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Health Risks of Chronic Moderate and Heavy Alcohol Consumption: How Much Is Too Much?

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This article presents the proceedings of a symposium held at the meeting of the International Society for Biomedical Research on Alcoholism (ISBRA) in Mannheim, Germany, in October 2004. Most of what we know about the deleterious effects of alcohol *in vivo* has been gleaned from studies in sober alcoholics recruited from substance abuse treatment programs. Little is known about effects of chronic drinking in the moderate or heavy range encountered in a much larger fraction of modern society. Extrapolation of information on the adverse effects of chronic drinking on organ function from clinical samples to social drinkers in the general population has to be met with great skepticism, as it may lead to wrong conclusions about the chronic effects of alcohol in social drinkers. Several recent studies suggest that moderate alcohol consumption has certain beneficial health effects, whereas heavy social alcohol consumption has recently been associated with organ abnormalities and cognitive deficits. These social drinking effects have attracted great public interest; reports of benefits of moderate drinking have also inspired inappropriate publications by the media, including misleading advertisements by the alcohol producing and distributing industry. Although adverse effects of moderate to heavy drinking on heart, liver, and cancer development have attracted attention by clinicians and researchers for some time, its compromising effects on brain and cognition have only recently been studied. This symposium brought together researchers from different disciplines, who reviewed and presented new data on consequences of social drinking in the areas of clinical neuropsychology and behavior (Drs. Nixon and Meyerhoff), neurophysiology (Dr. Nixon, Ms. De Bruin), neuroimaging (Ms. de Bruin, Dr. Meyerhoff), hepatic disease (Dr. Bode), and cancer (Dr. Seitz). The symposium aimed to clarify both the potential health benefits of moderate alcohol consumption and risks of moderate and heavy drinking on proper organ function and to provide insights and new data to practicing physicians and public health authorities for education on problem drinking.

Key Words: Social drinking, Brain, Cognition, Liver, Cancer.

MOST OF WHAT we know about the deleterious effects of chronic alcohol consumption *in vivo* has been gleaned from studies of sober alcoholics recruited from substance abuse treatment programs. This population has been studied mostly for reasons of convenience and of maximizing the likelihood of detecting chronic alcohol–induced organ changes in research studies. However, these treated alcoholics represent only a very minor fraction of individuals in the general population, who exhibit an alcohol use disorder at some time during their lives but never undergo alcoholism treatment (approximately 9% in the United States). Therefore, very little is known about effects of chronic drinking in the moderate or heavy range encountered much more frequently in modern society. Recent studies show that treatment-naive heavy drinkers may in fact derive from different populations with regard to alcohol use histories than alcohol-dependent individuals in treatment (Fein and Landman, 2004) and that genes can influence long-term alcohol consumption levels (Whitfield et al., 2004) and development of alcohol dependence (Enoch, 2003; Ray and Hutchison, 2004; Schuckit, 2000). The Fein and Landman study also suggests that alcohol-dependent individuals who seek treatment or are in treatment may not only have greater coexisting pathology (both prevalence and severity of substance abuse, depressive and affective symptoms, and other psychopathology) than the socially functioning heavy drinking population but also more severe consequences of alcoholic drinking on the brain and other organs. Therefore, extrapolating our infor-

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mation on the adverse effects of chronic drinking on organ function from clinical samples to social drinkers in the general population needs to be met with great skepticism and may lead to wrong conclusions about the chronic effects of alcohol in the much larger population of social drinkers (Berkson's fallacy).

Recent studies suggest that moderate alcohol consumption has certain beneficial health effects: moderate drinking has been described to be associated with lower risk for total and ischemic stroke (Reynolds et al., 2003), coronary heart disease (Mukamal et al., 2003), and dementia later in life (Anttila et al., 2004). These social drinking effects have attracted great public interest, and reports of benefits of moderate drinking have also inspired inappropriate publications by the media, including misleading advertisements by the alcohol producing and distributing industry. Although adverse effects of moderate to heavy drinking on heart, liver, and cancer development have attracted attention by clinicians and researchers for some time, its compromising effects on brain and cognition have only recently been studied after the realization that brain structure and function are impaired in alcohol-dependent individuals in treatment. Although brain shrinkage is now recognized as a risk factor for cognitive decline and impairment in the elderly, very little is known about brain shrinkage possibly associated with drinking chronically moderate to heavy amounts of alcohol (and possibly with associated cognitive deficiencies).

This symposium combined two proposals originally submitted to the ISBRA Program Committee, both dealing with the effects of chronic alcohol consumption in treatment-naive alcohol drinkers as opposed to those in alcoholics recruited from alcoholism treatment centers. These proposals asked the question of "how much alcohol is too much?" for the brain or for other organ systems. Eventually, researchers from different disciplines, who work extensively with both of these populations, presented an overview and new data on consequences of social drinking in the areas of clinical neuropsychology and behavior (Drs. Nixon, and Meyerhoff), neurophysiology (Dr. Nixon, Ms. De Bruin), neuroimaging (Ms. de Bruin, Dr. Meyerhoff), hepatic disease (Dr. Bode), and cancer (Dr. Seitz). The symposium aimed to clarify both the potential health benefits of moderate alcohol consumption and risks of moderate and heavy drinking on proper organ function and to provide insights and new data to practicing physicians and public health authorities for education on problem drinking.

Nota bene: In discussing effects of certain quantities of chronic alcohol consumption, it is important to acknowledge that obtaining a good self-reported history of an individual's alcohol consumption over a longer time period or even an entire lifetime is not necessarily reliable but at best is a good-faith estimate by the consumer that probably underestimates consumption the more the individual drinks. Furthermore, comparison of international studies is often complicated by the fact that many countries have different definitions as to how many grams of pure ethanol are contained in "one drink" or in "one unit": Austria, 6 to 7 g; United Kingdom and Ireland, 8 g; Italy and Spain, 10 g; Denmark and France, 12 g; United States and Canada, 12 or 14 g; Japan, 20 g (Conibear and Holmgren, 2002; Fillmore et al., 2000; Kelly et al., 1995; MacKenzie et al., 1996; Richardson et al., 1989; Shaper et al., 1988). All presenters were specific as to the quantities used in their research studies.

MODERATE ALCOHOL CONSUMPTION, THE BRAIN, AND THE CONTINUING CONUNDRUM

Sara Jo Nixon

The effects of alcohol consumption on cognitive functioning are widespread throughout the brain and are dependent on whether chronic or acute consumption are considered, on the amount of alcohol consumed, on the duration and pattern of chronic consumption, and whether function is measured on the ascending or descending limb of the blood alcohol curve; they are also dependent on sex, age, and individual health status of the consumer (Eckhardt et al., 1998; Mumenthaler, et al., 1999; Nixon and Phillips, 1999). Therefore, a complete overview of this area is beyond the scope of this presentation, or indeed, the entire symposium. Therefore, the focus of this presentation is narrowed to the effects of moderate chronic alcohol consumption on neuropsychologic and neurophysiologic effects, with specific attention to age and sex effects and to provide a cursory overview of the associations between neurobehavior, alcohol intake, and liver disease.

Parsons and Nixon (1998) reviewed studies of moderate or social drinking published between 1986 and 1996. In this overview, they found 10 studies that failed to find any effect of alcohol intake on cognitive functions, whereas seven of the reviewed studies did demonstrate significant effects. However, the mean number of weekly standard alcoholic drinks in the studies showing cognitive effects was more than 30 drinks per week (12–14 g alcohol per drink). Thus, it could be argued that some of these participants were heavy as opposed to moderate drinkers, although all were non–treatment seeking and recruited from the community. Interestingly, when the studies with excessive levels were not considered, it was evident that those studies with neurophysiologic measures (i.e., Event Related Potential (ERPs)) appeared more sensitive to the effects of moderate alcohol consumption than did those that obtained only behavioral measures.

Given the rapid growth of the aging population, some research has focused on the effects of moderate drinking in older men and women. In an early study from our laboratory (Nixon, 1998), we examined drinking patterns and selective cognitive tasks in a sample with a mean age of 60 years. Using a median split to identify light versus heavy drinkers, we examined change in performance over a one-

year period. However, neither measures of verbal fluency nor of verbal memory showed hypothesized cross-sectional alcohol effects nor alcohol by time interactions.

Hepatic function has a significant influence on brain function. Alcohol-induced liver disease is common in alcohol dependence and not uncommon in treatment-naive heavy drinkers and may in fact also influence performance in moderate drinkers without detectable liver disease (Maher, 1997; Tarter, et al., 1993). To the best of our knowledge, there are no published studies of liver function and neurocognition in moderate drinkers. However, Richardson et al. (1991) conducted a study of male and female inpatients seeking alcoholism treatment who either did or did not have elevated biomarkers of liver function but did not have cirrhosis. When the participants had attained 21 days of sobriety, they completed a neuropsychologic battery that included assessment of memory, set-shifting, visual-spatial application, perceptual-motor skills, and problem-solving/abstraction. Using an overall performance index, they found that participants with elevated liver biomarkers performed significantly more poorly than those with markers in the normal range. Furthermore, follow-up analyses showed that the majority of the effect was due to the more complex tasks that require integration of neuropsychologic domains.

In summary, the effects of moderate, ongoing alcohol consumption on neurocognitive function remain somewhat elusive. With very moderate levels, no readily measurable negative consequences appear to be apparent. Inefficiencies in neurocognitive test performance become apparent at long-term chronic consumption levels around 100 drinks per month. On the other hand, individuals with physical disorders that either directly or indirectly (e.g., through medication effects) affect hepatic function may have an increased risk for negative consequences on cognitive functioning, even with drinking at moderate levels. More research directed at understanding this complex interaction is needed.

BRAIN VOLUME LOSS WITH CHRONIC DRINKING: CONTINUUM OR THRESHOLD?

Eveline A. De Bruin

Alcohol-dependent individuals in alcoholism treatment have smaller gray and white matter tissue volumes (Fein et al., 2002; Jernigan et al., 1991; Pfefferbaum et al., 1997) and greater ventricular and sulcal volumes (Agartz et al., 2003; Pfefferbaum et al., 1995). This is consistent with autopsies of alcoholic brains that reveal demyelination, glial damage, neuronal loss, and cell body shrinkage. There are preliminary indications that heavy drinkers who are not alcohol dependent also have slightly larger ventricles (Ding et al., 2004; Mukamal et al., 2001) and wider sulci (Kubota et al., 2001) than light drinkers. This suggests that the effects of alcohol on brain structure may be dose dependent, with the damage representing a continuum spanning the chronic drinking range.

Genetic factors related to alcohol dependence may also be involved in the brain's vulnerability to the damaging effects of alcohol. Thus, previous studies of brain volumes in non–alcohol-dependent drinkers with alcohol-dependent relatives are potentially confounded with effects of genetic factors related to alcohol dependence on brain structure. Therefore, in this study, the relationship between alcohol intake and brain volumes was investigated in non–alcohol-dependent chronic drinkers with a negative family history of alcohol dependence. Based on our own preliminary findings in excessive drinkers and the literature on brain shrinkage in alcohol-dependent patients, it was expected that higher alcohol intake in these non–alcohol-dependent drinkers would also be related to smaller brain tissue volumes.

Brain structure was measured with quantitative magnetic resonance imaging (MRI) in 47 healthy men (50 $\pm$ 9 years) consuming on average 20 standard drinks per week and 44 healthy women (50 $\pm$ 7) consuming 15 standard drinks per week (containing about 12 g of alcohol per drink). All participants were treatment-naive, free of current or lifetime psychiatric disease including alcohol dependence, and did not use any medication or psychoactive drugs besides alcohol. Volumes of total brain, cerebellum, ventricles, and gray and white matter in the major lobes of the brain were determined with volumetry (Mandl et al., 1999; Schnack et al., 2001). Focal gray and white matter densities were analyzed with voxel-based morphometry (Collins et al., 1995; Maes et al., 1997). Using the same methods in a small group of 8 male excessive drinkers (consuming on average 81 standard drinks per week), a significantly smaller total brain volume was found relative to men consuming less than 21 drinks per week (as in Parsons and Nixon, 1998), primarily due to less gray matter in the frontal lobes and a larger third ventricle.

In the sample of non–alcohol-dependent drinkers, there were no negative associations between alcohol intake and global brain volumes. In female drinkers, alcohol intake did not relate to brain structure. The male drinkers demonstrated a significant positive relationship between lifetime alcohol intake and frontal white matter volume. Consistent with this dose-dependent global increase in frontal white matter, voxel-based morphometry demonstrated a focal decrease in gray matter in the right frontal gyrus and the right parietal gyrus. The brain matter densities in the right frontal gyrus correlated with brain function, as estimated by the P3 amplitude during a visual attention task (which tended to be lower with higher alcohol intake in men). The brain matter densities in the right parietal region correlated with brain function as measured with fast-beta electroencephalography synchronization during rest and mental rehearsal (which was lower with higher alcohol intake in men).

In conclusion, the global white matter increase in non–alcohol-dependent male drinkers consuming less than 100

standard alcoholic drinks per month could be a response to focal gray matter damage related to chronic moderate alcohol intake. In these individuals, chronic alcohol consumption is related to brain structure and function, even in the absence of a positive family history of alcohol dependence. This work would support dose-dependent brain damage caused by chronic alcohol consumption and thus the continuum hypothesis.

TREATMENT-NAIVE CHRONIC DRINKERS HAVE BRAIN METABOLITE ABNORMALITIES

Dieter J. Meyerhoff

Volumetric MRI and *in vivo* proton magnetic resonance spectroscopic imaging (1H MRSI) were used to measure regional brain structures and metabolite concentrations throughout the brain of 46 chronic, heavy drinkers (41 ± 9 years, including 8 women) and 52 light drinkers (41 ± 9 years, including 20 women) recruited from the general community via newspaper advertisements and flyers. The light drinkers had never consumed more than 45 drinks per month (mean, 11; approximately 12–14 g of alcohol per drink), whereas the heavy drinkers consumed regularly between 90 and 400 alcoholic drinks per month (mean, 204), with the majority having a DSM-IV diagnosis of alcohol dependence. These "socially functioning heavy drinkers" did not consider themselves alcoholic and mostly did not recognize that their level of drinking constituted a problem that would warrant treatment. Neuropsychologic performance was also tested to assess the potential functional significance of brain injury. The cumulative lifetime alcohol consumption among these treatment-naive heavy drinkers was about 60% of that typically found among treated alcohol-dependent populations of the same age.

Nevertheless, the heavy drinkers had widespread reductions of cortical gray matter volumes measured by quantitative high-resolution MRI (Cardenas et al., 2005), and *N*-acetylaspartate (NAA), a marker of neuronal/axonal injury, was lower in the frontal white matter of heavy drinkers compared with light drinkers despite normal white matter volumes (Durazzo et al., 2004). Frontal white matter NAA also tended to be lower in women than in men (despite comparable alcohol consumption) and lower in those heavy drinkers with a negative family history of alcoholism than in family history–positive drinkers. Family history of alcoholism also affected regional concentrations of myo-inositol, an astrocyte marker, and NAA in frontal gray matter. Among heavy drinkers, measures of parietal glial cell metabolism were more abnormal in alcohol-dependent than alcohol-abusing individuals. As expected, the severity of brain metabolite abnormalities was generally greater with older age and with greater drinking severity.

Among heavy drinkers, lower frontal NAA concentrations correlated with diminished executive functioning and processing speed. Although subtle, such cognitive inefficiencies may be of behavioral significance by interfering with the drinker's decision to seek treatment or reduce drinking, thus perpetuating drinking behavior. Overall, the heavy drinkers demonstrated fewer and less pronounced abnormalities in brain metabolites than alcohol-dependent individuals in treatment, but these brain changes were nonetheless associated with lower brain function, which probably will deteriorate with continued drinking. Indeed, when some of the heavy drinkers were examined again after 2 years of continued heavy drinking, they showed further significant decreases of NAA and myo-inositol in frontal white matter and in the cerebellar vermis. These studies suggest cross-sectional and ongoing axonal glial damage in treatment-naive chronic drinkers that is functionally significant. It is modulated by sex (women tend to have greater injury despite similar drinking severity), age, alcohol use disorder diagnosis, and family history of alcoholism (a positive family history appears to protect against greater brain metabolite damage).

Metabolite damage was also assessed in a subset of 16 drinkers (47 ± 6 years) who regularly drank at much lower levels, averaging 131 alcoholic drinks during the last year and 108 drinks over lifetime. These individuals demonstrated significant NAA loss in the frontal lobes, suggesting that regular chronic drinking at greater than 4 drinks per day is associated with frontal axonal injury. These alcohol quantities are close to what has been associated in the literature with measurable neurocognitive inefficiencies.

MODERATE ALCOHOL CONSUMPTION AND THE LIVER

J. Christian Bode

Epidemiologic studies have shown that light-to-moderate alcohol consumption is associated with a decreased risk of coronary heart disease (Mukamal et al., 2003; Rehm et al., 2001). Although the reported benefit of light-to-moderate alcohol consumption on coronary heart disease morbidity and mortality rates varies distinctly between different studies (ranging from no effect up to 80% risk reduction), the results of the studies claiming a major benefit have received broad public attention. On the basis of these findings, the effect of light-to-moderate alcohol consumption on the risk of other organ injury is of interest.

Earlier studies on the relation between mean alcohol consumption and the risk of advanced alcoholic liver disease focused on the effects of higher doses of alcohol (Lelbach, 1985; Péquignot et al., 1974). However, when looking on the data of these earlier studies again, it becomes obvious that moderate amounts of alcohol (20 to 50 g per day) increase the risk of cirrhosis significantly by a factor 2 to 4. In a recent meta-analysis of 15 epidemiologic studies, an increased relative risk to develop cirrhosis in subjects drinking up to 25 g alcohol per day compared with abstainers has been confirmed (Corrao et al., 1998). The increased overall risk for development of cirrhosis in individuals with chronic moderate alcohol consumption is likely to be caused by the disposition to or the presence of several

types of nonalcoholic liver disease. Moderate alcohol consumption has been shown to enhance the development of fibrosis in patients with chronic hepatitis C and is likely to have adverse effects on the course of nonalcoholic steato hepatitis (Bode, 2004). Certain metabolic disorders linked to genetic defects, such as hemochromatosis or deficiency of acetaldehyde dehydrogenase type 2, frequently observed in the Asian population, may lead to increased sensitivity to develop alcoholic liver injury (Bode, 2004) (for how this relates to cancer, risk see next presentation). The data underline the importance of considering the individual risk to the potentially harmful effects of generally accepted amounts of social drinking and even those amounts considered harmless by public health authorities.

MODERATE ALCOHOL CONSUMPTION AND CANCER

Helmut K. Seitz

Evidence has accumulated that even moderate alcohol consumption when associated with certain genetic or environmental preconditions increases the risk of developing certain types of cancer, such as cancer of the upper aerodigestive tract (UADT) in alcohol dehydrogenase (ADH) 1C*1 homozygotes (Visapää et al., 2004), hepatocellular cancer in patients with chronic hepatitis C (Inoue and Seitz, 2001) as well as colorectal cancer (Pöschl and Seitz, 2004) and breast cancer in women (Coutelle et al., 2004). The mechanisms of alcohol-associated carcinogenesis include the production of acetaldehyde (AA), a known carcinogen, and the generation of reactive oxygen species through Cytochrome P-450 2E1 (CYP2E1). Since AA is a known carcinogen, its accumulation may favor cancer development. Forty percent of Asians have a mutation of the acetaldehyde dehydrogenase (ALDH) 2 gene, leading to a low enzyme activity followed by increased AA levels after ethanol intake. It has been shown that individuals with this mutation have a significantly increased risk for development of cancer of the UADT and the colorectum (Yokoyama et al., 1998). We have investigated the role of ADH1C polymorphism. The ADH1C*1 allele codes for an enzyme that produces approximately 2.5 times more AA compared with the corresponding allele ADH1C*2. We found an increased allele frequency of the ADH1C*1 allele as well as an increased homozygosity of ADH1C*1 in patients with UADT cancer (Visapää et al., 2004), hepatocellular cancer (Stickel et al., 2003), and breast cancer (Coutelle et al., 2004), even at moderate levels of alcohol intake. In fact, the risk for development of UADT cancer in these patients was similar, regardless of whether they had an alcohol intake of 20 to 50 g per day or more than 100 g of alcohol per day. In addition, even moderate alcohol consumption as much as 40 g alcohol per day over 2 weeks induces CYP2E1 (Oneta et al., 2002) not only in the liver but also in the UADT and in the colon. This is associated with an increased production of reactive oxygen species that can be reduced by vitamin E (Vincon et al., 2003). This induction of CYP2E1 also leads to a deficiency of retinoic acid due to an increased degradation of retinoic acid via CYP2E1 associated with an increased expression of the AP1 gene, which leads to hyperproliferation and lack of cellular differentiation (Wang et al., 1998). This is especially interesting since β-carotene is a precursor of retinol that has been used to prevent lung cancer in smokers, and it has been found that smokers who drank more than 11 g of alcohol per day and take β-carotene have an increased risk to develop lung cancer, possibly due to an enhanced generation of retinol or retinoic metabolites due to CYP2E induction (Albanes et al., 1996). Finally, a lack of folate may enhance alcohol-associated carcinogenesis. This has been shown for the colorectum, where low methionine and low folate levels in addition to moderate alcohol intake of 20 g or more increases the risk of distal colon cancer by a factor of 7 (Giovanucci et al., 1995).

In conclusion, even moderate alcohol consumption may increase cancer risk in the UADT, colorectum, liver, and breast when associated with certain genetic preconditions, such as ADH1C*1 homozygosity, ALDH2 mutation or high inducibility of CYP2E1, environmental factors such as smoking, poor dental status with bacterial overgrowth, preexisting liver disease such as hepatitis C, hepatitis B, nonalcoholic steatohepatitis (NASH) or hemochromatosis, or a lack of retinoic acid and folate

SUMMARY

This symposium presented evidence that chronic drinking far below the levels generally found in clinical samples of treated alcoholics is associated with (1) brain damage with functional and behavioral consequences, (2) increased risk of liver disease, and (3) increased risk of cancer. This is in contrast to recent reports of beneficial health effects of moderate alcohol consumption on lowering the risks for ischemic stroke, coronary heart disease, and dementia later in life. The material presented in this symposium suggests that no measurable brain injury or cognitive compromise is present if alcohol consumption stays within the standard recommendations of no more than 2 drinks per drinking day in healthy men and 1 drink per drinking day in healthy women. However, special populations with genetic defects and preexisting liver disease increase their relative risk for development of alcoholic liver injury, possibly cognitive deficiencies, and certain types of cancers, even if drinking not more than the recommended amount in men. New experimental evidence suggests that chronic drinking at 80 to 100 drinks per month, which is above the recommended levels but still short of alcoholic drinking, is not only associated with liver injury and development of cancers but also with brain injury and cognitive deficiencies.

The much larger fraction of chronic alcohol drinkers from the community is recognized to constitute a vulnerable population with potential organ damage, which cannot necessarily be extrapolated from studies of a small fraction

of alcohol-dependent individuals in treatment who have stayed sober for a short while. It also constitutes a new patient pool to answer alcohol-related research questions not possible via the clinical alcoholic population. In an atmosphere of shrinking health services and provider coverage, prevention is the key. Therefore, it is important and in fact responsible research to detect potential health hazards at an early stage and not simply to describe the end stage of alcohol-induced organ damage. It is hoped that this symposium increases the awareness of the wide range of health risks associated with moderate and heavy drinking at levels often accepted in our modern society. Health policy makers can use the presented information for public education on problem drinking.

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