirin and alcohol reinforce each others' damaging effects on the gastric mucosa. The production of gastric acid stimulated by ethanol promotes this damage. How ethanol enhances bleeding time prolongation is unknown.

Obviously, any patient who is prescribed disulfiram (Antabuse, Ayerst, Philadelphia, PA) should be advised about the drug-drug interactions, and especially be advised about alcohol in cooking, OTC drugs, and mouthwashes.

Welage, elsewhere in this issue, describes the interaction between alcohol and cimetidine,[65] resulting in increased peak plasma ethanol levels and areas under the curve. It is postulated that cimetidine enhances intestinal absorption and interferes with the microsomal GI transport

time of the oxidizing system's metabolism of ethanol. Reports indicate increased sensitivity to ethanol with concomitant cimetidine administration.[66] Metoclopramide elevates the rate of absorption of ethanol by increasing gastric motility, thereby decreasing the time it takes ethanol to reach the small intestine from where it is rapidly absorbed.[67] (One wonders when criminal defense attorneys will be calling expert witnesses to describe this drug interaction to the court in an attempt to make their clients appear as having been less drunk!)

Intolerance of bromocriptine due to severity of side effects has been reported. Ethanol is believed to enhance the sensitivity of dopamine receptors, thus augmenting the side effects of bromocriptine.[68,69]

Ethanol may increase the solubility of drugs through additive and interactive effects. Alcohol can interfere with and, usually, enhance the effects of other drugs. Pharmacists would be prudent to caution patients not to use alcohol while taking prescription and OTC drug products. Even if there is no interaction, the alcohol is not necessary, and to err on the side of safety, avoidance is the best advice. An auxiliary label stating "Do *Not* Drink Alcohol" is advisable.

THE FRYE CASE

In 1988, after undergoing an arthroscopic procedure by an orthopedic surgeon, Stephen Frye was prescribed Fiorinal (Sandoz, NJ), which he had filled at a local Medicare-Glaser pharmacy by a young woman pharmacist. The pharmacist dispensed the prescription with the correct drug and with the appropriate number of capsules. Further, on the prescription container, the pharmacist affixed two labels: one, a label with a picture of a "drowsy eye" and the words "May cause drowsiness"; and two, a federally required label stating "Caution: Federal law prohibits the transfer of this drug to persons other than the patient to whom it was prescribed." Five days later, the patient was found dead in his home, and his date of death was estimated to be the evening that he filled the prescription. At autopsy, a toxicology report showed aspirin and butalbital.[70-72]

The pharmacist testified that the computer system she used to fill the prescription suggested warning labels that might be placed on the container. In this case, the computer suggested three warning labels: "drowsiness, alcohol, impairing the ability to drive." She testified that the warning pertaining to the use of alcohol and Fiorinal said "something to the effect that alcohol may intensify the effect of this drug." She also stated that a pharmacist filling a prescription has the discretion of whether to place a specific label on a container. Here, she stated that she did not place a label warning about the effects of alcohol when combined with Fiorinal because "It offended so many people that I would think that they might drink." The pharmacist testified that she had been "chewed out" (by patients) in the past for placing such labels on containers.[73]

The family of the decedent (plaintiffs) argued that since the pharmacist undertook a warning, although according to Illinois Case Law no duty existed to warn, that to do so inadequately was negligent. Specifically, plaintiffs alleged that the defendants failed to adequately warn of the dangerous side effects of Fiorinal and to place a warning label showing "drowsy eye" when the proper warning label should have warned that anyone taking (Fiorinal) should avoid the use of alcohol, because alcohol would intensify the effects. Plaintiffs argued that the "drowsy eye" label could mislead someone into thinking that the worst side effect of Fiorinal was drowsiness.

"It offended so many people that I would think that they might drink."

The Illinois Supreme Court disagreed with the plaintiffs, and dismissed the lawsuit against the pharmacy, stating that even though the pharmacist undertook a duty, it was not exercised negligently. Interestingly, two amici curiae (friends of the court) briefs were filed. The Illinois Pharmacists Association and the National Association of Boards of Pharmacy argued that the court should place an affirmative duty on pharmacists to counsel consumers on the dangerous side effects of prescription drugs. These associations contended that the "learned

intermediary doctrine" should not stand in the way of a pharmacist's affirmative duty to warn consumers of a drug's dangerous side effects.

Noting the outcome of the case, many pharmacy jurisprudence experts predict that since Omnibus Budget Information Act (OBRA) requirements for pharmacists counseling Medicare patients, and subsequent expansion of counseling requirements by pharmacy practice acts, had the case occurred after the introduction of OBRA, the pharmacist would have had to counsel and warn to avoid alcohol.

How, in good professional and ethical conscience, can any pharmacist stock and sell any type of alcoholic beverage in a pharmacy?!

Had the pharmacist counseled against alcohol use, the patient arguably would not have died, and certainly the pharmacist would not have been sued even if the patient ignored the warning to avoid alcohol while taking Fiorinal.

The Intoxicated Patient

An interesting report was recently published regarding an intoxicated patient's ability to provide informed consent.[74] A victim of a vehicular accident was admitted to a hospital as a surgical emergency. The admitting emergency room physician acted on the assumption that internal bleeding was occurring. In addition to drawing blood (alcohol content was 233 mg%), X-rays were taken, and a Foley catheter was inserted to test for blood in the urine. In addition, a diagnostic peritoneal lavage was ordered. Overhearing the order for an abdominal incision, the patient objected and tried to get up. He was restrained, anesthetized, and the lavage was performed. The patient left the next day against medical advice.

The patient sued the hospital for battery because of the procedure performed against his will. The trial judge ruled in favor of the plaintiff, assuming that "intoxication did not affect a patient's competence to consent." The Supreme Court of Rhode Island overturned this judgment on appeal, concluding that "a finding of legal competence or unsound mind was not a prerequisite to determine that a patient lacked the ability to make decisions regarding treatment." Whether an intoxicated patient is competent to make an informed consent before undergoing a surgical procedure is a question of fact for juries to decide and may not correspond to the legal definition of intoxication.

WHAT'S A PHARMACIST TO DO?

Considering what pharmacists know about the devastating effects of alcohol, I ask how, in good professional and ethical conscience, can any pharmacist stock and sell any type of alcoholic beverage in a pharmacy?!

The same argument has been made about tobacco products. We need to see the same anti-alcohol sale admonitions that we have seen for tobacco products.

Addendum: As this manuscript was being prepared for mailing to the publisher, I was consulting on a benzodiazepine addiction case with an attorney. Discussions about addictions led to his description of his own battle with alcohol, and how addicting and devastating alcohol had been in his own life, and how he was now in his 18th year of sobriety. He reached into his wallet and unpeeled the following prose which he carried with him for unknown years, and he claimed ignorance as to the source:

> Dear One:
>
> I am more powerful than the combined armies of the world;
> I have destroyed more men than all the wars of the nation;
> I have caused millions of accidents and wrecked more homes than all the floods, tornadoes and hurricanes put together;
> I am the world's slickest thief. I steal billions of dollars each year;
> I find my victims among the rich and poor alike, the young and the old, the strong and the weak;
> I loom up to such proportions that I cast a shadow over every field of labor;
> I am relentless, insidious, unpredictable;
> I am everywhere—in the home, in the street, in the factory, in the office: on the sea and in the air:
> I bring sickness: poverty and death:
> I give nothing and take all:
> I am your worst enemy:
> I am alcohol.

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