Adverse physical effects of alcohol misuse

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Abstract   This article outlines the majority of the adverse physical effects that have been described secondary to the consumption of alcohol at levels above recommended sensible limits. These conditions are cited according to the organ system they belong to. Only brief descriptions are provided because of the vastness of this topic. The underlying pathophysiology of tolerance and withdrawal is touched upon as this is of relevance to the psychiatrist. Definitions of the terms used describing alcohol misuse, and sensible upper limits of alcohol consumption are also mentioned.

It has been estimated that 38% of men and 16% of women (aged 16–64) in the UK consume more alcohol than the recommended sensible limit, and about 1.1 million, or 3.6% of the adult population (6% of men, 2% of women) are thought to be dependent on alcohol (Alcohol Needs Assessment Research Project, 2005). The annual cost of alcohol-related crime and public disorder in the UK has been put at up to £7.3 billion, workplace costs at up to £6.4 billion and healthcare costs at £1.4–1.7 billion (Prime Minister's Strategy Unit, 2003). As well as this very significant public cost there are direct effects on the individual, with alcohol causing around 60 different types of disease and condition (Anderson & Baumberg, 2006). These are usually divided into the psychosocial and the physical, with obvious overlaps. Consumed in moderation, alcohol has a number of beneficial effects, but this article describes only the detrimental physical effects of alcohol misuse. In keeping with the nature of *APT* articles we have not exhaustively referenced every result discussed here. A full list of references is available from us on request.

Definitions within alcohol misuse

Definitions of the disorders covered by the term alcohol misuse in the UK vary slightly between sources, including the World Health Organization, the Department of Health and the medical Royal Colleges.

Hazardous ('at-risk') drinking

This term is used to describe an alcohol intake that is likely to increase the individual's risk of developing alcohol-related harm. The most frequently quoted amount is a weekly alcohol consumption of 22–50 units for men and 15–35 for women.

Binge drinking (more than 8 units in any single day during the previous week for men, and more than 6 units for women) is also included in this category, if the individual does not fulfil the criteria for harmful drinking.

Harmful ('problem') drinking

In harmful drinking there is clear evidence that alcohol use is responsible for (or substantially contributes to) physical or psychological harm, including impaired judgement or dysfunctional behaviour which may lead to disability or have an adverse consequence for interpersonal relationships (World Health Organization, 1992). A Working Party of the Royal College of Psychiatrists and the Royal College of Physicians (2000: p. 5) describes a weekly alcohol consumption of over 50 units for men and over 35 units for women as 'definitely harmful'.

Alcohol dependence syndrome

The definition of alcohol dependence is widely known and clearly defined in ICD–10 (World Health Organization, 1992).

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> **Box 1 Symptoms of moderate intoxication (blood alcohol level of 50–150 mg/dl)**
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> - Impaired sense of time and space
> - Poor coordination
> - Reduced reaction times
> - Poor concentration
> - Memory difficulties
> - Impaired judgement
> - Pinpoint pupils
> - Conjunctival injection

Sensible limits of alcohol consumption

The Department of Health (1995) advises that regular consumption of 3–4 units a day by men (2–3 units by women) of all ages, with two alcohol-free days a week, will not accrue any significant risk. These limits have been derived partly from evidence-based research and partly from expert opinion.

Acute effects of bingeing and alcohol poisoning

Binge drinking can lead to a rapid increase in blood alcohol concentration (due to rapid absorption, distribution and zero-order kinetics) and consequently to 'drunkenness'.

In adults who do not drink regularly, relatively low blood alcohol levels (50–150 mg/dl) result in intoxication in which all modalities of perception are adversely affected (Box 1).

Severe intoxication (300–500 mg/dl) is associated with further deterioration in these symptoms and a number of more serious physical reactions (Box 2). The depression of vital centres in the central nervous system (CNS) can result in stupor, respiratory failure, hypotension or cardiac arrest. Hypoglycaemia, as described below, typically occurs within 6–36 h of consumption of alcohol. Coma generally occurs with blood alcohol levels greater than 500 mg/dl.

Death may occur from respiratory or circulatory failure, or from aspiration of gastric contents. Cardiac arrhythmias are another potentially fatal complication of an alcohol binge.

In individuals who have built up tolerance of alcohol, all of these CNS symptoms may still occur but at higher blood alcohol levels.

The acute effects of alcohol consumption on other organ systems are outlined in the sections below on the respective organs.

> **Box 2 Additional symptoms of severe intoxication (blood alcohol level of 300–500 mg/dl)**
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> - Depression of consciousness and of the respiratory and cardiac centres
> - Depressed reflexes (including the gag reflex)
> - Hypothermia
> - Hypoglycaemia with or without convulsions
> - Cardiac arrhythmia
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> *Rarely:*
> - Lactic acidosis
> - Ketoacidosis
> - Acute renal failure

Effects of long-term alcohol misuse

The liver

Alcohol is the most common cause of liver injury in high-income countries. Since the early 1970s, deaths due to cirrhosis (which is an important population marker of alcohol misuse) have been rising at an increasing rate in the UK, particularly in Scotland, in both men and women of all ages. This is in contrast to the rest of Western Europe, where corresponding mortality rates in all groups have been steadily decreasing (Leon & McCambridge, 2006).

Alcohol causes three types of liver injury: fatty liver (or steatosis), alcoholic hepatitis and cirrhosis.

Fatty liver

Fatty liver is the initial and most common finding in heavy drinkers. It is characterised by the accumulation of triglyceride in hepatocytes. It is asymptomatic and presentation is usually through incidental biochemical tests showing abnormal liver function. The prognosis of fatty liver is benign provided that patients abstain from alcohol. However, up to 30% of patients who continue to drink progress to cirrhosis within 10 years.

Alcoholic hepatitis

Alcoholic hepatitis is characterised histologically by steatosis, the presence of hepatocyte injury, a neutrophil infiltrate and pericellular ('chicken-wire') fibrosis. Similar features are seen in several other conditions, including obesity and diabetes, in which they are called 'non-alcoholic steatohepatitis'. Presentation can be asymptomatic, but severe alcoholic hepatitis often presents with painless jaundice on the background of heavy alcohol consumption.

Cirrhosis

Cirrhosis is characterised histologically by collagen deposition in a perisinusoidal distribution enveloping hepatocytes. Patients can present with symptoms of reduced synthetic liver function and/or symptoms of portal hypertension. Up to 90% of deaths in patients with alcoholic cirrhosis are liver-related; 33% of these are caused by hepatocellular carcinoma.

Although most heavy drinkers develop fatty liver, only around a third will develop advanced fibrosis or cirrhosis. The reasons for this are unclear. Alcohol dose and the pattern of drinking, body weight, the presence or absence of type II diabetes, and gender have all been implicated as possible risk factors. Specific genes have also been described in the literature as affecting susceptibility to developing alcoholic cirrhosis.

For a comprehensive review of the hepatic effects of alcohol misuse the reader is referred to Stewart & Day (2006).

The gastrointestinal tract

As the first site of exposure after alcohol ingestion, the gastrointestinal system is a prime candidate for toxicity (Box 3). Mortality from gastrointestinal side-effects is low, however, compared with morbidity.

The direct toxic effects of alcohol, as well as indirect effects due to nutritional deficiencies (B vitamins, vitamin C and iron) associated with long-term alcohol misuse, can cause stomatitis in the lips and glossitis in the tongue. The salivary glands can be affected, with reduced salivary production and adiposity in the parotid glands, resulting in their bilateral enlargement. The oropharyngeal mucosa can become chronically inflamed, resulting in leukoplakia, erythroplakia and submucous fibrosis (Elwood *et al*, 1984). These pre-cancerous lesions have malignant transformation rates of between 3% and 16%, generally becoming squamous cell carcinomas. Oral lichen planus, but not cutaneous lichen planus, is also associated with chronic alcohol misuse. Rarely, the erosive variety may also undergo malignant transformation.

Reduced clearance, changes in oesophageal sphincter pressures (lower sphincter pressures in the acute situation, and increased lower oesophageal pressures in chronic drinking), painful spasms ('nutcracker' oesophagus) and increased gastro-oesophageal reflux disease all occur in the oesophagus. Nausea and vomiting are frequently associated with alcohol misuse and may induce Mallory–Weiss tears. Gastritis and duodenitis can both be sequelae to alcohol misuse. Peptic ulcers have in the past been associated with alcohol misuse; however, more recent studies suggest that the prevalence is the same in people

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Box 3 Gastrointestinal effects of alcohol misuse

- Stomatitis
- Glossitis
- Reduced salivary production
- Enlarged adipose parotid glands
- Leukoplakia, erythroplakia and submucous fibrosis of oropharyngeal mucosa
- Oral lichen planus
- Disrupted oesophageal function
- Gastritis and duodenitis
- Oesophageal and gastric varices
- Malnutrition due to altered small bowel function
- Acute and chronic acute pancreatitis

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with and without alcohol dependence, although alcohol remains an accepted exacerbating factor of peptic ulceration. Oesophageal and gastric varices may occur secondary to portal hypertension.

Alcohol is one of the main causes of malnutrition in the Western world. Although pancreatic and hepatic dysfunction can play a role, particularly in fat malabsorption, the most important cause of malabsorption is probably altered small bowel function. The most significant deficiencies are of thiamine, niacin and vitamin C, resulting in Wernicke–Korsakoff syndrome and beri-beri (typically dry), pellagra, and symptoms of scurvy respectively. Significant increases in motility in both the small and the large bowel result in reduced transit time and diarrhoea (Keshavarzian *et al*, 1986).

Alcohol is second only to biliary disease as a leading cause of acute pancreatitis. It is also an important cause of chronic pancreatitis. Pancreatic exocrine insufficiency is common and, occasionally, endocrine insufficiency can also result.

The cardiovascular system

Acute and chronic alcohol ingestion can have a variety of often underestimated deleterious effects on the cardiovascular system (Box 4). Almost 50% of the excess deaths occurring with alcohol misuse

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Box 4 Effects of alcohol on the cardiovascular system

- Systolic and diastolic hypertension
- Stroke
- Non-ischaemic, dilated cardiomyopathy
- Cardiac arrhythmias

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are attributable to circulatory disease rather than to liver disease (Ashley & Rankin, 1980).

Alcohol is a common cause of both systolic and diastolic hypertension. The attributable risk for hypertensive disease has recently been estimated to be 16% (Puddley & Beilin-Lawrence, 2006), with women apparently less susceptible.

All types of stroke have been associated with drinking, especially with binge drinking (Puddley & Beilin-Lawrence, 2006). This is perhaps not surprising in view of the association between alcohol and most of the established stroke risk factors, including hypertension, cardiomyopathy, arrhythmias, diabetes and cigarette smoking (Taylor, 1982).

It has been recognised since the early 1960s that long-term, heavy alcohol consumption is the main cause of a non-ischaemic, dilated cardiomyopathy ('beer-drinker's heart'). Initially this was attributed to nutritional deficiencies, but the prevailing opinion now is that excessive alcohol intake over many years can directly lead to the development of an alcoholic cardiomyopathy.

Heavy drinking increases the risk of cardiac arrhythmias regardless of whether or not heart disease is present. Atrial fibrillation is the best-known arrhythmia secondary to alcohol misuse ('holiday heart syndrome'), but supraventricular and ventricular tachycardias also occur. Factors that may play a role in alcohol's arrhythmogenic effect include the possible presence of a subclinical cardiomyopathy producing conduction delays, potassium and/or magnesium depletion, the hyperadrenergic state accompanying alcohol withdrawal, autonomic neuropathy and a direct effect of ethanol on cardiac conduction (Greenspon & Schaal, 1983).

Although alcohol has protective effects against coronary heart disease when drunk in moderation, when consumed in levels greater than 20 g (2.5 units) per day (the level of alcohol consumption with the lowest risk of coronary heart disease) alcohol increases the risk (Anderson & Baumberg, 2006).

The respiratory system

At high doses, alcohol decreases respiratory rate, airflow and oxygen transport, hence increasing many symptoms of pulmonary disease (Box 5).

One of the most serious complications of alcohol binges is aspiration pneumonia, which usually occurs secondary to the obtunded state that alcohol can induce. Gamma-aminobutyric acid (GABA) is the main CNS inhibitory neurotransmitter and alcohol's depressant effect on consciousness occurs mainly through activation of the GABA system. This effect is largely mediated through the 'long' form of the γ_2 subunit of the $GABA_A$ receptor. At low levels alcohol potentiates the effect of GABA at its

> **Box 5 Alcohol's effects on the respiratory system**
>
> - Aspiration pneumonia
> - Obstructive sleep apnoea
> - Reduced pulmonary defences against infection
> - Acute respiratory distress syndrome

receptor site, and at blood levels over 250 mg/dl it has a direct excitatory action on this receptor. Levels above 300 mg/dl can cause death from respiratory depression (Nutt, 1999). The *N*-methyl-D-aspartate (NMDA) system is also implicated in level of consciousness/arousal. Alcohol inhibits the NMDA receptor at blood levels above 100 mg/dl, and this adds to its CNS depressant effect.

Alcohol consumption is a common cause of obstructive sleep apnoea because of its muscle relaxant effects (affecting the pharynx and laryngeal musculature) and, in the longer term, its effects on obesity. It can also cause central sleep apnoea through its depressant effect on the respiratory centres of the brainstem.

Alcohol reduces key pulmonary defences against infection, including mucociliary clearance; macrophage mobilisation, killing and clearance; and phospholipid metabolism. These actions directly contribute to the increased rates of pulmonary infections (e.g. pneumococcal and Gram negative pneumonias, and tuberculosis) in chronic heavy drinkers.

Long-term alcohol misuse has been known for over a decade to be associated with exacerbation of acute respiratory distress syndrome. A decrease in lung glutathione levels has been proposed as the means whereby increases in oxidative stress, derived from activated neutrophils, results in decreased surfactant production, apoptosis and increased permeability of type II alveolar cells. Ethanol inhibition of prostaglandin E_2 production by alveolar macrophages has recently been demonstrated and proposed as a further cellular mechanism of susceptibility to the syndrome (Wakabayashi & Kato, 2006).

The nervous system

Both acute and chronic alcohol intake are associated with a wide range of effects on the nervous system (Box 6). Alcohol and its metabolite acetaldehyde are almost certainly directly neurotoxic, but associated nutritional deficiencies undoubtedly contribute to the pathogenesis of some, if not all, alcohol-related neurological diseases (Butterworth, 1995).

The acute effects of alcohol intoxication on the CNS have been described above.

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Box 6 Alcohol's effects on the nervous system

- Neurotoxicity
- Alcohol dependence syndrome
- Alcohol withdrawal syndrome
- Seizures
- Cognitive deterioration, leading to Korsakoff's psychosis, Wernicke's encephalopathy and Wernicke–Korsakoff syndrome
- Progressive cerebellar degeneration
- Acute confusional state
- Peripheral neuropathy
- Autonomic neuropathy

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Alcohol dependence syndrome

Alcohol dependence syndrome is a mental rather than a physical disorder and so we will not discussed it in detail. However, we mention it here as some of its biological underpinnings are now known. Dependence on alcohol requires the presence of tolerance, withdrawal symptoms on reduction or cessation of consumption, and subjective cravings, among other criteria.

Estimates of the heritability of alcohol dependence generally vary between 50% and 60%. To date, most of the implicated genes are involved in the metabolism of alcohol, personality traits or neuronal transmission in the GABA, opioid, dopaminergic, cholinergic or serotonergic systems. Some genes have been implicated in predisposing the individual to developing dependence, whereas others are considered to be protective. Such genes interact with other biological, psychological, social and environmental factors in determining the development of alcohol dependence.

On a neurochemical level alcohol dependence syndrome is characterised by neuroadaptation of a number of different types of receptor, the most important being the glutamate and GABA systems. Up-regulation occurs in NMDA receptors secondary to the long-term, direct inhibition of these receptors by alcohol. Long-term, direct excitation of the GABA receptors leads to their down-regulation in alcohol dependence.

Alcohol withdrawal syndrome

Symptoms   In most cases of alcohol withdrawal syndrome the clinical picture is uncomplicated, i.e. without psychotic symptoms, confusion and seizures. The presence of any of these three denotes 'complicated alcohol withdrawal syndrome'. Uncomplicated alcohol withdrawal syndrome commences within 6–8 h of the last drink, and is usually associated with insomnia, anxiety, agitation, headache, diaphoresis, tremor, tachycardia, hypertension, weakness, nausea and vomiting. Many of these symptoms reflect the overdrive of the sympathetic nervous system that occurs during withdrawal. This uncomplicated withdrawal syndrome is short lived.

With more prolonged and heavier alcohol consumption, a complicated and longer withdrawal syndrome may occur. Confusion, altered perception, vivid dreams and seizures may be present. Of note, the hallucinations that occur with complicated alcohol withdrawal syndrome are not the same as those occurring as part of delirium tremens or of alcoholic hallucinosis. They generally develop 24 h after onset of the syndrome, occur in clear and oriented consciousness (unlike the fluctuating levels of consciousness and states of confusion in delirium tremens), and generally disappear after another 24 h. They do not require treatment with antipsychotics (which may exacerbate the clinical situation by reducing seizure threshold). Any distress they cause should be treated by psychosocial means and/or benzodiazepines.

Alcohol withdrawal seizures occur in 5–15% of people with alcohol dependence, 7–48 h (can be up to 72 h) after cessation of drinking (Brennan & Lyttle, 1987). Such seizures are the fourth most common cause of status epilepticus in the general population (after cardiovascular or cerebrovascular accidents and cardiac arrests; medication changes; and anoxia), accounting for just over 12% of cases.

Delirium tremens (confusion, disorientation, altered level of consciousness, delusions, hallucinations, marked tremor, hyperthermia, agitation and profoundly increased sympathetic activity) generally occurs 2–5 days after alcohol cessation and has been shown to occur in 5% of patients with withdrawal syndromes (Victor & Adams, 1953). About 5% of people suffering from 'the DTs' die of acute cardiovascular events, metabolic complications, respiratory failure or trauma.

Mechanisms underlying symptoms   A number of mechanisms underlie substance withdrawal symptoms. Most research has concentrated on the Himmelsbach concept, i.e. that physiological mechanisms developed to maintain homoeostasis in the presence of the substance of misuse are exposed in its absence. As mentioned above, GABA is the dominant inhibitory neurotransmitter in the CNS and is stimulated by alcohol. Activity of the NMDA system is implicated in numerous brain functions, including sensory perception, memory and levels of consciousness, and is inhibited by alcohol. With chronic alcohol misuse, neuroadaptation by NMDA and GABA receptors in the brain (up-regulation of NMDA receptors and down-regulation

of GABA receptors) leads to tolerance while drinking and to relative hyperactivity of NMDA receptors and hypoactivity in the GABA system at times of lowered blood alcohol levels. On acute withdrawal of alcohol this results in excitatory effects via, respectively, an increased calcium flux and a reduced chloride shift in CNS neurons (Nutt, 1999).

Other mechanisms of tolerance and withdrawal include neuroadaptation (up-regulation) in voltage-operated L-type calcium channel receptors, altered magnesium levels, hypercortisolism, changes in the dopaminergic and noradrenergic systems, and de-ranged thyroid hormone levels.

Alcohol-dependent individuals are often mal-nourished to a degree, and as such can become hypomagnesaemic. Magnesium is the brain's natural glutamate antagonist at the NMDA receptor. Hence, individuals with chronic alcohol dependence are even more likely to suffer from marked NMDA hyperactivity during periods of abstinence, resulting in hyperarousal.

Hypercortisolism can occur in chronic alcohol misuse, both while drinking and during withdrawal (discussed below), and it increases levels of excitatory amino acids such as glutamate within the CNS, further leading to tolerance and withdrawal symptoms.

The dopaminergic and noradrenergic systems are both up-regulated in alcohol dependence, thus contributing to tolerance during periods of drinking and to withdrawal symptoms, secondary to their neuronal excitation, when alcohol levels are reduced. Overactivity in the dopaminergic system possibly causes altered perceptions. Overstimulation of noradrenergic neurons during periods of lowered blood alcohol is the cause of well-recognised symptoms such as tremor, diaphoresis, anxiety and agitation, as well as signs such as tachycardia and hypertension. It is further enhanced by both the state of increased glutamate function and the loss of noradrenergic autoinhibition caused by reduced presynaptic α_2 adrenoceptor function (Nutt *et al*, 1988). Thyroid hormones T_3 and T_4 may also be increased during the withdrawal period (Heinz *et al*, 1996) and may further contribute to this adrenergic effect. However, other studies regarding thyroid hormones have found the converse (Ozsoy *et al*, 2006).

Other detrimental CNS effects

Alcohol-related seizures Occurring in association with chronic alcohol misuse, these are defined as adult-onset seizures. The relative risk of developing epilepsy in alcohol misuse has been estimated at 6.8–7.5 (Anderson & Baumberg, 2006). Alcohol lowers the seizure threshold in general. Seizures may occur during binge drinking or during a period of withdrawal (as above). Repeated episodes

of withdrawal symptoms, as may occur during repeated detoxifications, can be detrimental to the CNS, a process known as 'kindling of withdrawal symptoms'. Among other effects, such as increased anxiety, withdrawal seizures have been shown to become more severe with this epileptic kindling effect (Becker & Littleton, 1996). As may be expected, the risk of status epilepticus increases. Proposed mechanisms underlying these harmful kindling effects include repeated bouts of excitatory-induced neuronal cell death, along with repeated episodes of lability of the hypothalamus–pituitary–adrenal (HPA) axis. Other risk factors underlying alcohol-related seizures include structural brain lesions, use of illicit substances and pre-existing epilepsy.

Cognitive deterioration A spectrum of brain damage occurs with long-term alcohol misuse, ranging from mild cognitive deficits, which are relatively common, to full-blown Korsakoff's psychosis. Wernicke's encephalopathy, caused by acute CNS thiamine deficiency (the B vitamins being required for proper glucose metabolism and adenosine triphosphate (ATP) production, as well as for the production of acetylcholine, glutamate and GABA neurotransmitters), is characterised by oculomotor disturbances (lateral gaze nystagmus, palsies of conjugate gaze or complete ophthalmoplegia), cerebellar ataxia affecting the trunk and lower extremities, and mental confusion with or without an impaired level of consciousness. This triad of symptoms is present in only 16% of cases (Harper *et al*, 1986). Presentation usually consists of just one or two symptoms, confusion and drowsiness being the most common (in about 80% of cases). This condition can lead to Korsakoff's psychosis, characterised by a diencephalic amnesia, confabulation and irritability, against a background of an otherwise well-preserved and functioning cognition.

Treatment of Wernicke–Korsakoff's syndrome is with parenteral thiamine during the acute phase but, unfortunately, recovery is incomplete in more than 50% of cases and individuals may be left with devastating memory deficits. It is important to note that thiamine must be given before any glucose during the withdrawal state. This will reduce the likelihood of precipitating a glucose-induced exacerbation of thiamine deficiency while the patient is in a state of neuronal hyperexcitation where thiamine demands are already markedly raised.

Progressive cerebellar degeneration Alcohol misuse is the most common cause of progressive cerebellar degeneration in adults. Typically, there is a relatively pure midline cerebellar degeneration affecting the anterior and superior parts of the vermis and hemispheres. This is characterised clinically by an ataxic gait and truncal ataxia (often worse during

periods of abstinence) while the upper limbs typically remain unaffected (Charness, 1993). Speech is usually unaffected and nystagmus is generally absent. Pathologically there is degeneration of the cerebellar cortex, particularly of the Purkinje cells, and also of the olivary nuclei. Thiamine deficiency is probably the main (but not sole) explanation for the chronic progressive cerebellar syndrome found with long-term alcohol misuse. Individuals with this syndrome are almost invariably malnourished. In most cases the syndrome evolves over a period of several weeks or months, after which it remains unchanged for years. Acute cerebellar degeneration may respond to large doses of thiamine and abstinence from alcohol, but patients usually present long after the onset of their symptoms.

Acute confusional state Alcohol is a very common cause of an acute confusional state, especially in elderly people. Alcohol misuse accelerates shrinkage of the brain, which in turn leads to cognitive decline, in which there is a continuum of brain damage. Alcoholic dementia is a recognised complication of chronic alcohol misuse. Kindling of withdrawal symptoms is implicated in the brain damage of alcoholic dementia. The relative NMDA receptor hyperactivity that occurs after reduction of alcohol intake is considered to be one of the causes of neurotoxicity and ultimately dementia (Nutt, 1999). Frontal lobe dysfunction is particularly prominent with this picture of dementia (O'Malley & Krishnan-Sarin, 1998). Structural changes include dilated lateral ventricles, loss of grey matter both cortically and subcortically, and a thinning of the corpus callosum (Chick, 1997). Both cognitive and structural changes can remit to a certain extent after cessation of alcohol misuse.

Rare complications Marchiafava–Bignami disease and central pontine myelinolysis are both very rare but interesting complications of alcohol misuse that have a mention in almost all textbooks on psychiatry, to which the reader is referred for more details.

Retrobulbar neuropathy has been described as a complication of alcohol misuse. Tobacco-alcohol amblyopia (toxic-nutritional optic neuropathy) is another uncommon consequence of alcohol misuse whereby the patient develops sudden or subacute bilateral visual failure, associated with bilateral centrocaecal scotomas. The condition has been attributed to a disorder of vitamin B_{12} metabolism.

Peripheral neuropathy (typically of the 'glove and stocking' distribution) is another common nutritional complication of alcohol misuse. Other neuropathies, such as polyneuropathy and detrusor neuropathy, may result in part from alcohol withdrawal (possibly through mechanisms similar to those involved in the CNS kindling effect (Jun-Ichi *et al*, 2005)) and

from vitamin deficiencies. Treatment of neuropathies consists of nutritional supplementation, particularly with B vitamins, and abstinence from alcohol. Recovery is slow and often incomplete.

An association between alcohol misuse and autonomic neuropathy is becoming increasingly recognised and has been supported by evidence of an improvement in autonomic function 3 months after successful liver transplantation (Mohamed *et al*, 1996). Importantly, autonomic neuropathy is associated with an adverse prognosis in patients with liver disease, attributed either to an impaired response to stresses or to the associated prolongation of the QT interval and subsequent risk of ventricular arrhythmias (Day *et al*, 1993). As many as 50% of people with alcoholic liver disease experience typical symptoms of autonomic neuropathy, including postural dizziness, abnormal sweating and impotence (Thuluvath & Triger, 1989).

The endocrine system (Box 7)
The pituitary–gonadal axis

Alcohol is thought to down-regulate the pituitary–gonadal axis, resulting in reduced serum levels of luteinising hormone and follicle stimulating

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Box 7 Alcohol's effects on the endocrine system

The pituitary–gonadal axis
Men
- Hypoandrogenisation
- Impotence
- Leydig cell toxicity
- Gynaecomastia

Women
- Menstrual irregularities

Both genders
- Spider naevi

The HPA axis
- Alcohol-induced pseudo-Cushing's syndrome
- Osteoporosis
- Diabetes mellitus
- Hypertension
- Impaired growth, reproductive ability and immune function

Glucose metabolism
- Glucose intolerance
- Hypoglycaemia
- Types I and II diabetes

Adipose tissue
- Modulated hormonal activity

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hormone, and consequently gonadal atrophy. Falls in the serum levels of sex hormones occur, resulting in reduced libido and infertility. Hypoandrogenisation is common in men (due not only to alcohol's effect on the pituitary–gonadal axis, but also to its direct toxic effects on the androgen-releasing Leydig cells of the testes). Impotence and gynaecomastia may also occur. In women, the pituitary–gonadal dysfunction can lead to menstrual irregularities. Hyperoestrogenisation can occur in alcoholic liver disease and may be clinically manifested by gynaecomastia in men and by spider naevi in both men and women.

The HPA axis

Long-term, heavy alcohol misuse is associated with activation of the HPA axis. The physiological and psychological stress induced by alcohol withdrawal may also transiently increase activity of the HPA, although its responsiveness is generally temporarily dampened following alcohol withdrawal. As alcohol-dependent individuals cycle through periods of intoxication and withdrawal, the HPA cycles through hyper- and hypoactivity.

This alcohol-induced cyclical pattern of deranged levels of corticotropin-releasing factor (CRF) and cortisol may induce various pathological states. Alcohol-induced pseudo-Cushing's syndrome has the same clinical and biochemical characteristics as classic Cushing's syndrome, namely moon face, central obesity, muscle wasting, abdominal striae, fatigue, easy bruising and hypertension (Frajria & Angeli, 1977). This syndrome can be indistinguishable from true Cushing's syndrome, except for the fact that it resolves with abstinence from alcohol and may recur if heavy drinking is resumed. Episodes of sustained hypercortisolism may exacerbate osteoporosis, diabetes mellitus and hypertension, as well as impair growth, reproductive ability and immune function. Furthermore, as mentioned above, hypercortisolism accompanying alcohol withdrawal increases excitatory amino acid levels within the CNS, thus exacerbating withdrawal symptoms such as seizures.

Glucose metabolism

Glucose intolerance (pre-diabetes) is frequent among chronic alcohol misusers (up to 40% of alcohol-dependent people). Alcohol and its first metabolite acetaldehyde both inhibit glucose-induced insulin secretion in a dose-dependent manner. Alcohol metabolites have also been shown to increase basal glucagon secretion. Alcohol has been associated with peripheral insulin resistance. Other detrimental effects of alcohol on glucose metabolism are mediated via alcohol-induced increases in corticosteroids, as

well as altered levels of circulating catecholamines (Patel, 1989).

Hypoglycaemia is commonly associated with alcohol misuse. Depleted hepatic glycogen stores, inhibition of hepatic gluconeogenesis and deranged glucocorticoid secretion may all contribute to presentation with severe hypoglycaemia. Patients are often malnourished and are prone to episodes of ketoacidosis which, when compounded with starvation and vomiting, can be life-threatening.

Type I diabetes mellitus is associated with alcohol misuse in both men and women. In view of alcohol's effects on carbohydrate metabolism it is not surprising that long-term misuse is also associated with an overall increased prevalence of type II diabetes. There are conflicting data with regard to alcohol and type II diabetes (Anderson & Baumberg, 2006). Most research supports the view that there is a J-shaped dose–response curve for both men and women, with low alcohol consumption having protective effects against type II diabetes, and higher consumption increasing the risk of developing the disorder. The protective effect of low-dose alcohol (10–20 g/day) may be attributable to the fact that at low doses alcohol increases insulin sensitivity, and this effect is possibly greater in women (Hodge *et al*, 2006). The detrimental influence of higher alcohol consumption arises from its deleterious effects on carbohydrate metabolism, as described above (including insulin resistance at higher blood alcohol levels), as well as to its calorific effect.

Adipose tissue

White adipose tissue, a highly active metabolic tissue and an important endocrine organ producing numerous adipokines, is adversely affected by long-term alcohol misuse (Pravdova & Fickova, 2006). Subsequent alterations in serum levels of leptin, adiponectin, resistin, vascular endothelial growth factor, plasminogen activator inhibitor, tumour necrosis factor and interleukins are all implicated in a vast array of endocrine abnormalities that can ensue.

Other abnormalities

Other endocrine abnormalities described in chronic alcohol misuse include obesity, sodium retention, hypoparathyroidism, hypomagnesaemia, hypocalcaemia, parathormone resistance, hyperuricaemia (secondary to hyperlactacidaemia and the alcohol-induced increase in urate synthesis due to the increased degradation of adenine nucleotides) and gout, and hyperlipidaemia (mainly hyper-triglyceridaemia).

Further endocrine functions adversely affected by alcohol misuse include alcohol-induced lactic

acidosis, haemochromatosis, mildly deranged thyroxine levels (Heinz *et al*, 1996) that are possibly attributable to alcohol-induced dysfunction in the hypothalamic–pituitary–thyroid axis (Liappas *et al*, 2006) and acute crises in the four main porphyrias (porphyria cutanea tarda, acute intermittent porphyria, hereditary coproporphyria and variegate porphyria).

The musculoskeletal system (Box 8)

Long-term alcohol misuse is a risk factor for the development of osteoporosis and osteomalacia, partly attributable to reduced calcium absorption, other nutritional deficiencies, endocrine abnormalities such as hypercortisolism, reduced levels of serum osteocalcin and the direct toxic effects of alcohol on osteoblasts. However, a recent review of the long-term bony effects of moderate alcohol consumption has demonstrated an increase in bone mineral density (Jugdaohsingh *et al*, 2006). Hypothesised mechanisms for this effect include an ethanol-induced inhibition of bone resorption (in a non-parathormone-, non-calcitonin-dependent fashion); the presence of silicon in drinks, promoting bone formation; and the effects of phytochemicals in certain alcohols.

Trauma and falls secondary to alcohol misuse are a very common cause of fractures, especially of the neck of the femur in elderly people.

Alcohol is one of the most common causes of avascular necrosis. The femoral head and condyles, humeral head, and cuboidal bones of the hand and foot are the most commonly affected bones. Fat embolisation has been proposed as the mechanism of subchondral ischaemia in these cases, although other metabolic effects secondary to long-term alcohol misuse (e.g. hyperlipidaemia, hypercortisolaemia and glucose intolerance) will also confer an increased susceptibility. Trauma and falls while intoxicated can also precipitate avascular necrosis.

Acute alcohol poisoning can produce a dramatic toxic myopathy. Symptoms include severe pain and tenderness in the muscles, weakness and oedema. Myoglobinuria may ensue, leading to renal damage and hyperkalaemia, which may precipitate arrhythmias. The condition is reversible if the necessary

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Box 8 Effects of alcohol on the musculo-skeletal system

- Osteoporosis and osteomalacia
- Fractures
- Avascular necrosis
- Toxic myopathy

Box 9 Alcohol's effects on the skin

- Psoriasis and discoid eczema
- Telangiectasias
- Post-adolescent acne
- Superficial infections
- Porphyria cutanea tarda
- Basal cell carcinomas
- Cutaneous stigmata

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intensive support is given. A subacute painless myopathy resolving after withdrawal of alcohol has also been described. Chronic alcohol misuse is commonly associated with a painless myopathy causing weakness and atrophy of the proximal musculature.

The skin

The skin is affected by alcohol misuse (Box 9), both directly and secondary to alcohol-induced changes in immune function and the cutaneous vasculature (Higgins & du Vivier, 1994) and to the associated nutritional deficiencies and liver disease that can occur with long-term alcohol misuse. Psoriasis and discoid eczema are common conditions that are particularly susceptible to these direct and indirect effects. The skin can develop telangiectasias with long-term alcohol misuse. Rhinophyma (acne rosacea) is no longer associated with alcohol misuse, although alcohol remains an accepted exacerbating factor. Post-adolescent acne, superficial infections and porphyria cutanea tarda are all associated with alcohol misuse. All these disorders occur distinct from the cutaneous stigmata of alcoholic liver disease. Allergic skin reactions (type I) are more common in alcoholic liver disease, the mechanism being both direct, through alcohol itself, as well as through raised immunoglobulin E levels. Basal cell carcinomas have also been shown to be more common among drinkers (Fung *et al*, 2002).

The haemopoietic system

The haemopoietic system is frequently adversely affected by heavy alcohol misuse (Box 10). Thrombocytopaenia is the most common associated haematological abnormality. It can be due to hypersplenism or alcohol suppression of the marrow megakaryocytes, as well as to nutritional deficiencies of folate and vitamin B_{12}. Platelet function may also be impaired by chronic alcohol misuse, with reduced thromboxane A_2 production and dysfunctional platelet aggregation. On cessation of drinking, platelet count and function will return to normal within days to weeks.

Box 10 Effects of alcohol on the haemopoietic system

- Thrombocytopaenia
- Impaired platelet function
- Anaemia
- Leucopaenia
- Neutropaenia
- Immunosuppression

A number of different anaemias (microcytic, macrocytic, sideroblastic, spur cell and Zieve's syndrome) as well as generalised leucopaenia (reduced number and functioning of macrophages, neutrophils and T-lymphocytes) are recognised complications of chronic alcohol misuse. Macrocytic anaemia and neutropaenia are caused by a combination of the direct toxic effects of alcohol on the bone marrow, as well as deficiencies of B$_{12}$ and folate. There is also some evidence that alcohol can interfere with neutrophil locomotion and phagocytosis.

Alcohol has acute and chronic profound suppressive effects on both the innate (including adhesion, migration, inflammation and wound healing) and the adaptive (especially antigen processing and presentation) immune responses. As noted above, reduced numbers of immune cells and their dysfunctioning are commonplace among drinkers (Waldschmidt *et al*, 2006).

The urinary system

The acute effects of alcohol on the kidneys and bladder are well-known (Box 11) and include an increased urinary excretion rate secondary to alcohol's inhibitory effect on the secretion of antidiuretic hormone from the posterior pituitary. Urinary incontinence can be a complication, especially in the elderly. Long-term alcohol misuse is associated with water and salt retention, causing an expanded extracellular volume (Vamvakas *et al*, 1998). Impaired renal function, secondary to the long-term effects of

Box 11 Urinary system

Acute effects
- Increased urinary excretion rate
- Urinary incontinence

Effects of long-term misuse
- Water and salt retention
- Electrolyte disturbances
- With severe misuse, acute renal failure

alcohol misuse, also results in a metabolic acidosis, as well as other electrolyte disturbances such as hypomagnesaemia, hypophosphataemia and hypocalcaemia. Severe alcohol misuse predisposes to acute renal failure, as does myoglobinuria, as described above. Rarely, bladder dysfunction occurs with alcohol misuse, possibly secondary to an alcohol-induced neuropathic bladder (Jun-Ichi *et al*, 2005). Urinary retention and abdominal distension can result.

Effects on the fetus and newborn

The Department of Health (2007) now advises that women should completely abstain from drinking throughout pregnancy. This parallels trans-Atlantic advice. The UK's Royal College of Obstetricians and Gynaecologists (2006), however, maintains that there is no evidence for any detrimental effects of light consumption of alcohol (defined as 1 or 2 units of alcohol, once or twice a week) during pregnancy.

Alcohol is both teratogenic and fetotoxic, especially to neural networks. Neural development occurs throughout pregnancy but the most vulnerable period for the fetus is from 4 to 10 weeks of gestation. Proposed mechanisms of fetal neurotoxicity include direct neuronal injury from alcohol and acetaldyhyde, as well as excess apoptotic injury resultant from increased glutamate levels during withdrawal. Other research suggests an alcohol-induced inhibition of cell adhesion molecules, resulting in altered neural migration, fasciculation and synaptogenesis (Charness *et al*, 1994).

Most of the different forms of alcohol-induced damage to the newborn that occur during pregnancy are covered by the term 'fetal alcohol-spectrum disorder' (Hoyme *et al*, 2005). A conservative estimate for the incidence of fetal alcohol syndrome has been put at 0.33 per 1000 live births, with many more children suffering from various alcohol-related effects not amounting to the full syndrome (Abel & Sokol, 1991).

Alcohol has other detrimental effects on the reproductive process and the fetus. These include infertility (in both men and women) and miscarriages, and infant perinatal death, aneuploidy, structural congenital anomalies, prematurity, intra-uterine growth retardation, low birth weight and susceptibility to disease in adult life. There is also limited evidence that paternal consumption of alcohol can have pre-conception epigenetic effects (such as DNA methylation in susceptibility genes and/or their promoter regions) on the newborn, including reduced birth weight, cognitive and behavioural effects, and cardiac malformations (Abel, 2004).

There is some evidence that alcohol may reduce milk production in breast-feeding mothers (Gunzerath *et al*, 2004).

For further information regarding the effects of alcohol on the fetus and for descriptions of fetal alcohol-spectrum disorder see Royal College of Obstetricians and Gynaecologists (2006) and Mukherjee *et al* (2006).

Alcohol and cancer

Results from several large epidemiological studies have firmly established that heavy alcohol consumption is associated with a higher cancer incidence and mortality (Longnecker & Enger, 1996).

There is evidence that moderate alcohol consumption may be slightly protective against cancers, especially among wine drinkers; this may be due to polyphenols such as resveratrol and other flavonoids that are found in alcoholic drinks derived from red grapes. Moderate amounts of alcohol reduce mercury absorption and this may also have a protective effect. However, more recent studies with greater methodological rigour generally find no significant protective effects of alcohol against most cancers (Corrao *et al*, 2004).

Probable mechanisms of carcinogenesis with heavy consumption of alcohol involve its initial metabolite acetaldehyde, which is a reactive compound that forms covalent complexes with proteins and DNA, and thus may act as a mutagen. Alcohol misuse also induces the production of a specific cytochrome P450 enzyme (CYP2E1) that, apart from working with alcohol dehydrogenase to oxidise alcohol, also forms dangerous oxygen species that can activate environmental procarcinogens (Goodsell, 2006). A reduced immune system associated with chronic alcohol misuse leads to increases in infection rates and to reduced immunosurveillance of early tumours, and has also been implicated in alcohol-induced carcinogenesis. Nutritional deficiencies associated with alcohol misuse may also play a role. Furthermore, some alcoholic beverages are made from grains that can be contaminated with moulds that produce carcinogenic mycotoxins.

Alcohol consumption is most strongly associated with cancers of the mouth and oropharynx (relative risk RR≤5.4), followed by laryngeal cancers (RR≤4.9), oesophageal cancer (RR≤4.4) and cancer of the liver (RR≤3.6) (Anderson & Baumberg, 2006). The increased risk is particularly prominent in smokers. Gastric carcinomas are also more prevalent with long-term alcohol misuse. A recent meta-analysis has demonstrated that high alcohol intake is significantly associated with both colon (RR=1.50) and rectal (RR=1.63) carcinomas; this was further quantified as representing an overall 15% increase in risk of colorectal carcinomas for every 12.5 units of alcohol consumed per week (Moskal *et al*, 2007). A large meta-analysis has shown a linear correlation between increased alcohol consumption and increased risk of breast cancer (Hamajima *et al*, 2002). Carcinomas of the nasopharynx, bronchial tree (Freudenheim *et al*, 2005), prostate, ovaries and skin (as described above) have all been reported as being more prevalent among chronic alcohol misusers. Studies have reached conflicting conclusions on the carcinogenic potential of long-term alcohol misuse on the bladder but the largest and most recent to date reports no association (Djousse *et al*, 2004). Controversy over whether or not alcohol may increase the likelihood of pancreatic, endometrial and salivary gland carcinomas remains. Similarly, controversy remains regarding whether or not alcohol consumption confers a protective effect against thyroid carcinomas.

Conclusions

The consumption of alcohol has long been part of everyday life in Western society and it will continue to be so in the future. In moderation there are some potential physical benefits to the individual (such as modest beneficial cardiac effects, mainly restricted to middle-aged men), although more recent evidence suggests that these have probably been over-estimated and are generally offset by harmful effects. However, there is no doubt that alcohol misuse is a serious risk factor for increased morbidity and mortality. The World Health Organization (2004) found that alcohol consumption represents the third largest risk factor for disease burden in high-income countries, behind only smoking and hypertension, both of which are associated with alcohol misuse. The primary causes of excess mortality include liver disease, cardiovascular disease, severe respiratory infections (including aspiration pneumonia), cancer of the upper respiratory and digestive systems, suicide and violence.

In the UK, harmful levels of drinking continue to increase in prevalence, especially among young women. With licensing laws recently becoming more flexible, along with a continuation in the widespread promotion of alcoholic beverages and a reduction in their real price, this trend of increasing alcohol consumption is likely to continue. It is therefore important for doctors to have a comprehensive knowledge of the physical as well as the psychosocial effects of alcohol misuse.

Declaration of interest

None.

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MCQs

1 Alcohol and the liver and gastrointestinal system:

a steatosis is characterised histologically by the accumulation of cholesterol in hepatocytes

b alcohol is the most common cause of acute pancreatitis

c non-alcoholic steatohepatitis can be caused by both obesity and diabetes and shares features with alcoholic hepatitis

d fatty liver is the most common finding in alcohol-dependent people and up to 15% of those that continue to drink will develop cirrhosis within 10 years

e sialorrhoea is a common complication of chronic alcohol misuse.

2 Alcohol and the cardiorespiratory and haemopoietic systems:

a alcohol increases mucociliary clearance of pathogens and particles from the bronchial tree

b up to 33% of the excess deaths associated with alcohol misuse are related to cardiovascular disease

c the dilated cardiomyopathy associated with alcohol misuse is predominantly caused by the nutritional deficiencies that are prevalent

d macrocytic anaemia, thrombocytopaenia and neutropaenia can all be caused by the nutritional deficiencies of folate and B_{12} that may occur in chronic alcohol misuse

e alcohol-induced thrombocytopaenia usually resolves after 3–4 months of abstinence from alcohol.

3 Proposed mechanisms of the withdrawal state include:

a down-regulation of the NMDA receptor system

b hyperaldosteronism

c increased conductance of Ca_{2+} through voltage-gated L-type calcium channels secondary to their up-regulation

d reduced blockade of the $GABA_A$ receptor secondary to hypomagnesaemia

e increased presynaptic α_2 adrenoceptor function.

4 Harmful effects of alcohol in other systems include:

a an alcohol-induced dementia, characterised by parietal lobe and cerebellar dysfunction

b a painful myopathy causing weakness and atrophy of the proximal musculature, commonly associated with long-term alcohol misuse

c avascular necrosis, largely attributable to the vitamin deficiencies associated with alcohol misuse

d dehydration and salt loss as a complication of long-term alcohol misuse, secondary to the long-term effects of alcohol on the secretion of antidiuretic hormone from the posterior pituitary

e dizziness and impotence secondary to autonomic neuropathy.

5 Alcohol and cancer:

a alcohol misuse is associated with an increased incidence of carcinomas of the liver, larynx, lung, oesophagus, colon, breast, bladder and skin

b reduced immunosurveillance has been proposed as a mechanism of alcohol-associated cancer risk

c the liver enzyme CYP4502D6 has been implicated in carcinogenesis associated with alcohol misuse

d thyroid carcinomas are more prevalent among heavy drinkers, secondary to the increased activity in the HPA axis that occurs in this population

e hepatocellular carcinoma accounts for 20% of deaths in patients with alcoholic cirrhosis.

MCQ answers

1		2		3		4		5	
a	F	a	F	a	F	a	F	a	F
b	F	b	F	b	F	b	F	b	T
c	T	c	F	c	T	c	F	c	F
d	F	d	T	d	F	d	F	d	F
e	F	e	F	e	F	e	T	e	F