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Editorial

Alcohol-related dementia: a 21st-century silent epidemic?

Susham Gupta and James Warner

Summary
Evidence suggests a J-shaped relationship between alcohol consumption and cognitive impairment and other health indicators, with low levels of consumption having better outcomes than abstention or moderate to heavy drinking. Most research to date has focused on the protective effects of drinking small amounts of alcohol. As alcohol consumption is escalating rapidly in many countries, the current cohort of young and middle-aged people may face an upsurge of alcohol-related dementia. The dangers of heavy drinking and its effect on cognition require further attention.

Declaration of interest
None.

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Many adverse consequences of excessive drinking have been highlighted in both the medical and popular press, but one that remains relatively obscure and poorly addressed is that of alcohol-related dementia. The 'Alcohol Harm Reduction Strategy for England'[1] fails to mention the possibility of dementia as a consequence of excessive drinking and does not address the problems of older drinkers or potential challenges posed by alcohol-related dementia on the health and social services. Various definitions have been used to describe excessive drinking in medical literature. The Department of Health's 'sensible drinking' document recommends no more than 3–4 units of alcohol daily for men and 2–3 units for women. Some evidence suggests limited drinking in earlier adult life may be protective against incident dementia later. Long-term alcohol consumption above these limits is generally considered harmful. The concurrent increase in use of recreational drugs may contribute to later-onset cognitive problems.

Changes in alcohol consumption

Attitudes towards alcohol and its use have undergone significant changes in this country over the past few decades. These started in the baby-boomer years with liberalisation of social values and greater individual freedom. Alcohol has become cheaper in relative terms and more widely available. There is a close link between affordability and consumption. The price of alcohol relative to the average UK income has halved since the 1960s, while per capita consumption of total alcohol has nearly doubled from under 6 l/year in the early 1960s to over 11.5 l/year by 2000.[2] This is still increasing in all age groups. Alcohol misuse in the elderly is also underestimated and under-diagnosed. If the present trend of alcohol consumption continues, within a decade the UK will rise from the middle range to the top among European countries.

Alcohol and its effects on the brain

Harper[3] has reported a statistically significant loss of brain tissue in chronic alcoholics compared with controls.[3] This loss appears to be primarily from the white matter with reduction in the number of cortical neurons in the superior frontal cortex, hypothalamus and cerebellum; but not in basal ganglia, nucleus basalis, or serotonergic raphe nuclei. This seems to occur independently of Wernicke's encephalopathy but nutritional deficits may make the situation worse. Chronic alcoholism inhibits *N*-methyl-D-aspartate (NMDA) causing upregulation of the NMDA subtype of glutamate receptors in the frontal cortex, probably reflecting alcohol-induced chronic neurotoxicity with increased intracellular calcium (mediating oxidative stress) along with loss of cholinergic muscarinic receptors. This may be related to the clinical symptoms of alcohol withdrawal and alter seizure activity in the brain.

A review on the effect of alcohol on the frontal lobe noted that neuroradiological findings support the occurrence of morphological abnormalities in brains of chronic heavy drinkers, suggesting cerebral atrophy.[4] Structural imaging using computed tomography scans of male alcoholics showed larger ventricles and wider cerebral sulci and fissures compared with controls.[5] Functional imaging studies have reported decreased frontal lobe glucose utilisation and reduced cerebral blood flow. Women are probably more vulnerable to the effects of alcohol, exhibiting earlier changes but also faster recovery on abstinence.[6]

Various mechanisms have been attributed to the effects of alcohol on the brain including a direct neurotoxic effect of alcohol, oxidative stress, excitotoxicity, mitochondrial damage and apoptosis. Repeated withdrawal may be associated with greater cognitive impairment due to neuronal damage and may have a bearing on the dementing process. Those having two or more detoxifications showed a greater degree of cognitive impairment compared with those with one or none.[7] Repeated withdrawals may be associated with 'kindling-effect' of worsening of withdrawal symptoms and associated brain damage. A study found structural brain changes in treatment-naïve alcoholics to be less severe than those of clinical samples of alcoholics.[8] However, difference in severity, concomitant psychopathology and the age at drinking onset may confound the effect of repeated detoxification.

Adverse effect of heavy drinking

The protective effect of light-to-moderate drinking is considered to be via a number of mechanisms, both direct and indirect. These include increased serum concentration of high-density lipoprotein, lowering of cholesterol, beneficial effects on platelet function, clotting and fibrinolysis, and improved insulin

sensitivity. The non-alcoholic components may have antioxidant, anti-inflammatory and vasorelaxant properties.

Growing evidence suggests that these benefits are reversed on heavier drinking, often in a dose-dependant fashion leading to raised triglycerides, hypertension and other factors, which could contribute to adverse cerebrovascular changes. Chronic alcoholism has been linked with hyperhomocysteinaemia – considered toxic to the endothelium and associated with increased risk of arterial thrombosis, cardiac disorders and strokes.[9] Consuming more than six drinks per week is also associated with increased risk of ischemic stroke and lacunar infarcts, which further increased in those who are apoE4 positive.[10] Hepatic encephalopathy in chronic alcoholics, raised toxins like ammonia and manganese can all exert harmful effects which interfere with normal neurotransmitter activity, impair motor functions, and cause structural alterations in the astrocytes, which have neuroprotective functions. Current opinion suggests that the specific alcoholic beverage is less important than the quantity and pattern of drinking.

Cognitive impairment and alcohol use

People over 65 years constitute 16% of the population in England and in an aging population the change in drinking pattern could be expected to have a greater longer-term impact. The Alzheimer's Society estimates that 700 000 people in the UK currently suffer from dementia. Alzheimer's disease, vascular and Lewy body dementia are considered to be the main causes, while alcohol-related dementia is largely overlooked or seen as a comorbid factor. It is worth considering that the current prevalence of alcohol-related dementia is manifest in a cohort whose alcohol consumption was half the current levels of today's younger and middle-aged generations. Chronic alcohol misuse is associated with increased mortality and, given this attrition rate, one can assume that alcohol-related dementia rates would be even higher if the life span of heavy drinkers were similar to the general population.

Harmful use of alcohol is a variable and non-specific term, encompassing various patterns of excess drinking leading to physical, psychological and other indirect impairment. Age, chronicity, pattern of alcohol use, nutritional, genetic and gender factors can all have an impact on the outcome. The direct association between worsening of cognitive performance, chronicity and severity of use has been highlighted.[11] Binge drinking is associated with increased overall risk of dementia.

A number of studies looking into the consequences of long-term excessive alcohol use on cognitive impairment have found a J-shaped relationship with the level of drinking, with light-to-moderate alcohol intake associated with a lower risk of dementia,[12,13] while some noted a higher risk in heavy drinkers.[14] The results of a large, nested case–control study concluded that, compared with abstention, consumption of 1–6 drinks weekly is associated with a significantly reduced incidence of dementia among older adults.[15] It also identified a non-significant trend of increased risk with higher consumption (greater than two standard drinks daily).

In contrast to other common causes of dementia, it has been suggested that the decline in cognitive or physical functioning in alcohol-related dementia is relatively non-progressive in abstinent ex-drinkers, or even partially reversible; this is supported by imaging studies.[16] There may be improvement in working memory, visuo-spatial functioning, problem solving and attention, with some increase in brain volume over a period of up to a year in recovering alcoholics.[17] Impairments in areas of learning and short-term memory are more persistent.

There is a relative paucity of research into the epidemiology of alcohol-related dementia partly due to problems in nosology and recognition, variable ascertainment of drinking patterns and difficulty in establishing exposure using case–control methods. Various studies have suggested the prevalence of alcohol-related dementia to be about 10% of all cases of dementia.[18] 'Heavy alcohol use' was seen as possible contributing factor in 21–24% cases of dementia in a review of epidemiological, neurological, cognitive and imaging data.[19]

Nosology

Despite notions that alcohol use can lead to cognitive impairment, (excluding Korsakoff's syndrome) the understanding of the impact of long-term alcohol use on cognition is uncertain. The syndrome has been recognised by the DSM–IV under the term 'alcohol-induced persistent dementia', manifested by a progressive intellectual and cognitive decline without a profound amnestic disorder. The term 'alcoholic dementia' has been generally superseded by the concept of alcohol-related dementia, encompassing a broader definition of alcohol-related cognitive deficits. The existence of alcohol-related dementia is widely acknowledged but not often used as a diagnosis and needs greater validation through research.

Current diagnostic criteria for alcohol-related dementia are based almost exclusively on clinical judgement. Few guidelines are available to assist clinicians and researchers in distinguishing alcohol-related dementia from other causes of dementia, despite suggestions that neuropsychological profiles may differ. This distinction may have implications for the prognosis and treatment of patients, as evidence suggests that alcohol-related dementia is less progressive than Alzheimer's disease and even potentially partially reversible. These factors are important in the long-term management of these patients, including treatment for alcohol misuse and selection of residential placements, as their prognosis and needs may differ from those of other dementia patients.

Oslin proposed clinical diagnostic criteria based on epidemiological and neuropathological evidence to support the clinical criteria, which were validated.[20] The criteria for the clinical diagnosis of 'probable alcohol-related dementia' include a clinical diagnosis of dementia at least 60 days after last exposure to alcohol, significant alcohol use (i.e. minimum 35 standard drinks/week for males and 28 for women) for more than 5 years, and significant alcohol use occurring within 3 years of the initial onset of cognitive deficits. There are other supporting physical, neurological and investigational criteria. This was established by consensus opinion based on the review of available literature, primarily to help standardise the definition and stimulate research.

Conclusions

Given the neurotoxic effects of alcohol and the inexorable increase in per capita consumption, future generations may see a disproportionate increase in alcohol-related dementia. This could be compounded by the effects of increasing use of recreational drugs such as ecstasy, whose long-term effects on cognition are still uncertain. Detection of these cases could be improved by the use of screening tests like the Michigan Alcohol Screening Test combined with tools such as the Lifetime Drinking History interview. There is a need to develop tools for assessment of alcohol-related cognitive impairment. It is always difficult to

motivate change in public behaviour when there is a delay between the risk-taking behaviour and the onset of complications. Calls for public health initiatives aimed at educating people about the risk of alcohol-related dementia, on top of the other physical and mental health risks posed by drinking, may be unpopular and ineffective. This might need similar legislation to that used in the fight against tobacco-related health problems; and there is a pressing need to try to quantify this potentially major challenge from both the medical and socio-economic points of view. This is an under-recognised problem and urgent action is needed to prevent a new epidemic.

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