CONFERENCE REPORT

Alcohol-Related Brain Damage: Report from a Medical Council on Alcohol Symposium, June 2010


1Molecular Psychiatry Laboratory, Rockefeller Building, University College London, 21 University Street, London, UK, 2Institute of Psychiatry, King’s College London, UK, 3Bexley Substance Misuse Service, South London & Maudsley NHS Foundation Trust, London, UK, 4Imperial College London, UK and 5Chelsea and Westminster Hospital NHS Foundation Trust, London, UK, 6Addictions Department, National Addiction Centre, Institute of Psychiatry, King’s College London, 7Windsor Walk, London SE5 8BB, UK, 8School of Psychology, University of Sussex, Falmer, Brighton BN1 9QG, UK, 9School of Psychology, University of Liverpool, Liverpool L69 7ZA, UK, 10Academic Unit of Neuropsychiatry, King’s College London, Institute of Psychiatry, 3rd Floor, Adamson Centre, South Wing Block 8, St Thomas’s Hospital, Westminster Bridge Road, London SE1 7EH, UK, 11Neuropsychopharmacology Unit, Centre for Pharmacology and Therapeutics, Division of Experimental Medicine, Department of Medicine, Imperial College London, UK, 12Gartnavel Royal Hospital, Glasgow, Scotland, 13NIHR Comprehensive Local Research Network, University of Liverpool, Liverpool, Scotland and 14South London & Maudsley NHS Foundation Trust and National Addiction Centre, Institute of Psychiatry, King’s College London, UK

*Corresponding author: Tel: +44-203-228-2345; Fax: +44-203-228-2349; E-mail: jane.marshall@slam.nhs.uk

INTRODUCTION

Alcohol-Related Brain Damage: Challenges and Opportunities

Colin Drummond
National Addiction Centre, Institute of Psychiatry, King’s College London, UK

Alcohol is a toxic and dependence-producing substance that can damage most organs in the body, and is implicated in more than 60 different diseases (Oforei-Adjei et al., 2007). Alcohol is now the third leading cause of ill health in Europe (Rehm et al., 2009). In the UK, alcohol-related morbidity and mortality have been increasing over the last 30 years, and alcohol-related hospital admissions now exceed 1 million per annum in England (North West Public Health Observatory, 2011).

The brain is particularly sensitive to the toxic effects of alcohol either directly, particularly in the foetus and young people, or in the context of malnutrition and thiamine deficiency leading to Wernicke–Korsakoff syndrome; or following repeated episodes of alcohol withdrawal. The precise mechanisms of alcohol-related brain damage (ARBD) remain to be fully understood and several papers in this series describe the limits of knowledge. However, enough is already known to make a significant impact on the prevalence of ARBD through relatively inexpensive preventive strategies. Yet, such preventive strategies are poorly implemented in the UK. Why is this the case?

First, there has been a lack of training and clear guidance to clinicians on preventing and managing alcohol problems, including ARBD. This has resulted in low levels of identification and intervention of patients at risk of alcohol-related complications in medical and psychiatric care (Barnaby et al., 2003; Cheeta et al., 2008). The recently published suite of NICE guidance on alcohol-use disorders aims to improve detection, prevention and management (NICE, 2010a, b, 2011). However, effective implementation will require a significant investment in staff training to raise awareness, knowledge and skills.

Secondly, there is the issue of stigma. Patients who misuse alcohol face stigma and opprobrium, with some clinicians holding the view that alcohol-related illnesses are ‘self-inflicted’ and hence are not worthy of medical care (Royal College of Psychiatrists, 2011). Those with ARBD are often subject to additional stigma. Alcohol-related diseases including hepatic cirrhosis and ARBD are compounded by health inequality, with the most disadvantaged in society suffering the most severe consequences (Marmot et al., 2010). There is a need for a sustained campaign against such stigma within the medical profession, which denies access to effective preventive interventions for those most in need. Patients with ARBD should be treated with the same level of care and respect as those who acquire brain damage from other causes such as Alzheimer’s disease or traumatic brain injury.

Thirdly, patients with ARBD require well-integrated care, which presents significant challenges to a health and social care system that is increasingly fragmented in the UK. This fragmentation often results in patients falling between the remit of different services and being ‘passed from pillar to post’ (Wilson, this paper). Recent NICE clinical guidance on alcohol misuse emphasizes the need for high-quality specialist assessment and care coordination to deliver seamless integrated care pathways for alcohol-misusing patients with complex needs (NICE, 2011). There are examples of best practice in managing patients with ARBD in Scotland and North West England (Wilson, this paper; Smith, this paper). However, these beacons of clinical practice are sadly far from the norm across the UK.

A national initiative to improve the prevention and management of ARBD is required, and this timely series of papers provides a compelling basis for action. There is also a need for implementation of effective whole-population public health strategies to combat the rising tide of alcohol-related harm, including restricting access to alcohol through the evidence-based mechanisms of increasing price and restricting availability which have been successful in the tobacco field.

PART I: DEFINING THE MECHANISMS OF CHANGE

The Interactions of Thiamine Deficiency and Alcohol Metabolism in the Pathophysiology of Wernicke’s Encephalopathy

Allan Thomson1, Irene Guerrini2, and E. Jane Marshall3
1University College London and Institute of Psychiatry, King’s College London, UK
2Bexley Substance Misuse Service, South London & Maudsley NHS Foundation Trust, London, UK

© The Author 2012. Medical Council on Alcohol and Oxford University Press. All rights reserved
Wernicke’s encephalopathy (WE) is an acute neuropsychiatric condition caused by an inadequate supply of thiamine (vitamin B1) to the brain (Cook et al., 1998). The condition was first described in 1881 by Wernicke, who drew attention to the signs and symptoms that have become known as the ‘classic triad’ (Thomson et al., 2008a). Unfortunately, the triad is present only in ~16% of the affected patients. Autopsy studies indicate that the diagnosis is not made prior to death in up to 80% of patients. Those who survive usually have permanent brain damage—Korsakoff’s syndrome (KS).

The body stores of thiamine are small, being ~30 mg, and can rapidly be depleted in patients misusing alcohol. Reduced nutrient supply due to a poor diet is exacerbated by vomiting and diarrhoea. Liver damage reduces the storage of the vitamin, and malabsorption of thiamine due to alcohol and malnutrition expedites the decline, often rendering treatment by oral thiamine inadequate (Thomson et al., 1971; Thomson, 2000). Failure to treat deficient patients with therapeutic amounts of thiamine (IV/IM) is an important cause of WE.

Thiamine diphosphate acts as a co-factor for a number of thiamine-dependent enzymes. Thiamine deficiency leads to a reduction in the activity of these enzymes, and this further leads to alterations in mitochondrial activity, impairment of oxidative metabolism, decreased energy status and eventually selective neuronal death.

Preliminary findings indicate that some individuals are probably genetically predisposed to develop WE. Two genes involved in the cellular transport of thiamine have recently been established: SLC19A2 thiamine transporter-1 (THTR1), the high-affinity transporter, and SLA19A3, the low-affinity transporter (THTR2). Our preliminary work has identified changes in the genes of some WE patients that could potentially affect gene expression (Guerrini et al., 2005, 2009a).

Subsequently, Subramanian et al. (2010) have reported that chronic alcohol consumption in rats fed a Lieber–DeCarli diet showed a decreased carrier-mediated thiamine transport across the renal brush-border and baso-lateral membranes and in transcriptionally mediated inhibition of the THTR1 and THTR2 expression. In addition, the expression of thiamine pyrophosphokinase (TPKase), the rate-limiting enzyme in the synthesis of the coenzyme form of thiamine was modestly, but significantly reduced. They also found that chronic alcohol administration reduced intestinal thiamine absorption in the rat which is accompanied by a decrease in transcription and expression of the SLA19A2 and SLA19A3 genes (Subramanya et al., 2010).

It was recently estimated that, at any given time, there are more than 3 million people in the UK who are either malnourished or at risk of being malnourished. The vast majority of these individuals (93%) live in the community. This problem is not adequately recognized since the number of malnourished people leaving NHS hospitals in England has risen by 85% over the past 10 years. A recent report indicated that, in 2006–2007, almost 140,000 patients left hospital with their malnutrition left uncorrected (British Association for Parenteral and Enteral Nutrition, 2009).
considered at high risk of incipient WE, less than one-third of hospitals were found to give the Royal College of Physicians recommended starting high-dose regime of two pairs of vials (four vials) of Pabrinex intravenously thrice daily for 3 days (Ward et al., 2009).

The new NICE guidelines (NICE, 2010) are helpful, but unfortunately the treatment recommendations are not clearly or simply stated. For instance, they use terms such as ‘offer’ instead of ‘administer’ and advise giving doses of thiamine ‘towards the upper end of the British National Formulary range’, rather than giving specific dosing recommendations. There is therefore still considerable risk that patients in need of parenteral thiamine will go untreated. Given the circumstances of most patients who present acutely with potential WE, time is of the essence. Immediate rational discussion is often impossible due to intoxication or underlying medical problems such as seizures. In these circumstances, clinicians working at the frontline of care need clear guidance.

In the UK, we need to adopt and use a single risk assessment tool with clear treatment guidelines. This could be readily developed using a care bundle approach at the point of entry to care.

The Alcoholic Korsakoff Syndrome: Clinical, Neuroimaging and Neuropsychological Findings
Michael Kopelman
Academic Unit of Neuropsychiatry, Institute of Psychiatry, King’s College London, UK

The amnesic syndrome may be defined as ‘an abnormal mental state in which memory and learning are affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient’ (Victor et al., 1971). In the alcoholic Korsakoff syndrome, this results from nutritional, i.e. thiamine, depletion.

The Korsakoff syndrome may, or may not, follow an acute Wernicke encephalopathy. In other cases, the patient may emerge from coma or a confusional state (secondary to, for example, a chest infection or head injury), and then is found to be suffering a Korsakoff syndrome. In yet other cases, there is an insidious onset of memory disorder with perhaps just transient Wernicke episodes in the community. Various sources have found that 12 to 15% of alcoholics manifest the classical Wernicke–Korsakoff neuropathology at autopsy, but many such cases have never been diagnosed in life (Kopelman et al., 2009).

Many of the classical features of the Korsakoff syndrome were described by Korsakoff (1889) himself. These features included the severe amnesia in someone ‘in complete possession of his [or her] faculties’, who can still make witty remarks, play chess or a game of cards. There is a dense anterograde amnesia and a variable retrograde amnesia, which often extends back 20–25 years with what is known as a ‘temporal gradient’ (relative sparing of early memories).

Autopsy studies show loss of neurons, gliosis and microhaemorrhages in the paraventricular and peri-aqueductal brain regions. This is often (but not always) accompanied by cortical atrophy, especially in the frontal regions. There is a loss of large neurons in frontal cortex, the hypothalamus and cerebellum, and a loss of pre-frontal white matter. There is also neuronal dendritic shrinkage. There has been extensive debate over what is the critical lesion giving rise to the persistent memory impairment, and this is now thought to be within the pathway encompassing the anterior thalamic nuclei, the fornix and the mammillary bodies. Many of these structures can show signal alteration in the acute Wernicke phase on MRI (Sullivan and Pfefferbaum, 2009). In the chronic (Korsakoff) phase, the volume loss can be demonstrated, particularly in the thalami and mammillary bodies (Colchester et al., 2001; Sullivan and Pfefferbaum, 2009). PET changes in glucose uptake have been demonstrated in the thalami, orbito-medial region and retro-splenial cortex (Reed et al., 2003).

The neuropsychological deficits in anterograde episodic memory show correlations with the degree of atrophy in these brain regions, but the nature of the retrograde amnesia remains hugely controversial. There is at least some evidence that it relates more to superimposed frontal lobe atrophy and executive dysfunction than to the diencephalic pathology per se.

Also of great interest and controversy has been the nature of confabulation. In fact, the so-called ‘spontaneous confabulation’ is seen only in a minority of patients in the chronic phases of the Korsakoff syndrome. Evidence during the last 15 years suggests that this type of confabulation results from pathology in a relatively small region of the ventro-frontal and orbito-medial frontal cortex. At a psychological level, such confabulation has been attributed to (i) faulty mechanisms involved in the temporal sequencing of memories; (ii) problems in specifying and verifying (editing) the traces retrieved; (iii) motivational factors—a bias towards retrieving memories from a happier/more pleasant time and (iv) some combination of these factors.

Cognitive and Emotional Dysfunction in Alcoholics: Possible Brain Mechanisms
Theodora Duka
School of Psychology, University of Sussex, UK

It is well established that alcoholic patients experience increased severity of withdrawal with repeated cycles of abstinence. Although the incidence and intensity of seizures have been the most common dependent variables studied in relationship to multiple withdrawals from alcohol (Ballenger and Post, 1978; Brown et al., 1988; Lechtenberg and Worner, 1990), there is also evidence for more general changes in brain function after repeated withdrawals.

Clemmesen et al. (1988) reported enhanced metabolic activity in the limbic and cortical brain areas of rats after repeated withdrawals and, more recently, Stephens et al. (2001) reported that animals that had undergone repeated withdrawal from alcohol showed a deficit in learning associations between neutral stimuli and aversive events; furthermore, they were unable to discriminate a safe stimulus that does not predict an aversive event if this stimulus has properties in common with the conditioned stimulus (Stephens et al., 2005). In addition, using slices of lateral amygdala from the animals which had undergone repeated withdrawal, a reduced capacity for long-term potentiation (LTP) was found, consistent with the reduced ability for associative learning following repeated periods of alcohol exposure. Impaired associative learning was also found in alcoholic patients (Stephens and Duka, 2008) and binge drinkers when compared with their matched counterparts. Associative
learning in these populations was tested using a fear potentiation startle (Stephens et al., 2005); both bingers and alcoholic patients were unable to discriminate between a stimulus which was predicting an unpleasant event, and a safe stimulus. These data taken together support the findings from early studies showing that repeated withdrawal leads to a dysfunction of amygdala (withdrawal-induced kindling of the amygdala (Pinel et al., 1975)) and the findings by McCown and Breese (1990) that multiple withdrawals lead to impaired transmission in the amygdala. Amygdala dysfunction seen with repeated withdrawal from alcohol may be due to changes in the glutamatergic function during withdrawal. Chronic alcohol administration in animals leads to increased glutamate dialysate in amygdala which is further increased under acute alcohol administration (Roberto et al., 2004). Furthermore, Roberto et al., (2006) showed that chronic alcohol administration leads to compensatory upregulation of NMDAR receptors giving rise to increased NMDAR function in alcohol withdrawal contributing to hyperexcitability and probably to neuronal damage.

Impairments in amygdala function as a consequence of multiple withdrawals might also be consistent with our findings with alcoholic inpatients, who had undergone more than two medically supervised detoxifications, that more fear is seen in all facial expressions (Townshend and Duka, 2003) and that this exaggerated fear shows a positive relationship to the number of alcohol detoxifications. The purpose of the Townshend and Duka (2003) study was to measure deficits in decoding or overestimating an emotion from facial emotional expressions. The stimuli used were picture morphs in 90:10 and 50:50 proportions of the two emotions next to each other in the sequence of happiness, surprise, fear, sadness, disgust and anger (Townshend and Duka, 2003). Subjects had to rate how much of each of the six emotions could be seen in the picture of the morph. The scores for fear perception in the morphs were higher in the patients than in controls, indicating an exaggerated perception of fear in the patient group. In addition, the more exaggerated the perception of fear in the morphs, the more detoxifications the subjects had experienced (Pearson correlation coefficient, 0.577; P = 0.05).

Neuropsychological and functional imaging studies have highlighted the role of the amygdala in the recognition of facial expressions of fear (Calder et al., 2001) and the enhanced fear recognition found in alcoholic patients might be related to withdrawal-induced kindling of the amygdala.

Impairments in cognitive function as a result of alcohol abuse are well established. Because (as noted above) exposure to previous detoxifications may accelerate disruption of the amygdala function, it is plausible to suggest that previous detoxifications may impair cognitive function through damage of this area and of its connections. Several morphological abnormalities in the frontal lobe system in alcoholics have been reported (Moselhy et al., 2001), and animal studies have provided evidence of increased brain damage after multiple withdrawals from alcohol or when repeatedly high amounts of alcohol in the brain are followed by periods of abstinence (Obernier et al., 2002a, b). We have examined cognitive impairment and its relationship to previous experiences of withdrawal in an alcoholic inpatient population undergoing alcohol detoxification (Duka et al., 2003). We used tasks that measure the ability to disinhibit a prepotent response and the ability to wait before a response to receive a reward. Compared with a group of 43 social drinkers, the alcoholic patients (n = 42) produced more commission errors in the vigilance task and were unable to wait for a reward, both measures demonstrating impulsive behaviour.

Thus, in summary, alcohol dependence (associated with multiple detoxifications) is associated with impaired aversive conditioning leading to inappropriate emotional responses. Alcohol dependence is also associated with increased fear perception in facial emotional expressions and impulsive behaviour. There is evidence that amygdala and prefrontal dysfunction may be associated with these emotional and cognitive changes. Facilitated transmission in the amygdala and reduced inhibitory control may increase responsiveness to previously conditioned stimuli including alcohol-related cues, leading to relapse. Impaired learning may lead to failure to learn from the consequences of abuse and inability to inhibit an inappropriate response or more generally impulsive behaviour may lead to excessive alcohol drinking.

PART II: UNRECOGNIZED CLINICAL NEED AND CONSEQUENCES

Alcohol Misuse in Pregnancy
Irene Guerrini
South London & Maudsley NHS Foundation Trust, London, UK

The toxic effects of ethanol on the foetus are well known. However, controversy still persists on how much it is 'safe to drink' during pregnancy, and whether low doses of ethanol are dangerous for the foetus.

Alcohol Misuse and Foetal Brain Neurotoxicity
An extensive experimental and clinical literature shows that alcohol misuse results in foetal brain neurotoxicity associated with life-long behavioural, social and cognitive impairments (Guerrini et al., 2007). It is true that only a small proportion of children born to mothers with alcohol misuse fulfil the diagnostic criteria for foetal alcohol syndrome (FAS), including facial dysmorphism, growth retardation and central nervous system (CNS) dysfunction (Guerrini et al., 2009). Associated anatomical abnormalities may range from a reduction in brain volume to a decrease in cell numbers and neural connections which occur in particular brain regions such as the corpus callosum, the hippocampus and the cerebellum (Guerrini et al., 2009).

No consensus has been reached, as yet, regarding the clinical definition of the foetal alcohol spectrum disorders (FASD) phenotypes. Several behavioural and cognitive abnormalities have been reported including hyperactivity and attention deficits, deficits in motor coordination, lack of control of social behaviour, poor psychological functioning and impairment in verbal fluency, spatial memory and impaired mathematical abilities (Riley et al., 2005; Guerrini et al., 2009).

Animal studies have shown that heavy ethanol intake during the brain growth spurt in the early postnatal period (corresponding to the third trimester and early infancy in humans), significantly reduces the weight of forebrain, brain stem and cerebellum (Guerrini et al., 2009). Furthermore, the
effect on the foetal brain of binge-like exposure has also been extensively analysed. Several authors reported that even a single exposure to a high dose of ethanol in infant rodents during synaptogenesis may cause a significant neuro-apoptosis (Olney, 2004; Wozniak et al., 2004).

**Alcohol Misuse Management in Pregnancy**

The clinical management of alcohol dependence is complex and multidisciplinary. Several researchers have shown the efficacy of brief intervention as a technique to help pregnant women to achieve abstinence from alcohol (Carson et al., 2010). The brief intervention approach can be offered by GPs, practice nurses and midwives in antenatal clinics (Guerrini et al., 2009b). A fundamental role is played by antenatal clinics working in partnership with addiction and social services, with liaison midwives acting as bridges between the professions (Carson et al., 2010).

Abrupt cessation of drinking in alcohol-dependent individuals is not recommended, as withdrawal symptoms can threaten mother and baby. Alcohol detoxification should be carried out in an inpatient setting to allow monitoring of maternal and foetal well-being (Guerrini et al., 2009b).

Guidelines for the management of in-patient alcohol detoxification suggest the use of short-acting barbiturates or benzodiazepine compounds. Chlordiazepoxide and other benzodiazepine compounds such as diazepam are the drugs of choice for symptomatic treatment during medically assisted withdrawal from alcohol. Since both benzodiazepines and barbiturates are potentially teratogenic, their use is recommended after the first trimester of pregnancy (Guerrini et al., 2009b).

Nutritional deficiencies are common in alcohol-dependent individuals due to poor nutrition, malabsorption and vomiting. In pregnancy, vitamin-B-complex deficiencies (folic acid, thiamine, pyridoxine etc.) can have serious consequences for the mother and the baby. For instance, the Wernicke–Korsakoff syndrome is a serious complication of hyperemesis gravidarum (Guerrini et al., 2007). Therefore, the use of B complex vitamins is highly recommended during alcohol detoxification and in the following months post-detoxification especially if weight loss, frequent vomiting and diarrhoea are reported (Guerrini et al., 2007).

**Conclusions**

More epidemiological studies are needed to evaluate the effects of heavy drinking. Screening, identification, brief intervention and correct clinical management are all important aspects of the care pathway. Brief intervention is a widely used, cost-effective approach in the management of hazardous/harmful drinking while medically assisted, in-patient alcohol detoxification is highly recommended for alcohol-dependent pregnant women.

**The Effects of Alcohol on the Adolescent Brain**

Matt Field

School of Psychology, University of Liverpool, Liverpool, UK

Among adolescents, evidence points to an association between heavy drinking and structural brain changes, with accompanying cognitive impairment. Adolescent heavy drinkers show reduced white matter integrity in the corpus callosum, and reduced hippocampal volumes, compared with controls (Tapert et al., 2004). Heavy drinking adolescents also show impairment in neurocognitive tests, including those which measure memory, attention, visuospatial skills and executive function. Reduced blood flow to frontal areas and the cerebellum during performance of spatial working memory tasks suggest a mechanism through which underlying structural changes might translate into functional deficits during cognitive tasks (Tapert et al., 2004). Although these structural and functional changes associated with heavy drinking during adolescence are similar to those observed in adult heavy drinkers, it has been suggested that alcohol may be more neurotoxic to the developing adolescent brain than it is to the mature adult brain (Nixon and McClain, 2010). Recent animal work demonstrates that high doses of alcohol administered in a ‘binge’ pattern to adolescent rats led to marked cell death in brain regions, including the hippocampus and cerebellum; these deficits were associated with impairments in discrimination learning that persisted until at least 3 weeks after the last dose of alcohol was administered (Pascual et al., 2007). In terms of direct comparisons between adolescent and adult rodents, one study demonstrated that the neurotoxic effects of high doses of alcohol were substantially larger when administered to adolescent rats as compared with when administered to adult rats (Crews et al., 2000). However, although alcohol seems to be particularly neurotoxic to adolescents, it is important to note that many of the cognitive deficits associated with heavy drinking, such as executive dysfunction, may occur premorbidly, and act as a risk factor for the development of heavy drinking later on in adolescence (e.g. Wong et al., 2006). Further laboratory work with animals, and longitudinal work with human adolescents, is required to untangle the extent to which structural and functional changes associated with heavy drinking are a consequence of heavy drinking, or represent a risk factor that can be detected prior to the onset of heavy drinking.

**The Case for an ARBD Service**

Kenneth Wilson

Division of Psychiatry and NIHR Comprehensive Local Research Network, University of Liverpool, UK

Despite the recognized need, rarely does a single service take responsibility for ARBD patients (Leenane, 1986; Price et al., 1988). A recently commissioned study of ARBD patients in England and Wales (Boughey, 2007) highlights a lack of diagnostic expertise, general medical and nursing staff ignorance, no evident pathways of care with patients being ‘passed from pillar to post’, stigma and lack of resources with direct impact on the length of stay in acute hospital settings and increasing unplanned re-admission (Popoola et al., 2008). Cox et al. (2004) estimated that, in the context of service provision, 25% of patients make a full recovery, 25% make a partial recovery, 25% make minor recovery and the remainder shows no improvement at all.

The Cheshire and Wirral Partnership Trust and Wirral PCT have commissioned the first specialized service in England, which caters for a total population of 300,000 and takes referrals from acute hospital wards. At any one time,
Alcohol-related brain damage is common and often challenging to manage. The reviews demonstrated that the impact of alcohol on brain function is quite well characterized in terms of which parts of the brain are commonly affected and how this results in cognitive and behavioural difficulties. Indeed, it is often the ‘silent’ contributor to other dementias that gets ignored. So, whilst diagnosis may not be a problem, management certainly is, particularly in young individuals, because services, if they exist, are generally geared towards more elderly populations. Their alcohol misuse also often makes them unsuitable for services for young people with head injuries. With a few exceptions, borne out of determination and drive of an individual, services with expertise to manage ARBD are rare.

Conclusion

Anne Lingford-Hughes

Neuropsychopharmacology Unit, Department of Medicine, Imperial College London, UK

ARBD is common and often challenging to manage. The increasing numbers of such individuals, and their tendency to present to acute medical services, leads to subsequent difficulties in setting up appropriate arrangements for long-term care. Services for this group need to be better coordinated. Following recommendations made by the Scottish Alcohol Action Plan and the Scottish Dementia Centre (Cox et al., 2004), services are being established in areas with highest need. There have also been a number of examples of poor practice (Mental Welfare Commission for Scotland, 2006).
Given how common it is, this is a tragedy and a missed opportunity. So, can we do more to prevent it, or at least treat it more effectively? Whilst adding thiamine to alcoholic drinks has been mooted, as Thomson et al. state, this approach is unlikely to ameliorate thiamine deficiency and raises ethical issues.

It is striking that other than thiamine there is little research into the causes of ARBD. The role of neuroinflammation in a number of neuropsychiatric disorders is currently receiving much attention. As described by Field in his review, preclinical models have shown inflammatory changes from binge-type drinking and significantly this could be reduced by an anti-inflammatory (Pascual et al., 2007). Research is just beginning to characterize the role of inflammatory factors in alcoholism though alterations in peripheral markers have been demonstrated. Whilst drinking is harmful to the brain, alcohol withdrawal is a toxic time for the brain. Here, hyperglutamatergic states appear key and preclinical models have shown that ‘anti-glutamatergic’ compounds can reduce cell death. Some clinicians therefore use more ‘anti-glutamatergic’ drugs during alcohol withdrawal, e.g. anticonvulsants, or add in acamprosate rather than solely ‘GABAergic’ drugs such as benzodiazepines. Inflammatory processes, thiamine deficiency and glutamatergic systems are all inter-linked. Given that prevention of ARBD is unlikely given it is best achieved by stopping harmful alcohol use, how can we treat it better—other than abstinence? Given withdrawal is toxic, maybe a ‘super pill’ containing drugs to reduce inflammation, replace vitamins, reduce glutamate and boost GABA would be advantageous? As the underlying neurobiology of these inter-linked systems becomes clearer, promising pharmacological targets will be realized improving our approaches to managing ARBD. This will hopefully improve recovery in a greater number of people with ARBD, thus improving their quality of life as well as reducing the burden on their family and friends in addition to acute ill-equipped services.

REFERENCES


NICE (2010) Alcohol Use Disorders: Diagnosis and Clinical Management of Alcohol-Related Physical Complications. NICE Clinical Guideline CG100. London: NICE.


NICE (2010b) Alcohol-Use Disorders: Diagnosis and Clinical Management of Alcohol-Related Physical Complications. Clinical Guideline 100. London: NICE.


Alcohol-related brain damage


Smith I (2012) Alcohol related brain damage in the longer term: Scottish initiatives to maximise recovery. Alcohol Alcohol (this paper).


Wilson K (2012) The case for an ARBD service. Alcohol Alcohol (this paper).

