AIM Alcohol in Moderation

For more information please email Helena.Conibear@aim-digest.com or Alison.Rees@aim-digest.com

Alcohol - boon or bane for the elderly? Part II

by Erik Skovenborg of the Scandinavian Medical Alcohol Board

The net protective or adverse association between alcohol and mortality from all causes in a particular population is a balance of increased risk of death from alcohol-related causes (such as cirrhosis, cancers of certain sites, accidents) and decreased risk of others (mainly coronary heart disease). Cohort studies using all-cause mortality as an outcome strike this balance implicitly, and these studies can be used to provide estimates of the net effect of alcohol on mortality in a population. However, no guidelines on safe drinking limits should be based on results of mortality studies alone. Prevention of alcohol problems must be based on the full spectrum of epidemiological and clinical research, including results on mortality, morbidity, social consequences and quality of life in general.

Medical conditions for which alcohol is contraindicated

The list of contraindications from the National Institute of Alcohol Abuse and Alcoholism includes hypertension, cardiac arrhythmias, ulcers, a history of alcohol abuse or dependence, liver disease, and cognitive impairment (1). The prevalence of at-risk drinking in the United States between 1971 and 1974 in older adults (data from NHANES I and NHANES Epidemiologic Follow-up survey 1992) was 10% (18% of men, 5% of women). The majority of at-risk drinkers (69%) were identified as such because their use of alcohol in amounts deemed risky in the presence of relevant comorbidities (e.g. drinking 2-3 drinks per day and having gout or anxiety or taking medication for pain). At-risk drinking men had a 20% higher mortality than not-at-risk drinking men. Men and women abstainers had a 8% higher mortality rate than not-at-risk drinkers, whereas at-risk-drinking women had no greater mortality than not-at-risk-drinking women (2). In 1999, 82% of Medicare beneficiaries aged 65 years and older had one or more chronic medical conditions, and 65% had multible chronic conditions (3). To support recommendations for abstinence in special medical conditions, an understanding of how health status of low-to-moderate drinkers compares with non-drinkers in each separate case is needed so patients can understand the potential benefits of altering their drinking behaviour.

Hypertension

Hypertension is associated with a doubled risk for cardiovascular disease and may account for 30% of events associated with cardiovascular disease (4). The risk relationship between alcohol consumption and hypertension may best be described as a “threshold effect”: little increase in risk is found up to about 20-30 ml of alcohol per day, beyond which blood pressure increases markedly. At a drinking level ≥ 3 drinks/day net harm is usually seen in epidemiological studies. Because heavier drinkers frequently lie about the amount of their alcohol intake (self-reported alcohol intake in surveys (5) usually covers only half the amount sold), survey-based data lower the apparent threshold for harmful effects.

A biological mechanism for this link remains unclear, however, assuming a causal link heavy drinking may be the commonest reversible cause of hypertension (6).

An Italian study of 13 middle-aged, hypertensive, centrally obese individuals (8 women, 5 men) received, in an open randomized crossover experiment, 250 ml red wine (23 g of ethanol) and a placebo equivalent, together

with a standardized lunch. Wine with the meal produced a mean reduction of 5.3 mmHg in postprandial blood pressure which persisted for most of the day (7). Moderate drinking does not appear to pose a cardiovascular risk in men with hypertension, according to an observational study of 11,711 hypertensive men (40 to 75 years of age at baseline) who self-reported alcohol consumption every four years for 16 years. After adjustment for diet and other potential confounders, subjects consuming about 1 to 4 drinks per day (10-49 g alcohol/day) had an 32% lower risk for myocardial infarction than did abstainers, while heavier drinkers (> 49 g alcohol/day) had still lower risk. Alcohol consumption did not affect subjects' risk for stroke, cardiovascular-related mortality, or all-cause mortality (8). Results from the Physicians' Health Study even suggest that light to moderate alcohol consumption is associated with a reduction in risk of total and cardiovascular mortality in hypertensive men; the reduction in risk was of similar magnitude for men younger than 60 years and for men 60 years and older (9).

Cardiac arrhytmias

The development of cardiac arrhythmias, particularly atrial fibrillation, after bouts of heavy alcohol consumption, often at weekends or holidays, was first described by Ettinger, who coined the memorable term "Holiday Heart" (10). Cardiac arrhytmias presenting during weekend or holiday drinking episodes were associated with conduction delays and depressed cardiac performance in a group of patients, who all gave stories of consuming at least 6-10 drinks daily at least ten years.

Atrial Fibrillation: The prevalence of Atrial Fibrillation (AF) goes from 1.1 per 1000 patients at age 40 to 105 at age 90. Evidence for an association between alcohol consumption and risk of AF is conflicting. Cohort studies such as the Framingham Heart Study did not find any association between alcohol consumption and risk of AF (11). A nested case-control study in the UK General Practice Research Database reported an adjusted relative risk of 2.4 among subjects that consumed more than 42 units (>420 g) of alcohol per week (12). However, the prospective Cardiovascular Health Study reported that alcohol consumption reduced the risk of AF in older adults, in which the levels of alcohol use were low and in which binge drinking was uncommon (13). A similar association was found in men but not women in a cohort of people aged over 60 years in Busselton (14).

The discussion on alcohol as a risk factor for AF remains open, however, the conflicting results may be due to differences in the average alcohol consumption and the number of heavy drinkers in the cohort. In the Cardiovascular Health Study the average intake of alcohol was 2-3 drinks per week, while in the Danish Diet, Cancer, and Health Study the mean consumption of alcohol per day was 28.2 g in men and 13.9 g in women. When using the lowest quintile of alcohol consumption in men (4.1 g alcohol/d) as a reference, the adjusted hazard rate ratio of AF in men in the top quintile (68.7 g/d) was 1.46. In women moderate alcohol consumption did not seem to be associated with risk of AF (15). Neither the frequency of alcohol intake nor the preferred type of alcohol (beer, wine, or mixed) changed the risk estimates reported in the Danish Diet, Cancer, and Health Study.

Ventricular arrhythmias: Binge drinking has been shown to increase ventricular ectopic activity and to promote the onset of ventricular tachyarrhythmias (16). These are potentially life threatening and could be responsible for the finding that binge drinking accounts for a proportion of patients with sudden unexpected death. In a cohort study of survivors of acute myocardial infarction, who have a 4- to 6-fold increased baseline risk of sudden cardiac death, binge drinkers had a 2-fold higher risk of mortality than drinkers who did not binge (17). When compared with abstainers rather than other drinkers, binge drinking (3 drinks = 40-45 g of ethanol in 1-2 hours) was associated with an hazard ratio of 1.4 (CI 0.9-2.2.). Alcohol intake was inversely associated with mortality among patients who did not report binge drinking with hazard ratios of 0.75 (CI 0.57-1.00) among light drinkers and of 0.59 (CI 0.33-1.04) among heavier drinkers. In Finland the traditional way of drinking infrequently but heavily has remained quite common. In the Kuopio Ischaemic Heart Disease Risk Factor Study the risk of fatal myocardial infarction was substantially increased (relative risk 6.50 (CI 2.05-20.61)) in men whose usual dose of beer was 6 or more bottles per session compared with men who usually consumed less than 3 bottles after

adjustment for age and total alcohol consumption (18).

Heart Failure

Heart Failure (HF) is one of the leading causes of hospitalization of the elderly. In the New Haven EPESE cohort study of 2235 elderly persons (mean age 73.7 years) consumption of about 1.5 to 4 drinks per day was associated with a significantly reduced risk of HF: relative risk 0.53 (CI 0.32-0.88) compared with nondrinkers (19). However, long-term heavy alcohol consumption has been associated with worsening cardiac function, and chronic alcoholism is one of the most important causes of dilated cardiomyopathy (20). Therefore, it is not surprising that current HF guidelines note alcohol use in HF patients should be discouraged (21). However, among patients with ischemic left ventricular systolic dysfunction light-to-moderate alcohol intake (1-14 drinks per week) was associated with a reduced risk of all-cause mortality: relative risk 0.78 (CI 0.69-0.89) and trends toward reductions in the risk of arrhythmic death (22). In a group of 420 HF outpatients no adverse relationship between moderate alcohol consumption (2 or fewer drinks per day) and mortality, hospitalization, or health status (1-year outcomes) were identified (23). These data do not support the need for complete alcohol abstinence for all HF patients among those who drink in moderation. Patients reporting a lifetime consumption of alcohol greater than 7 kg ethanol/kg bodyweight should be considered to have a high risk of cardiac toxicity on continuation of alcohol consumption and abstinence should be recommended. However, in patients who do not reach the threshold dose of lifetime ethanol consumption, moderate drinking (maximum daily dose of 30 g/day in men and 20 g/day in women) may be considered in a controlled setting (24).

Ulcer

In residents of Olmsted County aged 20 to 64 years, alcohol intake was not associated with dyspepsia (25). However, in the presence of acute inflammation, irritation or ulceration in the mouth, throat, esophagus or stomach, strong alcoholic beverages should usually not be used, because the local irritation produced by these beverages will probably cause undue pain and discomfort (26). Alcoholic drinks are also contraindicated in conditions marked by suspected gastric hemorrhage. Compared with drinkers of <1 drink/week, the relative risks of upper gastrointestinal bleeding among current drinkers ranged from 0.8 for 1-6 drinks/week to 6.3 for ≥ 35 drinks/week (27). The risk of major upper gastrointestinal bleeding is highest among persons who are both heavy drinkers (≥21 drinks per week) and users of aspirin and other nonsteroidal anti-inflammatory drugs (28).

In the case of healing gastric or duodenal ulcer no rigid rule can be set. Since alcohol stimulates gastric acid secretion, a relation to peptic ulcer disease has long been suspected (29). Beer, wine and sherry significantly increase gastric acid output (by 57% to 95% of maximal acid output) and release of gastrin up to 5-fold compared with control (30). However, several large cohort studies did not provide any evidence for a relation between alcohol consumption and peptic ulcer disease (31). A recent Danish prospective cohort study assessing the impact of multiple risk factors, including Helicobacter pylori infection, on the incidence of peptic ulcer disease found a U-shaped relation between alcohol consumption and peptic ulcer disease. The nadir of the distribution was 6-12 drinks weekly due to a low number of ulcers among people who drank moderate amounts of wine. Intake of beer and spirits did not affect the overall ulcer incidence proportion (32). The in vitro bactericidal activity of red wine against Helicobacter pylori is very high (33). In a German population sample the inverse graded relation between alcohol consumption and active infection with Helicobacter pylori was particularly strong for alcohol consumed in the form of wine (34).

Bland diets with no alcoholic beverages have been prescribed for generations in patients with peptic ulcer disease. The diets didn't work, and that is no wonder; a recent meta-analysis suggested that 95% of all hospitalised ulcer cases in the USA were attributable to Helicobacter pylori infection, use of nonsteroidal anti-inflammatory drugs and tobacco smoking (35). Eradication of Helicobacter pylori provides potential cure in the majority of patients

with peptic ulcer disease, and omeprazole triple therapies given twice daily for one week produce high eradication rates, are well-tolerated, and are associated with high patient compliance (36).

Heartburn

Bland diets with no wine or beer is now history for ulcer-patients, however, patients with gastro-esophageal reflux disease (GERD) complaining to their doctor of heartburn are still met with a list of changes to make in their life-style: avoid alcohol, carbonated beverages, citrus fruit and juices, quit smoking, no coffee, do not eat spicy or fatty foods, be careful with chocolate and don't snack before bed. Although there are physiologic evidence that exposure to tobacco, alcohol, chocolate, and high-fat meals decreases lower esophageal sphincter pressure, no published evidence of the efficacy of dietary measures exists! Neither tobacco nor alcohol cessation was associated with improvement in symptoms (37). In fact, only weight loss in obese patients and head of bed elevation were effective lifestyle interventions for GERD. Gastro-esophageal reflux disease is a chronic disease that affects health-related quality of life of patients. Potent suppression of gastric acid secretion with proton pump inhibitors is a highly effective and safe treatment of heartburn and other troublesome GERD symptoms. And it is OK to swallow your pill with a glass of beer.

A **history of alcohol abuse or dependence**

Almost 9 percent (17.6 million adult Americans) have an alcohol use disorder. Alcoholism is best understood as a chronic disease with a peak onset by age 18 and with rapidly declining onsets after age 25 (38). Several lines of evidence suggest a substantial genetic component to the risk of alcoholism: siblings of alcoholic patients have a 3- to 8-fold increased risk of also developing alcoholism, and twin heritability estimates of 50-60% are reported by studies of twins (39). Alcohol dependence is a leading cause of morbidity and premature death, accordingly the best advice for patients with a history of alcohol abuse or dependence is total abstinence.

Alcoholism and mood and anxiety disorders have strong associations when considered on a lifetime basis. The National Epidemiological Survey on Alcohol and Related Conditions (NESARC) covers the comorbidity of DSM-IV substance use disorders and nine independent mood and anxiety disorders in a nationally representative U.S. sample of 43,093 respondents. The prevalence of any current mood disorder was 9.21 percent, representing 19.2 million adult Americans 20 percent of which had a comorbid substance disorder that was more likely to be alcohol. The prevalence of any current anxiety disorder was 11.08 percent, representing 23 million adult Americans 15 percent of which had a co-morbid substance use disorder (40). Individuals with co-occurring mental health and substance use disorders (CMSD) have worse clinical courses and outcomes and are at increased risk of suicide and social and occupational impairment and disability. For these patients total abstinence is mandatory.

Liver disease

The adverse effects of heavy drinking on the liver (hepatotoxicity and impairment of hepatic regeneration) is associated with the development of liver cirrhosis, a severe disease often leading to death. Some patients develop cirrhosis soon after having undertaken heavy abuse, whereas others remain unaffected for years; the average time is between 10 and 20 years. The Copenhagen City Heart Study (one drink = 12 g alcohol) observed a steep dose dependent increase in the relative risk of alcohol induced liver disease above a "threshold" of 7-13 drinks/week in women and 14-27 drinks/week in men. Women had a significantly higher relative risk of developing alcohol-related liver disease than men at any given level of alcohol intake; at an alcohol intake of 28-41 drinks/week, the relative risk for developing alcohol-induced cirrhosis in was 7.0 (CI 3.8-12.8) for men and 17.0 (CI 6,8-40.8) for women. Of those individuals consuming ≥ 70 drinks/week, only 7% were cirrhotic and only 19% had any evidence of alcohol induced liver disease at all. The study found a rate of development of alcohol induced liver

cirrhosis of 1.1% in 60- to 69-year old men with an alcohol intake ≥ 70 drinks/week (41).

The Dionysos Study found that 30 g alcohol/day is the minimal quantity of alcohol compatible with a measurable risk of developing cirrhosis. Only 4% of individuals consuming more than 6 drinks daily had cirrhosis and only 10% had any evidence of liver disease at all. Drinking alcohol outside mealtimes increased the risk of developing alcohol induced liver damage (42). Results from a Danish cohort study of 6152 alcohol misusing men and women aged 15-83 indicate that alcohol has a threshold effect rather than a dose-response effect on mortality from alcoholic cirrhosis. There was no additional risk of death from alcoholic cirrhosis when exceeding an average daily number of five drinks (>60 g alcohol) in neither men nor women. Men who drank periodically were found to have a significantly lower relative risk of 0.56 (CI 0.37-0.85) compared to the reference group of men who drank daily (43).

The role of nutrition: Most people who abuse alcohol will develop hepatic steatosis but only a few alcoholics develop more serious forms of liver disease: hepatitis, fibrosis and cirrhosis. The factors underlying between-individual variation in susceptibility to alcohol induced liver damage are likely to include both environmental and genetic influences (44). Nutrition may have a role in modifying the effect of alcohol intake on the risk of liver cirrhosis. Results from a large US population-based study show that persons who drank more than 2 cups of coffee or tea per day had less than half the risk of chronic liver disease of those consuming less than 1 cup per day (45). It is also possible that a "gin-drinker's liver" depends not so much on gin before dinner as on gin instead of dinner, however, the specific contribution of malnutrition to the development of alcoholic liver disease remains highly controversial. Most evidence suggests that high fat, low carbohydrate diets increase the risk of disease (46). Dietary excess leading to obesity also increases risk (47). There may be a range of alcohol intake that is tolerated without liver damage under optimum dietary conditions. However, it is also likely that there is a threshold of alcohol toxicity beyond which no protection is afforded by dietary manipulation. An intake of 160 g of alcohol daily for five years is probably the minimum associated with significant liver damage (48). The message seems to be: drink within sensible limits, consume your favourite tipple with healthy meals, and don't forget to have a nice cup of tea or coffee.

The role of heredity: Evidence supporting a genetic component to predisposition comes mainly from a large study of 15924 male twin pairs. The concordance rate for alcoholic cirrhosis was 14.6% in monozygotic twins and 5.4% in dizygotic twins. The difference in concordance rates could not be accounted for by different concordance rates for alcoholism alone (49). It seems likely that at least some of the pathological effects of alcohol are related to its tissue concentration of its metabolites, in particular acetaldehyde. Aldehyde dehydrogenase (ALDH) is the only enzyme that catalyses the oxidation of acetaldehyde to acetate. A polymorphic variant of human liver mitochondrial Aldehyde dehydrogenase (ALDH2), which have little or no acetaldehyde oxidizing activity, has been identified. Individuals with low ALDH2 activity might form more protein-acetaldehyde adducts that may increase the risk of alcohol induced liver disease. However, a recent meta-analysis of polymorphism studies found no associations between ALDH2 polymorphisms and liver disease (50).

The role of fatty liver: In a long-term follow-up of 88 patients with pure alcoholic fatty liver the risk of developing fibrosis or cirrhosis was associated with the continuing alcohol consumption and with histological features of the index biopsy. Eight of nine patients who had developed cirrhosis at follow-up had continuing alcohol consumption of more than 40 units (1 unit = 10 g alcohol) per week. Independent histological predictors of progression were: presence of mixed macro/microvesicular fat, and presence of giant mitochondria (51). Alcoholic fatty liver can no longer be regarded as benign. In the presence of continuing high alcohol consumption the above histological features identified those at high risk of disease progression. These patients should be counselled intensively regarding their alcohol consumption.

The role of Hepatitis C virus infection: Hepatitis C virus infection affects 1-3% of the population in industrialized countries. In a study on the natural history of chronic hepatitis C infection, the progression to fibrosis and cirrhosis in hepatitis C virus-infected patients was increased by alcohol intake > 50 g (52). In a study of 142 patients from Paris infected with hepatitis C virus the progression rate of liver fibrosis was about twice as high

among drinkers (men >30 g alcohol/day; women >20 g/day) with steatosis than among drinkers without steatosis or nondrinkers with or without steatosis (53). A French prospective study showed a dose dependent increase in fibrosis for an intake of 31-50 g/day in men and 21-50 g/day in women (54).

In patients infected with hepatitis C virus 20-30% will progress to cirrhosis in over two to three decades. The reports are highly supportive for a synergy between heavy alcohol use and hepatitis C virus in causing a liver injury. In 1997, a recommendation was made by the NIH consensus conference, specifying less than 10 g alcohol daily for hepatitis C virus infected patients (55). A recent study of 78 patients with hepatitis C virus infection from Sweden showed an increased fibrosis progression in a group of patients with a very moderate alcohol intake (5.7 g/day (2.0-16.0) and 34.5 drinking days per year) versus a group of patients with a very light alcohol intake (2.6 g/day (1.1-7.7) and 8.2 drinking days per year) (56). With the present limited information a prudent advise for patients with chronic hepatitis C would be complete abstinence or at least not more than the occasional drink.

Cognitive impairment

In most situations the cognitive potential for performing many tasks generally exceeds what is required, but the gap between level of performance and potential may diminish as people get older. A dose of alcohol may be considered to impose a kind of stress test of task performance and, if older persons are performing closer to their maximum potential, they may be less able to compensate for the alcohol-induced disturbances of their behaviour. If this is the case, then the amount of behavioural impairment induced at a given blood alcohol concentration (BAC) should be greater for older persons. A group of 14 younger pilots (mean age = 27, range 21-34) and older pilots (mean age = 60, range 51-69) flew a Frasca 141 simulator in a flight task that they had previously learned but not practiced for several months. After completing a baseline flight, pilots were tested during either an alcohol (BAC = 0.1%) or a placebo condition. Detrimental effects of alcohol on the main outcome measure was found at both the acute and the 8-hour post-drink (hangover) testing, however, there was no significant difference between the older and the younger pilots' performance of the flight task or in susceptibility to alcohol either while intoxicated or during hangover (57).

In a study of 57 subjects – 28 in the young (21-40 years) and 29 in the old (> 60 years) group – with a low dose of alcohol (0.3 g alcohol/kg given IV after a standard breakfast) age rather than alcohol accounted for most of the differences in the kind of neural functions that come into play in activities such as walking, driving and writing (58). Tupler et al examined the effects of aging on alcohol pharmacodynamics over progressive dosing schedules (0.4, 0.6, 0.8, 1.0 g/kg) in groups of young (25.0 ± 2.9 years), middle-aged (41.1 ± 6.6 years), and young-elderly adults (60.9 ± 2.6 years) using three computerized cognitive-neuromotor tasks. Results reflected differences in the patterns but not the magnitude of impairment for elderly subjects. Results failed to confirm that impairment would be either more severe, or more sustained, as a function of aging (59). The modest effects of aging in responses to alcohol should be viewed in the light of as much as 3- to 4-fold differences in the metabolism of alcohol and 2- to 3-fold differences in behavioural responses to alcohol between different individuals (60). Older drivers (>55 years) have consistently the lowest rate of alcohol-impaired driving of any age group (61).

Alcoholic beverage consumption may exacerbate cognitive impairment and dementias due to other causes. In a retrospective medical record review on 383 geriatric patients 35% of cognitively impaired patients were consuming alcohol at the time of evaluation. Recognition of heavy alcohol consumption in cognitively impaired patients is important, as chronic alcohol toxicity represents one cause of potentially reversible dementia (62). In a study of occurrence and risk factors of delirium in the Sub-Intensive Care Unit for the elderly, heavy alcohol use was independently associated with delirium (63).

Alcohol and dementia

Few things are as valuable as the unimpaired ability to reason, and loss of cognitive function in old age is a serious health problem. Dementia frequency increases with age and varies from 1% in people aged 65 years to

more than 28% in people aged more than 90 years (64). Heavy alcohol use have a significant and negative effect on everyday cognitive performance, and the presence of cognitive and neuropsychological deficits have been observed in heavy drinkers (65). Long-term abuse of alcohol is associated with alcohol dementia (Wernicke-Korsakoff's Syndrome).

However, a reduced risk of cognitive impairment and dementia associated with light to moderate alcohol consumption (1-28 drinks per week) has been shown in many cohort studies with different characteristics. Inverse association between moderate alcohol consumption and cognitive decline has been observed among older black Americans (66), men with diabetes or cardiovascular disease in the Zutphen Elderly Study (67), older people from the Bordeaux area (68), Framingham residents aged 55-89 years (69), elderly Japanese American men (70), participants if the Treatment Trial of Hypertension in Older Adults (71), elderly French non-ApoE _4 carriers (72), residents of Rotterdam aged 55 and older (73), participants aged 65 years and older of the Canadian Study of Health and Aging (74), very old Swedes from Stockholm (75), Baltimore residents in the Epidemiologic Catchment Area Study (76), Copenhagen men and women aged 65 years or more (77), subjects aged 45-70 years from the Netherlands (78), elderly American men and women (79), men and women from Finland aged 65-79 years (80), elderly persons from New York City without the ApoE _-4 allele (81), middle-aged Whitehall civil servants (82), postmenopausal women in the Women´s Health Initiative Memory Study (83), men and women from the British 1946 birth cohort (84), a representative elderly community sample from Pennsylvania (85), retired American nurses (86), men and women aged 60 years and older living in Dubbo, Australia (87), and a sample of oldest-old American women (88), However, in a cohort study of Finnish twins occasional excessive alcohol consumption in light-to-moderate drinkers (binge drinking at least monthly or passing out as a result of excessive alcohol use at least twice during the previous year) was associated with an increased risk of dementia (89).

Gout

The intake of alcoholic beverages may increase the level of serum uric acid. The increase in serum uric acid per serving per day was for: beer: 0,46 mg/dl; liquor: 0.29 mg/dl; and wine: 0.04 mg/dl. The study was performed in moderately drinking men and women; the possibility that wine drinking may have an effect on uric acid level at a higher consumption cannot be ruled out (90). Compared with men who did not drink alcohol the risk of gout was trebled in men drinking more than 5 beers per day. The increase in risk per drink per day was 17%. The increase in risk of gout varied among the individual alcoholic beverages: Beer: increase in risk per serving per day: 49%; Spirits: increase in risk per serving per day: 15%; and Wine: no increase in risk with increasing levels of wine consumption. Beer is the only alcoholic beverage acknowledged to have a large purine content, however, male "wine drinkers" may be different from "beer drinker" in other ways (91).

Adverse alcohol-medication interactions

Many prescription and over-the-counter medications can interact with alcohol, leading to increased risk of illness, injury, or death. Some of the most significant alcohol-drug interactions are reviewed in this passage.

How common are alcohol-drug interactions?

Prescription medications are used by 60-78% of older adults (92). Among the elderly receiving prescriptions, the mean number of drugs prescribed is two to three per patient. The image of the elderly as being surrounded by dozens of medicine bottles is not generally applicable. Nevertheless, a small minority of the elderly are prescribed and obtain a large number of drugs (more than five concurrently), and these deserve special consideration. Presence of chronic disease not only increases the number of prescription drugs, but also increases risk and

severity of potential drug-alcohol interactions (93).

Studies have demonstrated that concurrent alcohol and prescription medication use is common in older populations. Older drinkers who take one or more drugs, which place them at potential risk for negative drug-alcohol interaction, represent one-quarter of a random sample of elderly community dwellers (94). Thirty-eight percent of a sample of residents (mean age 83 ± 6 years) of retirement communities in Milwaukee reported using both alcohol and a high risk medication (95). High risk drugs commonly used by Milwaukee drinkers were: antihypertensives in 50%, aspirin in 27%, nonsteroidal anti-inflammatory drugs (NSAIDs) in 20%, medication for congestive heart failure in 18%, H2 blockers in 16%, sedatives in 5%, and warfarin in 5%. However, the review below found no evidence for high risk status for antihypertensives, congestive heart failure medication, H2 blockers, statins, and warfarin; drugs that account for 89 percent of the alleged 141 percent potential adverse drug-alcohol interactions!

How alcohol and drugs interact

To exert its desired effect, a drug generally must travel through the bloodstream to its site of action, where it produces some change in an organ or tissue. The drug's effect then diminish as it is metabolized by enzymes and eliminated from the body. The extent to which a dose of a drug reaches its site of action is termed availability. Alcohol can influence the effectiveness of a drug by altering its availability. First, an acute dose of alcohol (single drink) may inhibit a drug's metabolism by competing with the drug for a similar family of drug metabolizing enzymes. This interaction prolongs and enhances the drug's availability, potentially increasing the risk of adverse side effects. Second, in contrast, long-term ingestion of alcohol may activate hepatic drug-metabolizing enzymes, thus decreasing the drug's availability leading to diminished drug efficacy. Third, enzymes activated by long-term alcohol consumption may transform some drugs into toxic chemicals that can damage the liver or other organs. Fourth, alcohol can magnify the inhibitory effects of sedative and narcotic drugs at their site of action in the brain. And finally, some drugs affect the metabolism of alcohol, thus altering its availability and its potential for intoxication and adverse effects (96). However, even if the number of theoretically possible adverse alcohol-drug interactions is high, most of the interactions discussed here were first discovered in heavy drinkers or alcoholics. Researchers have not yet demonstrated the occurrence and relevance of those effects in moderate drinkers; surprisingly, robust data on the actual risk of adverse drug events associated with moderate drinking are extremely limited.

Antibiotics (drugs used to treat infections): In combination with acute alcohol consumption some antibiotics may cause disulfiram-like reactions (i.e. flushing, nausea, vomiting, sweating and headache): cephalosporins, chloramphenicol, furazolidone, griseofulvin, metronidazole, nitrofurantoine, quinacrine. Isoniazid and rifampicin are used to treat tuberculosis; acute alcohol intake decreases the availability of isoniazid; long-term alcohol use decreases the availability of rifampicin (97).

Anticoagulants (warfarin prescribed to retard the blood's ability to clot): According to an NIAAA review patients taking warfarin should avoid alcohol entirely (97). However, in a clinical experiment with seven normal subjects, daily ingestion of 296 ml/day of fortified wine during fasting had no effect on therapeutic levels of hypoprothrombinemia with warfarin (98). And most important, moderate drinking did not adversely influence the safety of low-dose warfarin in a randomized trial of men enrolled in the CABG Trial (99).

Antidepressants: Alcohol increases the sedative effect of tricyclic antidepressants impairing driving ability (100). Use of depressant medications is not related to higher use of alcohol but related to consuming alcohol for personal effects reason and having concerns about one's own drinking suggesting that those who both use alcohol and depressant medications are more likely to be more at risk for alcohol problems (101). In patients taking tricyclic antidepressants, alcohol consumption increases the risk of orthostatic hypertension, a sudden drop in blood pressure when a person stands up, especially among the elderly. SSRI's (e.g. fluoxetine, paroxetine, sertraline) have

the best safety profile of all antidepressants, even when combined in large quantities with alcohol. MAO inhibitors (e.g. phenelzine) can induce severe high blood pressure if consumed together with tyramine, a substance present in red wine, chocolate and cheese (97).

Antidiabetic medications: Alcohol may interact with antidiabetic medications like chlorpropamide, glyburide, and tolbutamide to produce disulfiram-like reactions (i.e. flushing, nausea, vomiting, sweating and headache) in 10-20% of patients receiving these drugs (97).

Antihistamines: Alcohol may intensify the sedation caused by some antihistamines and may cause drowsiness, decreased motor skills and impaired driving ability (100). The newer antihistamines (cetirizine, desloratadine, mizolastine, fexofenadine) have less interaction with alcohol and may not impair driving task performance (102).

Antihypertensives: In a population of men with hypertension, moderate intake of alcohol was associated with a decreased risk for myocardial infarction but not with risks for total death or death due to cardiovascular disease. Inclusion of the number of antihypertensive medications, that men reported taking, in the analyses did not alter the observed associations with alcohol, nor did adjustment for use of individual antihypertensive drug classes (103).

Antipsychotic medications: Alcohol increases the sedative effect of drugs like chlorpromazine resulting in impaired motor skills and coordination (104).

Antiseizure medication: Acute alcohol intake increases the availability and possible toxicity of phenytoin, while long-term intake may decrease availability, reducing the protection against epileptic seizures (105).

Antiulcer medication: H2-receptor antagonists like cimetidine and ranitidine may increase the availability of alcohol and produce increases in blood alcohol concentration (BAC), however, the interaction between H2 antagonists and alcohol is clinically insignificant (106).

Immune modulators: Medications like methotrexate that affect immune cell function are associated with risk of liver damage. This risk is increased with alcohol consumption. In case of rheumatoid arthritis a light intake of alcohol well within the recommended limits is allowed. In case of psoriasis it is recommended to avoid alcohol altogether (107).

Narcotic pain relievers: The combined use of opiates and alcohol enhances the effect of these narcotics on the central nervous system producing drowsiness, sedation, decreased motor skills, decreased cough reflex, increased choking risk, and increased risk of death from overdose (97).

Nonsteroidal anti-inflammatory drugs: NSAIDs like ibuprofen and naproxen are non-narcotic pain relievers known to increase the risk of gastrointestinal complications. The presence of either NSAID use or a history of alcohol abuse led to an odds ratio of 2.9 for severe gastrointestinal events, whereas the presence of both risk factors simultaneously led to an odds ratio of 10.2 (108). An increase in risk of gastrointestinal bleeding has been found if NSAID use was concomitant with three or more alcoholic drinks per day (109).

OTC pain medications: Alcohol inhibits thromboxane A2 formation and therefore may have a synergistic effect with aspirin as exemplified by an excessive bleeding time. Alcohol enhances the aspirin-induced prolongation of the bleeding time when given simultaneously or up to 36 hours after aspirin ingestion (110). Older people mixing alcoholic beverages with aspirin to treat pain are in high risk of stomach bleeding (109).

Acetaminophen (paracetamol) is a safe drug when used in therapeutic doses: up to 1 g every 4 hours and not more than 4 g/24 hours. Some 5-8% of a therapeutic dose of paracetamol is converted to a toxic metabolite; the theoretical single hepatotoxic dose in an adult is normally about 15 g. When a single dose of alcohol is given at or about the same time as paracetamol, it protects against liver damage by competing with the drug for the same family (CYP2E1) of drug metabolizing enzymes. Long-term heavy use of alcohol causes a modest (a factor of

two) and short-lived (about 5 days) induction of CYP2E1 enzymes potentially increasing the hepatotoxicity of paracetamol in alcoholics. Fasting may increase the risk of liver damage by decreasing the major detoxification pathway (glucuronide conjugation) of the toxic paracetamol metabolite in the liver. Chronic alcoholics thus may be at increased risk of paracetamol hepatotoxicity during the first few days of alcohol abstinence, especially if the alcoholic stops drinking due to acute illness including gastrointestinal symptoms and fasting. However, the available evidence do not support claims for a major toxic interaction between alcohol and paracetamol and acute liver damage has never been produced by therapeutic doses of paracetamol (111).

Sedatives and hypnotics: Benzodiazepines such as diazepam are generally prescribed to treat anxiety and insomnia. The additive effect of low to moderate doses of benzodiazepines and moderate doses of alcohol may cause drowsiness increasing the risk of accidents and impairing driving ability (100). Older adults who use psychoactive medications like sleeping pills and tranquilizers are more likely to drink to forget and to relieve tension and anxiety (112).

Statins (lipid-lowering drugs): Patients with coronary heart disease who need to be treated with lipid-lowering drugs could benefit from the effect of alcohol on cardiovascular risk (113). A moderate consumption of alcohol, in combination with simvastatin, has been shown to increase the beneficial effect upon HDL cholesterol (114). Alcohol ingestion of 20 g per day for 6 weeks together with fluvastatin 40 mg per day had no effect on the efficacy and safety of fluvastatin treatment in patients with primary hypercholesterolemia (115). An important issue is the safety of the combination of life-long statin treatment and alcohol consumption. These drugs have the potential to affect liver function, however, co-administration of simvastatin and alcohol in Wistar rats has been proved to be safe (116). And more important, moderate drinking did not adversely influence the safety of even high-dose lovastatin among men in the CABG Trial (99).

“Alcohol - boon or bane for the elderly? Part III” examines the problems of late onset alcoholism, alcohol intake as a risk factor for fall injury and fracture in the elderly, and will conclude with a discussion of the sensible limits for weekly alcohol intake in older people.

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