EBMH Section – Old Age Psychiatry

CLINICAL REVIEW

"Effects of drinking on late-life brain and cognition"

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Abstract

Alcohol consumption is common in Western countries and has been increasing in older adults. Latest figures from Great Britain suggest 75% of those over 65 years drink, an increase from 71% ten years ago. Chronic heavy intake is a well-established cause of brain atrophy and dementia, with a recent long-term prospective study from the US reporting a doubling of the odds of later severe memory impairment in those with a history of an alcohol use disorder. Drinking of moderate amounts has been reported to be protective for brain health in a number of epidemiological studies, including some claims of possibly reducing dementia risk. Rigorous recent research has questioned this belief, with new evidence of harmful associations in moderate drinkers compared to abstainers. This has raised suspicion that reported protective effects of moderate drinking were due to confounding by socioeconomic class and intelligence. Clinicians should look out for cognitive impairment in heavy drinkers, considering that abstinence may induce a degree of clinical improvement. Discussions with patients regarding moderate drinking should be informed by recent research. Health benefits of moderate drinking at least for cognitive function are questionable, and if they exist are probably limited to one unit of alcohol daily with respect to other body systems.

Introduction

Alcohol use is widespread and increasing across the developed world. Latest figures suggest that 58% of the UK population are drinking in excess of existing safe limits,(1) with 5% men and 4% of women consuming hazardous amounts (>50 units (400g) for men and >35 units (280g) for women weekly). Drinking in women and older adults of both sexes has been increasing,(2) with the percentage of those >65 years drinking increasing from 71% to 75% between 2005 and 2016. Those over 65 years of age are now more likely than any other age group to have drunk on at least five days in the preceding week.(1) Alcohol related harm is estimated to cost England around £21bn per year, with £3.5bn to the NHS, £11bn tackling alcohol-related crime and £7.3bn from lost work days and productivity costs. Health concerns associated with alcohol use have focused on liver dysfunction and more recently cancer. The public are largely ignorant of the potential risks of drinking with regards to cognition, in contrast to widespread knowledge of effects on the liver.(3) Recommended drinking guidelines have remained unchanged in the UK from 1987 until 2016. Safe limits for men were set at 21 units (168g) and for women at 14 units (112g) per week pre-2016. Recent evidence of associations with cancer risk(4) at lower doses prompted revision of UK government alcohol guidance to 14 units (112g) for both sexes, but current US guidelines still suggest that up to 24.5 units (196g) weekly is safe for men.

This clinical review summarises established effects of chronic heavy drinking on brain and behaviour/cognitive function, as well as the poorly understood impact of moderate consumption. Implications for clinicians from these findings are also discussed.

Methods

MEDLINE, PubMed and Google Scholar were searched with the following key words: “alcohol” AND (“dementia” OR “cognition” OR “brain”). Primary research and review articles published in English until September 10th 2017 were examined for information pertinent to the topic. Reference lists from included papers were hand searched for additional relevant articles.

Results

Our search retrieved a large consistent evidence base to suggest an increased risk of dementia and cognitive impairment, and brain atrophy in the context of chronic heavy alcohol consumption. In contrast, data pertaining to risks or benefits of lesser intakes was conflicting, perhaps in part because definitions of “moderate” consumption varied considerably. In this review we focus on five epidemiological studies and two meta-analyses pertaining to the risk of dementia with moderate alcohol use, five studies and two meta-analyses investigating the risk of cognitive impairment, and nine studies examining neuroimaging outcome measures. Table 1 gives a summary of the main findings.

Overall, acute intoxication with alcohol results in behavioural disinhibition, disrupted socio-emotional processing and impaired psychomotor performance. The molecular basis for these actions is thought to include NMDA and GABA-A receptors. High

doses of alcohol acutely reduce prefrontal and temporal lobe function, including planning, verbal fluency, memory and complex motor control including cerebellar function.(5) The pattern of impairment has been compared to that seen in hippocampal damage. Excessive alcohol consumption can also lead to a number of conditions with psychiatric symptoms, including psychotic disorders and delirium. In this review we focus on structural brain and cognitive sequelae of chronic alcohol consumption.

Outcome	Chronic heavy intake	Moderate intake
Cognitive outcomes		
Dementia risk	Consistently increased(6)	Conflicting results, with some studies reporting a protective effect(7-9) which others have failed to replicate.(10, 11)
Cognitive decline	Consistently increased(12, 13)	Conflicting results, with some studies reporting a protective effect(14, 15) which others have failed to replicate.(16-19)
Brain structure		
Grey matter	Widespread atrophy, especially of frontal lobes.(20)	Two studies reported atrophy(21, 22) but others have not.(23, 24)
White matter	Widespread atrophy, including of frontal lobes, cerebellum and corpus callosum.(25, 26)	Two studies have found negative associations(16, 27, 28) and others have not.(29)
Subcortical volumes	Hippocampi,(30) amygdalae,(31) mammillary bodies, hypothalamic and thalamic nuclei all potentially affected.(32)	Two studies report conflicting associations with hippocampal size.(16, 29)
Cerebellum	Atrophy.(33)	Insufficient evidence.

Table 1: Summary of associations between alcohol consumption, cognition and brain structure.

Chronic heavy alcohol

Cognitive sequelae

Chronic heavy drinking is associated with a number of serious neurological conditions, one of which is Wernicke's encephalopathy. This is an acute, often lethal, but potentially reversible neurological disorder caused by a severe deficit in thiamine (vitamin B1) aggravated by carbohydrate overload. It is characterized by the clinical triad of oculomotor disturbance, cerebellar dysfunction and altered mental state. Chronic alcohol users are at risk of this due to multiple potential factors including: poor diet, impaired absorption and altered metabolism of thiamine. The estimated mortality of Wernicke's encephalopathy is 17%. Untreated, 80% of survivors of Wernicke's encephalopathy will progress to the severe and usually permanent Korsakoff's syndrome.(34) This is characterized by anterograde (and retrograde) amnesia, and frequently occurs together with prefrontal deficits. Even in 'uncomplicated' alcoholism, without Wernicke's encephalopathy or Korsakoff's syndrome, over 80% of individuals have executive deficits,(35) although of a lesser severity. A strong evidence base supports the association of heavy alcohol consumption over long periods with increased dementia risk and cognitive decline.(12) A recent long-term prospective study from the USA reported that individuals with a history of an alcohol use disorder have more than double the odds of later severe memory impairment compared to controls (OR = 2.21, 95% CI: 1.27-3.85).(13) There is some debate as to whether primary alcohol dementia exists, as a result of direct neurotoxicity, or whether cognitive deficits are entirely secondary to an additional pathology for example due to thiamine deficiency. It is difficult to disentangle these possibilities, particularly in view of multiple confounders in dependent drinkers, such as smoking, comorbid substance abuse and increased

vascular risk. Similarly, establishing the prevalence of alcohol-related dementia is difficult, due to a lack of operationally defined diagnostic criteria. Estimates differ from 9-22% of all dementia patients,(36) or even higher in nursing homes. Dementia of alcoholic aetiology may be particularly prevalent in earlier onset dementia. There is no clear answer, as to what level of consumption is sufficient to cause Korsakoff's syndrome. Oslin et al. have suggested a five-year intake greater than 35 units (280g) weekly for men and 28 units (224g) for women, but this needs validation.(6) Thresholds are likely to be different according to sex, comorbid conditions and genetic susceptibility.

Effects on brain structure

Brain atrophy in chronic alcoholism is well described.(20) The frontal lobes are thought to be particularly vulnerable. Kril et al. found frontal cortex reductions of 23% in uncomplicated alcoholism, replicating earlier findings. MRI studies have also reported widespread cortical atrophy, which may particularly affect the frontal lobes.(25) Interestingly, longitudinal MRI has shown a degree of tissue recovery, especially of white matter, on abstinence.(37)

The hippocampus is consistently affected in animal models of chronic alcoholism. Despite the preclinical data, evidence for hippocampal involvement in humans is less convincing. However, Bengochea and Gonzalo, amongst others, have described hippocampal loss in individuals with chronic alcoholism compared to controls.(38) Reduced amygdala volume has also been described in those with lifelong high alcohol consumption (defined as >80g daily for the majority of their adult lives), and including those with Wernicke-Korsakoff's syndrome.(31) The cerebellum, known

for its importance in motor function, is now additionally thought to play a role in memory disturbance.(33) A number of neuropathological studies have established cerebellar atrophy in chronic alcohol abuse.(39) Mammillary body atrophy is almost universal in chronic alcoholism. However, animal studies suggest that other hypothalamic nuclei, particularly the supraoptic and paraventricular, may also be affected.(40) Anterior thalamic nuclei may be affected in humans.

Several pre-clinical and post-mortem studies have provided evidence of prominent white matter loss following chronic heavy alcohol use, which may exceed grey matter loss.(26) The frontal lobes and cerebellum are particularly vulnerable. Furthermore, white matter loss in the temporal lobes has been linked to alcohol withdrawal seizures.(41) The corpus callosum, a major commissural tract, may be particularly vulnerable. In their port-mortem study, Harper and Kril reported that corpus callosum thickness in a group of alcoholics (3.19mm) was significantly reduced compared to controls (4.02mm).

A number of different mechanisms have been proposed to account for the deleterious effects of chronically high alcohol consumption on the brain. Damage to the brain from chronically high levels of alcohol is thought to result, at least in part, from thiamine deficiency. Deficiency of thiamine has been linked to oxidative stress, excitotoxicity, inflammatory responses, dysfunction of the blood-brain barrier, and lactic acidosis. Ethanol could be also be directly neurotoxic. Alcohol inhibits glutamate receptors. Chronic exposure induces up regulation of NMDA receptors, which leaves neurons vulnerable to excitotoxicity from massive calcium influx. This may be driven especially by repeated binges and withdrawal. Cell death could also be

via neuroinflammation, the induction of inflammatory mediators and microglia.(42) Additionally, alcohol-related liver dysfunction could mean that neurotoxic substances such as ammonia and manganese are not removed from the blood, resulting in cerebral effects.

Moderate chronic alcohol use

There is no universal agreement about the definition of "light" or "moderate" drinking. Moderate drinking is defined variably in the literature from 9-18 units (72-144g) weekly.(43, 44) In contrast to heavy consumption, the long-term effects of moderate alcohol consumption on cognition are poorly understood. A J-shaped relationship of cognitive function with alcohol use has been suggested, similar to that with cardiovascular disease, i.e. small amounts of alcohol are associated with a reduced risk than abstinence, but large amounts with the greatest risk. Ethanol's inhibition of platelet aggregation, reduction in inflammatory markers, and alteration of plasma lipid profile have been proposed as underlying mechanisms for protection from cardiovascular disease, in addition to the antioxidant action of polyphenols present in some alcoholic drinks.(45)

Risk of dementia

Several large epidemiological studies have reported a reduced risk of dementia (of vascular and non-vascular aetiology) in light- to moderate drinkers compared with abstainers. For example, Ruitenberg et al. found those drinking 1-3 drinks (14-46g)

per day had a reduced risk of dementia (HR 0.58 95% CI 0.38-0.9) compared with abstainers in the Rotterdam study.(7) Subjects were over 55 years old at baseline, and followed up for an average of 6 years. Dementia was excluded at baseline using a variety of screening tests, such as the MMSE, GMS and CAMCOG. In the French prospective PAQUID study, individuals who were at least 65 years old at baseline were followed up for three years. Both 'light' wine drinkers (<1-2 drinks (14-32g) daily) and 'moderate' wine drinkers (3-4 drinks (46-64g) daily) had reduced odds of incident Alzheimer's disease.(46) Similarly, Mukamal et al. reported a lower dementia risk in those drinking 1-6 drinks (14-84g) per day in the Cardiovascular Health Study, using a nested case-control design.(8) Those thought to have dementia were excluded at baseline. A large Norwegian longitudinal study reported increased dementia-related deaths in moderate drinkers compared to abstainers.(10) However, others have not replicated these findings, including a recent study in an Australian cohort, which found no association with incident dementia or cognitive decline, and no interaction between alcohol and ApoE4 genotype.(11)

Meta-analyses of such studies have cited a protective effect of light to moderate alcohol consumption on the risk of dementia including Alzheimer's disease.(9, 19, 47) Anstey et al. analysed 15 prospective studies and reported a pooled risk reduction of 25-8% with late life drinking. They cautioned however that it was unclear whether this represented selection bias, i.e. those still drinking in late life were likely to be those *without* dementia, or a genuine protective effect.

Risk of cognitive impairment or decline

In a large study of women in the USA, the Nurses Health Study, Stampfer et al. followed up women aged 30-55 years at baseline, using a cognitive test modelled on the MMSE and later with a verbal recall task.(14) Those consuming one drink daily had better cognitive scores than non-drinkers at baseline, but also less cognitive decline at two-year follow-up. The analysis was controlled for age, education level, social integration and cardiovascular risk factors. In another US study, Ganguli et al. followed up individuals aged at least 65 years at baseline for two years on a range of cognitive tests, including the MMSE, TMT, word recall and category fluency. Both minimal (defined as <1 drink (14g) monthly) and moderate (<1 drink (14g) daily) drinkers displayed less decline on the MMSE and traits tests compared to abstainers.(15) Interestingly, the protective effects were more pronounced when the comparison group of abstainers also included former drinkers rather than only lifelong abstainers.

However, not all studies have replicated a protective effect of light drinking on cognition. Lobo et al. did not find less MMSE decline in light drinkers than in abstainers.(17) Bos et al. recently reported increased risk of cognitive decline (non Alzheimer types) with increased alcohol.(18) Others have found a protective effect of moderate alcohol use only in those not carrying the ApoE4 allele (a risk gene for late-onset Alzheimer's disease).(48)

Meta-analyses have been limited by the paucity of studies. Peters et al.(19) found no protective effect of moderate alcohol consumption on cognitive decline. Similarly, Anstey et al.(9) found no significant effect of alcohol consumption on cognitive

decline, but their analysis was limited to two studies and consequently had a high degree of heterogeneity**.**

Brain correlates

No convincing neural correlate for a protective effect of small amounts of alcohol on human brain structure has been found, although the field is poorly studied. Reported results are inconsistent.(23) Moderate alcohol consumption in older subjects has been associated with reduced total brain volume, increased ventricle size,(21) grey matter atrophy(22) and reduced frontal and parietal grey matter density, but others have not found such relationships,(23) or only at higher consumption levels.(24) Associations between moderate alcohol consumption and white matter findings are also inconsistent. De Bruin reported increased white matter volume in moderate drinkers compared with abstainers,(29) whereas Anstey found the inverse relationship.(27) Similarly, increased white matter hyperintensities have been described in moderate drinkers compared with abstainers(28) but others found no association.

In a cohort of 550 adults, we examined structural neuroimaging outcomes and cognitive decline in relation to alcohol consumption over the preceding 30 years. We found a novel dose-dependent association between alcohol intake and hippocampal atrophy. Just 14-21 units (112-168g) of alcohol weekly was associated with almost 3 times odds of hippocampal atrophy compared to abstinence.(16) Additionally, alcohol consumption in non-dependent drinkers was associated with lower white matter integrity, particularly of the corpus callosum, and faster cognitive decline on lexical fluency, a complex executive task necessitating generation of words beginning with a

specific letter within a time limit. Interesting we did not find moderate drinkers declined faster on semantic fluency (generation of words within a specific category) or memory recall, especially surprising given the hippocampal associations. Two possible explanations we can think of are that there are greater practice effects for semantic memory that were inadequately controlled for (despite best efforts), or that hippocampal atrophy represents an intermediate phenotype, similarly to in Alzheimer's disease, and cognitive symptoms were not yet evident at the last testing point in the study.

Discussion

How can the seemingly contradictory epidemiological protective claims be explained given the recent harmful brain associations of moderate drinking? One explanation is confounding. Moderate alcohol consumption is highly allied to socioeconomic status and education.(1) Therefore characteristics that predict higher performance on cognitive testing, or a later diagnosis of dementia, are also associated with likelihood of alcohol consumption. One method to try to obviate the problems of residual confounding is use of Mendelian randomisation.(49) This technique is akin to a randomised controlled drug trial, except instead of a medication being randomly allocated to individuals, genetic variants are the instrumental variable, allocated at meiosis. Alcohol metabolism genes, e.g. ADH or ALDH, explain some of the variance of consumption and have been used to investigate associations with cognition or dementia. Two studies thus far have attempted to apply this technique to the question of moderate alcohol and cognition. Almeida et al. found no protective effect of moderate drinking on cognitive decline (defined as MMSE <23/30) over a 6 year period in older men.(50) Nor did Yeung et al. find a protective association with

cross-sectional performance on the MMSE and word recall using Mendelian randomisation of ALDH2 genotype in the Guangzhou Biobank.(49) However, both these studies may have been underpowered.

Clinical implications

Identification of patients drinking large amounts of alcohol over a long period is important given the high risk of cognitive impairment and dementia, particularly as abstinence may improve symptoms to some degree. Clinicians should be vigilant for cognitive symptoms in such individuals. Screening instruments, such as the CAGE or AUDIT, may be helpful in achieving this. They are quick to administer, so applicable in primary care, and been found superior to laboratory tests, including the best performing gamma GT (sensitivity 33%) at detecting excessive drinkers (>16 drinks (224g) daily), with a sensitivity of 93%.(51) Neuroimaging in suspected alcohol-related cognitive impairment is an informative adjunctive source of information in the assessment. Cerebral atrophy (particularly of frontal white matter), white matter lesions and hippocampal atrophy are consistent with alcohol-related brain damage, although not discriminative from vascular or Alzheimer's dementias.

Recent associations between moderate alcohol intake and adverse brain outcomes should be highlighted in discussions with patients about their drinking. Any health benefits are likely to be limited to 1 unit (8g) daily, and even this has increased risks of breast cancer. Justification of moderate drinking on the grounds of brain health has become a little harder.(52)

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