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ABSTRACT

The alcohol withdrawal syndrome (AWS) is a common management problem in hospital practice for neurologists, psychiatrists and general physicians alike. Although some patients have mild symptoms and may even be managed in the outpatient setting, others have more severe symptoms or a history of adverse outcomes that requires close inpatient supervision and benzodiazepine therapy. Many patients with AWS have multiple management issues (withdrawal symptoms, delirium tremens, the Wernicke–Korsakoff syndrome, seizures, depression, polysubstance abuse, electrolyte disturbances and liver disease), which requires a coordinated, multidisciplinary approach. Although AWS may be complex, careful evaluation and available treatments should ensure safe detoxification for most patients.

The alcohol withdrawal syndrome (AWS) consists of symptoms and signs arising in alcohol-dependent individuals, typically within 24–48 hours of consumption of their last drink. Although AWS occurs intentionally in those seeking abstinence, it may arise unexpectedly in an alcohol-dependent patient, after an admission to hospital. Although alcohol withdrawal is common and usually mild, the abrupt cessation of alcohol consumption by a patient with alcohol dependence may lead to delirium tremens (a severe dysautonomic and encephalopathic state) and withdrawal seizures, both of which may be fatal. The following should be addressed by the treating doctor (fig 1): confirming the diagnosis; choosing an appropriate drug regimen and setting for management of alcohol withdrawal; monitoring for and treating other complications related to alcohol dependence (including Wernicke's encephalopathy (WE), physical trauma and depression). In this paper, we review the literature on AWS, and discuss our views regarding an approach to management.

EPIDEMIOLOGY

The prevalence of alcohol withdrawal in the general population is low (<5% in US adults in 1995), but is higher among those admitted for detoxification and rehabilitation for alcohol abuse (up to 86%).[1] In a UK national survey conducted in 2002, 38% of male respondents and 23% of female respondents self-reported hazardous drinking (5 or more drinks for a man or 3 or more drinks for a woman) on a typical drinking day.[2] However, in the setting of medical practice, this figure is higher, with the prevalence of alcohol abuse or dependence reaching 20% of hospital inpatients,[3] and up to 40% of patients attending Accident and Emergency departments.[4] The cost of alcoholism is a large burden on the UK economy, and was estimated to cost the NHS £1.5 billion in 2000/2001, with 1 in every 26 hospital bed days being attributable to some degree of alcohol misuse.[5] Despite this substantial problem, a survey of NHS general hospitals conducted in 2000 and 2003 indicated that only 12.8% had a dedicated alcohol worker.[6] In addition, few guidelines exist promoting the initiation of clear and uniform AWS treatment protocols.[7–9]

PATHOPHYSIOLOGY

Alcohol has an effect on multiple neurotransmitter systems in the brain. Pharmacological, electrophysiological (both often undertaken in a rat model of ethanol withdrawal) and genetic studies have helped to elucidate the mechanisms of AWS. Acute alcohol ingestion has an inhibitory effect at N-methyl-D-aspartate (NMDA) receptors, reducing excitatory glutamatergic transmission,[10 11] and has an agonistic effect at gamma-aminobutyric acid type-A ($GABA_A$) receptors. During prolonged exposure to alcohol, NMDA receptors are upregulated and $GABA_A$ receptors are downregulated, leading to tolerance.[12] The roles are reversed during abstinence, with enhanced NMDA receptor function, reduced GABAergic transmission and dysregulation of the dopaminergic system, leading to many of the symptoms and signs of AWS.[13 14] Although GABA levels increase in both plasma and CSF during withdrawal,[15] symptoms of withdrawal still evolve due to downregulation of $GABA_A$ receptors during prior prolonged alcohol exposure. $GABA_A$ and $GABA_B$ mechanisms are also critical for the development of anxiety-like behaviour that is induced by repeated ethanol intoxications and withdrawals[16]. Altered numbers and functions of NMDA (particularly NR1 and NR2B subtypes[17]) and $GABA_A$ receptors resulting from chronic alcohol exposure may be partly responsible for alcohol withdrawal seizures. Electrophysiologically, alterations in neurotransmitter receptor function translate into an absence of inhibitory postsynaptic potentials and currents in ethanol-withdrawn rats.[18] In addition, voltage-dependent calcium influx modulates neurotransmitter release and expression of genes that regulate production of NMDA and GABA receptor proteins; the continued presence of alcohol increases voltage-operated calcium channel expression and contributes to alcohol tolerance and AWS.[19] Acamprosate, an abstinence-promoting drug, probably has its effect through antagonism of glutamate receptor subtype-5 and NMDA receptors, thus inhibiting the rise in glutamate that occurs during AWS.[20] Dopaminergic transmission is enhanced during AWS (high plasma homovallinic acid has been observed in patients with delirium tremens[21]) and may play a role in hallucination formation;[22 23] increased dopamine

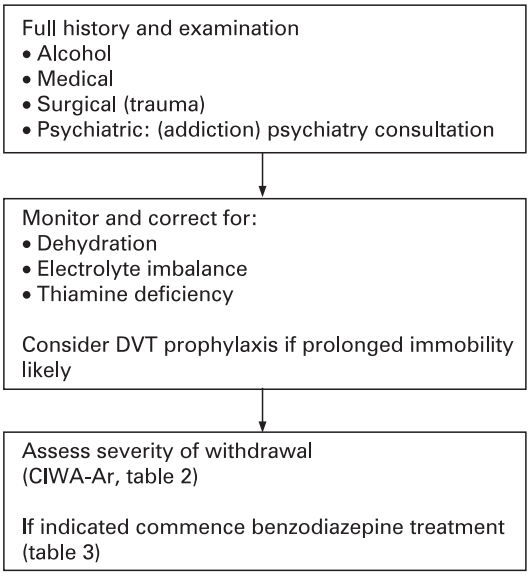

Figure 1 Algorithm for management of uncomplicated alcohol withdrawal.

receptor-binding density (D2 in the dorsal striatum and D1 in the amygdala) has also been observed.[24] The potential importance of the amygdala and the striatum in the pathophysiology of alcohol withdrawal has also been suggested by persisting high levels of cyclic guanosine 3′,5′-monophosphate (cGMP) in these regions in rats.[25] Neurons in the deep layers of the superior colliculus are also an important part of the neural network that initiates ethanol withdrawal seizures.[26] Increased noradrenergic activity has been observed in early AWS, which contributes to sympathetic overdrive during withdrawal.[27 28] However, the role of serotonin is less certain, but levels have been noted to be lower than controls at various stages of AWS.[28] Although a genetic influence is apparent in the development of alcohol dependence, this has not been demonstrated in delirium tremens, although the candidate gene approach has shown positive associations for eight different genetic polymorphisms in a variety of neurotransmitter pathways.[29]

CLINICAL FINDINGS

The DSM-IV definition of alcohol withdrawal encapsulates the key clinical findings of AWS[30]:

- Anxiety
- Tremor
- Headache
- Disorientation
- Agitation
- Delirium
- Hallucinations (tactile, visual, auditory)
- Insomnia
- Anorexia, nausea, vomiting
- Diaphoresis
- Hyper-reflexia
- Tachycardia
- Hypertension
- Seizures
- Low-grade fever
- Hyperventilation

By definition, the patient must have two or more of the following after cessation or reduction of alcohol use that has been heavy or prolonged: autonomic hyperactivity (sweating, tachycardia); increased hand tremor; insomnia; nausea or vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety and tonic-clonic seizures. Although, often, AWS is mild and does not require treatment, if severe it may be complicated by alcohol withdrawal seizures and delirium tremens (characterised by a severe hyperadrenergic state, disorientation, impaired attention and consciousness, as well as visual and auditory hallucinations).[31] The chronic heavy user of alcohol is the typical patient who develops alcohol withdrawal seizures, which are thought to occur secondary to a kindling effect of recurrent detoxifications.[32] Although distinct from a true alcohol withdrawal seizure, young people with primary generalised epilepsy may present with a seizure in association with alcohol consumption and sleep deprivation on the previous night.

In order to establish the risk of developing AWS and its complications, and to identify other alcohol-related problems, a careful alcohol history should be obtained. This allows for early detection, prevention and treatment of AWS. The components of the alcohol history are: estimating consumption (types of alcoholic drink consumed, volume, frequency and drinking pattern); establishing if the patient is alcohol dependent (daily drinking, drinking early in the day, rating the priority of alcohol in the patient's life, previous medical interventions required in relation to drinking); and establishing whether problems have arisen in relation to drinking (social, domestic, emotional, occupational, financial and legal).[33] Patients with a history of chronic heavy use of alcohol are more likely to require detoxification. Physical examination and investigations should be directed towards detecting signs of: intoxication (disinhibition, alcoholic fetor, global ataxia, stupor); AWS and delirium tremens (tachycardia, tachypnea, hypertension, hyper-reflexia, piloerection, diaphoresis, agitation, delirium); Wernicke's encephalopathy (one or more of ataxia, amnesia and ophthalmoplegia); physical injury or medical problems, including aspiration pneumonia, dehydration and electrolyte imbalance.

Rating scales

Once an alcohol history has been obtained, or if there is persisting suspicion for alcohol dependence or AWS, the severity of baseline withdrawal symptoms should be assessed in order to guide the need for treatment. A quick and useful assessment scale for measuring severity is the revised Clinical Institute Withdrawal Assessment Scale for Alcohol (CIWA-Ar) (table 1).[34 35] This ten-item scale scores the severity of nausea, sweating, agitation, headache, anxiety, tremor, sensory disturbances and orientation. Typically, the score is administered by a nurse and if >9, a benzodiazepine is given. The score is then repeated each hour until the score is <10, and benzodiazepine dosing continues until the score is <9. At this point, CIWA-Ar measurements occur every 8 hours, only discontinuing this when the score is <6 on four consecutive occasions. The CIWA-AD (D denotes 'based on DSM-IV') and another modified, simpler version of the original CIWA-A have also been implemented successfully in hospital practice.[36 37]

Biomarkers

Where a history is unobtainable or unreliable, and suspicion is present for alcohol dependence, biochemical markers of heavy

Table 1 Clinical Institute Withdrawal Assessment Scale for Alcohol, revised (CIWA-Ar)[34]

Nausea and vomiting

Ask "Do you feel sick to your stomach? Have you vomited?"

Observation

0 No nausea and no vomiting
1 Mild nausea with no vomiting
2
3
4 Intermittent nausea with dry heaves
5
6
7 Constant nausea, frequent dry heaves and vomiting

Tremor

Arms extended and fingers spread apart

Observation

0 No tremor
1 Not visible, but can be felt fingertip to fingertip
2
3
4 Moderate, with patient's arms extended
5
6
7 Severe, even with arms not extended

Paroxysmal sweats

Observation

0 No sweat visible
1
2
3
4 Beads of sweat obvious on forehead
5
6
7 Drenching sweats

Anxiety

Ask "Do you feel nervous?"

Observation

0 No anxiety, at ease
1 Mildly anxious
2
3
4 Moderately anxious, or guarded, so anxiety is inferred
5
6
7 Equivalent to acute panic states, as seen in severe delirium or acute schizophrenic reactions

Agitation

Observation

0 Normal activity
1 Somewhat more than normal activity
2
3
4 Moderately fidgety and restless
5
6
7 Paces back and forth during most of the interview, or constantly thrashes about

Tactile disturbances

Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?"

Observation

0 None
1 Very mild itching, pins and needles, burning or numbness
2 Mild itching, pins and needles, burning or numbness
3 Moderate itching, pins and needles, burning or numbness
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

Auditory disturbances

Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"

Observation

0 Not present
1 Very mild harshness or ability to frighten
2 Mild harshness or ability to frighten
3 Moderate harshness or ability to frighten
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

Visual disturbances

Ask "Does the light appear to be too bright? Is its colour different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"

Observation

0 Not present
1 Very mild sensitivity
2
3 Moderate sensitivity
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

Headache, fullness in head

Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.

Observation

0 Not present
1 Very mild
2 Mild
3 Moderate
4 Moderately severe
5 Severe
6 very severe
7 Extremely severe

Orientation and clouding of sensorium

Ask "What day is this? Where are you? Who am I?"

Observation

0 Oriented and can do serial additions
1 Cannot do serial additions or is uncertain about date
2 Disoriented for date by no more than 2 calendar days
3 Disoriented for date by more than two calender days
4 Disoriented for place/person

Total **CIWA-Ar** score:_____
Maximum possible score: 67

alcohol consumption are modestly helpful in clarifying the diagnosis. Gamma glutamyl transferase (GGT)[38] and carbohydrate-deficient transferrin[39] are both sensitive markers for alcohol overuse, particularly when tested as a combination.[40] In addition, GGT is relatively non-specific and is frequently elevated in patients taking hepatic enzyme-inducing medications, such as phenytoin and carbamazepine. Macrocytosis (increased mean corpuscular volume) may also be evident,[41] and may have multiple causes as alcohol-dependent individuals may have folate and vitamin B12 deficiency as a result of poor nutrition. Elevated alanine aminotransaminase and aspartate aminotransferase are seen in alcohol-dependent individuals who have acute or chronic hepatitis secondary to excessive alcohol consumption. The measurement of direct ethanol metabolites, such as ethyl sulphate, may serve as biomarkers of recent ethanol intake in the future.[42] Homocysteine levels are elevated in non-abstinent alcoholics and levels are associated with alcohol withdrawal seizures.[43] Homocysteine and a product of its metabolism, homocysteic acid, may overstimulate NMDA receptors, leading to a reduction in seizure threshold.[44] In addition, homocysteine levels have been shown to be significantly higher in patients actively drinking with a history of withdrawal seizures than in those actively drinking without a history of seizures,[45] and thus a homocysteine level has been thought to be a useful biomarker of risk for alcohol-withdrawal seizures.[46] However, difficulty in defining a cut-off value that will allow adequate sensitivity and specificity has hampered its clinical usefulness.[47]

MANAGEMENT

Choosing the appropriate setting for management of AWS is important. In one study, 94% of patients deemed suitable for outpatient management of AWS successfully completed detoxification in this setting.[48] Outpatient management of AWS is indicated where the patient is willing to participate, does not have significant comorbid medical, psychiatric, cognitive or polysubstance use problems, has transportation to/from the follow-up visits, and has support in the community. Pharmacological treatment is directed at treating the symptoms of AWS, including seizure prevention.

Benzodiazepines

Since their introduction in the 1960s, benzodiazepines have stood the test of time and are the first-line treatment for AWS and prevention of alcohol withdrawal seizures. They are effective against alcohol withdrawal symptoms—in particular, seizures (both preventing first seizures and the secondary prevention of further seizures)—when compared with placebo.[49] However, there is no consensus as to the best agent from this group to use, as randomised controlled trials have been limited in number and size. Long-acting benzodiazepines, such as chlordiazepoxide and diazepam, may allow a smoother course of withdrawal and may have superior efficacy in the prevention of delirium,[50] although agents with an intermediate half-life, such as lorazepam (10–20 hours) or oxazepam (8–12 hours), may be safer in those with co-existing hepatic dysfunction.[51 52] A commonly used agent is chlordiazepoxide, with a usual starting dose of 60–100 mg on the first day of treatment, in four divided doses, tapering down by 20–40 mg per day, to zero, over 5–7 days (table 2).

Chlordiazepoxide and diazepam have a complex metabolism, undergoing oxidation, and the respective active metabolites from this process (desmethylchlordiazepoxide and demoxepam) have long half-lives that prolong the sedative and anxiolytic effects of both drugs. Other potential disadvantages of chlordiazepoxide and diazepam are the unpredictable metabolism and enhanced sedative effects in patients with coexisting liver disease, or in the elderly, both of whom have reduced hepatic oxidation.[54] Diazepam, which is more lipophilic than either chlordiazepoxide or lorazepam, has a rapid onset of action by virtue of its rapid distribution into the central nervous system.[55] However, this process is rapidly reversed with redistribution to peripheral fat stores which, in the context of large doses of diazepam, become saturated at an unpredictable rate, and may quickly lead to oversedation.

Lorazepam, on the other hand, has a much simpler metabolism, primarily undergoing hepatic glucuronidation, which is though to be largely preserved in the cirrhotic liver.[51] An inactive metabolite is produced by this process and is eliminated. Lorazepam has been shown to be as effective as diazepam or chlordiazepoxide in the limited head-to-head studies available.[53 55 56] In a double-blind comparison of lorazepam (tapering from 6 to 2 mg daily over 4 days) versus chlordiazepoxide (150 mg to 50 mg over 4 days), lorazepam was as effective as chlordiazepoxide in reducing the symptoms of withdrawal.[53] Although with limited supporting evidence, once-daily dosing of a diazepam taper has been proposed as an alternative to divided daily doses of chlordiazepoxide, for ease of administration.[57]

As mentioned, the shorter duration of effect of lorazepam has been thought to be a disadvantage when compared with chlordiazepoxide or diazepam. However, contrary to this, there is some evidence that symptom-triggered regimens, when compared with 'round the clock' dosing, are as safe, as effective, and are associated with a reduction in the duration of treatment and quantity of medication used.[58–62] In one study of symptom-triggered versus fixed-schedule doses of oxazepam, only 39% of the symptom-triggered treatment group (those with CIWA-Ar scores of >8) received any medication during the period of withdrawal, and used 6 times less oxazepam than the fixed schedule group.[61] Another study that was conducted in an intensive care setting noted the elimination of the need for intubation and ventilation of over-sedated patients with AWS and a reduction in the use of restraining devices after the implementation of a symptom-triggered lorazepam regimen.[62] However, the success of symptom-triggered regimens is based on their protocol-driven, individualised nature and are distinct from *ad hoc* PRN orders, for which the frequency of administration of a drug is solely dependent on the judgment of an individual, and uniformity of treatment is less likely to occur.[63] The use of benzodiazepines in the secondary prevention of alcohol withdrawal seizures is discussed with 'Complications of the AWS'.

Anti-epileptic drugs

Despite the clear benefit of benzodiazepines in the treatment of AWS (with which we have greatest experience, and currently use in our own practices), there has been interest in developing other compounds with less addiction potential and less sedative side effects. Furthermore, several controlled comparative studies (benzodiazepine vs. anti epileptic) have suggested that secondary outcome measures such as anxiety and depression (when untreated, increase the likelihood of relapse) are more effectively treated with an anti-epileptic drug (AED). Other possible advantages over benzodiazepines include the absence of potentiation of alcohol intoxication and the long experience with AEDs for seizure prevention in epilepsy.

Table 2 Typical initial doses and tapering schedules for lorazepam (adapted from Solomon *et al*[53]) and chlordiazepoxide in the treatment of alcohol withdrawal

Day of treatment	Lorazepam	Chlordiazepoxide
1	2 mg three times daily	30 mg three times daily
2	2 mg in morning, 1 mg in the middle of the day, 2 mg at night	20 mg three times daily
3	1 mg three times daily	15 mg three times daily
4	1 mg twice daily	10 mg three times daily
5	1 mg once daily	10 mg twice daily
6	No medication	No medication

The drug most studied in this regard has been carbamazepine. Malcolm *et al* compared the effects of carbamazepine (600–800 mg/per day) and lorazepam (6–8 mg per day) in divided doses in a randomised double-blind controlled trial.[64] The CIWA-Ar was used to assess alcohol withdrawal symptoms on days 1–5 and then post-medication on days 7 and 12. Both drugs were equally efficacious at treating the symptoms of alcohol withdrawal, but carbamazepine had greater efficacy than lorazepam in preventing post-treatment relapses to drinking over the 12 days of follow-up. Furthermore, there was a greater reduction in anxiety symptoms, as measured by the Zung Anxiety Scale, in the group randomised to carbamazepine vs. lorazepam. A Cochrane database systematic review demonstrated that carbamazepine had a small but statistically significant protective effect over benzodiazepines. There was also a non-significant reduction in seizures and side effects favouring patients treated with anticonvulsants over patients treated with other drugs in that review.[65] Oxcarbazepine, an analogue of carbamazepine, has shown comparable effects to carbamazepine in the treatment of AWS in one randomised, single-blinded study.[66]

Valproic acid has also been studied, but only in a few small unblinded studies, and there is limited data to support its efficacy over benzodiazepines.[67] In a placebo-controlled study in the inpatient treatment of alcohol withdrawal, valproic acid (mean dose 1500 mg daily) in comparison to placebo was associated with less use of oxazepam for management of withdrawal symptoms.[68]

In a recent placebo-controlled study, both lamotrigine and topiramate significantly reduced observer-rated and self-rated withdrawal severity, dysphoric mood and supplementary diazepam administration when compared with placebo, and were as effective as diazepam.[69] Other drugs for which there is limited evidence for the treatment of AWS are: gabapentin,[70 71] tiagabine[72] and vigabatrin.[73]

Other agents

The informal dispensing of beverage alcohol to hospital inpatients to prevent AWS occurs in some settings. Intravenous alcohol may be a useful treatment for preventing AWS, but only if done within a strict protocol.[74 75] However, there is little evidence from controlled studies to support this practice over standard treatments, and there are concerns regarding the efficacy, pharmacokinetic profile and narrow therapeutic index of ethanol, particularly in critically ill patients.[76] Tiapride, a benzamide with D2 and D3 antagonist activity, reduces hyperhidrosis, agitation and tremor during alcohol withdrawal, and may be a useful adjunct to other agents used in the treatment of AWS.[77 78]

There is currently limited evidence to support the use of baclofen,[79 80] amisulpride[81] and gamma-hydroxybutyric[82] in the management of AWS. Beta-blockers[83 84] and clonidine[85] lower heart rate and blood pressure and tremor in AWS alone. Therefore, these drugs should only be considered as adjunctive treatments to benzodiazepine therapy.[7] The dynamics and kinetics of beta-blockers (decreased negative inotropic but increased bradycardic effects), nitrates (reduced hypotensive action) and calcium channel blockers (increased bradycardic effect with verapamil) may be altered during AWS, and thus influence the management of alcoholic patients with comorbid cardiac disease.[86]

COMPLICATIONS OF AWS

Alcohol withdrawal seizures

In a patient with AWS, the seizure threshold declines on cessation of drinking and seizures may occur, usually within 48 hours of stopping drinking.[87] The diagnosis is made by way of a history of a seizure within a few hours to 2 days after discontinuation of prolonged, heavy drinking or reduction in consumption, often accompanied by symptoms and signs of AWS. Patients at high risk for withdrawal seizures include those with a prior history of withdrawal seizures, a high total ethanol consumption[32] and multiple previous detoxifications.[88] Uncommonly, acute alcohol intoxication may also rarely precipitate seizures because of the excitatory effects of alcohol.[89]

However, the relationship between alcohol, alcohol withdrawal seizures and epilepsy is often a complex one. ''Alcohol-related seizures'' is a useful umbrella term to account for the various possible seizure aetiologies in the alcohol-dependent patient. Many alcohol-dependent patients have causes other than alcohol withdrawal that are likely to contribute to the seizure disorder, a history of head injury being particularly common.[90] Partial-onset seizures, which are suspicious for recent or remote traumatic brain injury, may occur in up to 51% of alcohol abusers.[91] EEG is useful in the setting of the first alcohol withdrawal seizure or where epilepsy is suspected; a normal low-amplitude record is typically seen after an alcohol withdrawal seizure,[92] whereas generalised spike and wave points towards generalised epilepsy. Other possible risk factors for alcohol-related seizures include electrolyte disturbances, hypoglycaemia, CNS infection, occult traumatic intracranial haemorrhage and illicit drug use.[93]

Seizures may also occur while the patient is still drinking, due to rapidly declining blood alcohol levels. Where there is a history of recent head injury, or where the patient is presenting with a first alcohol withdrawal seizure, it is important to screen with neuroimaging. After trauma where contusion or intracranial haemorrhage is suspected, CT is appropriate initially. Otherwise, a detailed study with MRI looking for alternative causes for seizures, such as tumour and other structural abnormalities, is the standard of care.

Benzodiazepines are the first-line treatment in alcohol withdrawal seizures. In a double-blind placebo-controlled study of patients with chronic alcohol abuse presenting with a generalised seizure, lorazepam demonstrated a significantly lower second seizure rate (3%) versus placebo (24%).[94] European

treatment guidelines recommend either diazepam or lorazepam, although lorazepam is recommended over diazepam in the setting of status epilepticus.[9] Placebo-controlled trials have demonstrated phenytoin to be ineffective in the secondary prevention of alcohol withdrawal seizures.[87] Some alcoholic patients may be taking isoniazid for prophylaxis or treatment of tuberculosis, and thus isoniazid toxicity should be considered as a possible cause of refractory alcohol-related seizures. Pyridoxine deficiency may occur with isoniazid ingestion, ultimately bringing about GABA depletion, which in turn predisposes to seizures. The treatment for seizures in suspected isoniazid toxicity is intravenous pyridoxine at the equivalent dose as the amount of isoniazid ingested, or at least 5 g if the dose is not known.[95]

Delirium tremens

Delirium tremens, commonly known as ''the DTs'', is the net result of no treatment or undertreatment of AWS, and is the most serious manifestation of alcohol withdrawal. It is characterised by a fluctuating disturbance of consciousness and change in cognition occurring over a short period of time.[96] It is accompanied by a further exacerbation of autonomic symptoms (sweating, nausea, palpitations and tremor) and an exacerbation of psychological symptoms including anxiety. It is thought to occur in approximately 5% of patients hospitalised for alcohol withdrawal.[8] Further complications may arise as sequelae of the delirium (injury to patient or staff) or medical complications (aspiration pneumonia, arrhythmia or myocardial infarction), which may lead to death. Older studies suggested a mortality of up to 20%,[97] although with adequate recognition and management, this figure should be as low as 1%.[98] Risk factors for developing delirium tremens after admission to hospital include a previous history of same,[96] more days since the last drink consumed, the presence of a comorbid medical illness, high urea, tachypnea, hypotension and low albumin.[98]

Benzodiazepines are the cornerstone of management, with the same considerations as previously discussed as to which agent is the best to choose. Although diazepam is of more rapid onset, lorazepam may be safer to use where concerns regarding prolonged sedation in the elderly or in those with liver disease are of concern. Lorazepam may be a reasonable choice for treatment of AWS from the outset, as it is also an effective therapy for alcohol withdrawal seizures and delirium tremens, and is available in oral and intravenous forms. Thus, one could avoid the potentially complex pharmacodynamics of using two different benzodiazepines, should either complication of AWS arise. A practice guideline from the American Society of Addiction Medicine has advised against the use of neuroleptic agents as the sole pharmacological agents in the setting of delirium tremens, as they are associated with a longer duration of delirium, higher complication rate and, ultimately, a higher mortality.[8] However, neuroleptic agents have a role as a selected adjunct to benzodiazepines when agitation, thought disorder or perceptual disturbances are not sufficiently controlled by benzodiazepines. Although haloperidol is well established in this setting, chlorpromazine is contraindicated as it is epileptogenic,[99] and there is little information available on atypical antipsychotics. In extreme cases, intubation and ventilation in an intensive care setting are required to facilitate adequate sedation.

Thiamine deficiency and the Wernicke's encephalopathy

Prolonged heavy alcohol consumption results in thiamine deficiency due to dietary deficiency, reduced absorption and increased excretion of thiamine, and may result in Wernicke's encephalopathy (WE), which is classically characterised by delirium with prominent anterograde amnesia, ataxia and ophthalmoplegia. However, in clinical practice, WE may present with limited features of the disorder (memory complaints, nystagmus, gait problems) or may overlap with other comorbidities of alcohol dependence (including intoxication, AWS and delirium tremens).[33] In addition, a subclinical variant of WE probably exists as many patients with an established amnestic dementia syndrome secondary to thiamine deficiency (Korsakoff's psychosis) have no documented history of WE.[100] Although this may be difficult to detect, the presence of small mamillary bodies and thalami on MRI may be helpful. Failure to identify or consider WE, and failure to institute adequate thiamine replacement therapy, has an associated mortality of 20%, with 75% developing a permanent severe amnestic syndrome (Korsakoff's psychosis).[101] Identifying those patients with AWS who are at risk from WE is difficult, although the greater the degree of malnutrition and the more severe the alcohol misuse, the more likely the patient is to develop the syndrome.[102] Oral thiamine hydrochloride cannot be relied on to provide adequate thiamine to the patient at risk, as there is evidence to suggest that only a maximum of 4.5 mg of thiamine can be absorbed form an oral dose over 30 mg.[102] The treatment of patients with WE using 50 mg of oral thiamine is known to be ineffective in treating ophthalmoplegia or delirium.[103 104] Therefore, intravenous delivery of a high potency B-complex vitamin therapy containing thiamine remains the standard of care for those patients with suspected WE (500 mg of thiamine three times daily for three days), or who are at risk for WE (250 mg three times daily for 3–5 days).[105] In the outpatient detoxification setting, the administration of a course of intramuscular thiamine 200 mg for 5 days has been recommended over oral therapy,[102] for the reasons stated above and, in particular, as absorption of thiamine is negated further by continued drinking after hospital discharge. Specifically, this should be done before the administration of oral or parenteral carbohydrates, as thiamine is a cofactor for enzymes required in glucose metabolism, and thus WE may be precipitated by administering glucose prior to thiamine.[106] Oral thiamine may be sufficient as prophylaxis for those who are at low risk of WE, and seem to be nutritionally replete. However, we believe that parenteral thiamine should be given where WE is suspected, where other comorbidities such as severe withdrawal or coma do not permit excluding the possibility of WE, and in alcohol-dependent individuals with poor nutrition. Facilities for treatment of anaphylaxis should be available when thiamine is administered, although this complication of treatment is rare.[105]

Electrolyte disturbances and dehydration

Hyponatraemia is frequently seen in chronic alcoholics, particularly beer drinkers, due to intake of a large volume of fluid. In most cases, this is chronic and is best treated with restoring normal hydration and resumption of a normal diet while abstaining from alcohol.[107] Attempts to correct the electrolyte disturbance with saline (particularly hypertonic saline, 3% sodium chloride) may result in central pontine myelinolysis (CPM),[108] which is thought to be triggered by rapid osmotic shifts in the brain causing complement-mediated oligodendrocyte toxicity. The clinical features of this are irreversible and severe (including dysarthria, dysphagia and spastic quadriparesis), so prevention is critical. There is some evidence to suggest that slow correction of chronic hyponatremia minimises the risk of CPM. Most reported cases of

osmotic demyelination occurred after rates of correction exceeding 12 mmol/24 hours,[109] although cases have also been reported after corrections of 9–10 mmol/day. General recommendations include slow correction, no more than 8–10 mmol/l of correction in any 24-hour period, and if severe symptomatic hyponatremia occurs, to obtain specialist advice prior to more rapid correction or use of hypertonic saline. Deficiencies in serum potassium, magnesium and phosphate are often seen in this setting due to poor nutrition and secondary to vomiting, and should be carefully corrected along with dehydration.

Although many patients who abuse alcohol have a hypocoagulable state secondary to bone marrow and hepatic toxicity, others may develop a rebound thrombocytosis, which may increase the risk of venous thromboembolism.[110] This is particularly important after hospital admission, as prolonged immobility may lead to deep venous thrombosis and pulmonary embolism. Thus, venous thrombosis prophylaxis using graduated compression stockings and subcutaneous heparin should be considered in such patients.[111]

Psychiatric co-morbidities

It has long been recognised that alcoholism and other major mental illness commonly co-occur. The Epidemiology Catchment Area Study reported a 13.8% lifetime prevalence for alcohol abuse or dependence in persons with bipolar I disorder in the US general population.[112] A subscale analysis showed that bipolar I and bipolar II populations had the highest lifetime prevalence rate of alcohol abuse or dependence (46.2% and 39.2%, respectively), followed by schizophrenia (33.7%), panic disorder (28.7%) and unipolar depression (16.5%).[113] In addition, patients with mania had an odds ratio of 6.2 for co-occurring alcoholism (abuse and/or dependence) which, second to other drug abuse/dependence diagnoses, represented the highest of all Axis I diagnoses. Similarly, in the National Comorbidity Survey, respondents with a lifetime diagnosis of alcohol dependence had a significantly increased odds ratio of having co-occurring lifetime diagnosis of mania in both bipolar men (OR = 12.03) and bipolar women (OR = 5.3).[114] Thus, this co-morbidity or co-occurrence represents a large public health problem. Furthermore, when alcohol is a component of the manic presentation, the rates of suicidality are higher versus manic presentations without concurrent alcohol use.[115] Risk factors for individuals with alcoholism who attempt or commit suicide include male gender, age greater than 50 years, serial interpersonal losses, poor social circumstances, polysubstance abuse, current depression and prior suicidal behaviour.[116] As many alcohol-dependent individuals have psychiatric symptomatology during alcohol detoxification (80% in one recent study[117]), it could be concluded that early psychiatric evaluation and intervention is preferable. However, the mental state of patients presenting with AWS may be clouded by withdrawal, delirium or the effects of treatment, and thus the timing of screening for and treatment of comorbid psychiatric illness may need to be deferred, unless already established, until after successful detoxification.

Although suicidal behaviour in the context of comorbid alcoholism and depression is more likely to occur during intoxication (due to increased aggressiveness and reduced inhibitions) than during abstinence, feelings of guilt, fear and low mood frequently come to the fore during alcohol withdrawal. Tricyclic antidepressants[118] and selective serotonin reuptake inhibitors (SSRIs)[119] are both efficacious in treating depression in the context of alcoholism, although SSRIs are the preferred choice because of their relative safety in overdose,[120] and lower likelihood of reducing seizure threshold. In either case, these treatment interventions would be ideally started after completion of detoxification. The possibility of a polysubstance abuse disorder should also be considered by screening for other drugs of abuse by history and by routine urine drug screening.

A detailed discussion of relapse prevention during and after detoxification is beyond the scope of this review. However, pharmacotherapeutic (disulfiram, naltrexone, acamprosate) and psychosocial interventions (including motivational interviews[121]) aimed at preventing relapse into drinking, should be initiated under the guidance of a psychiatrist.[122]

Conclusion

AWS is a common condition seen in hospital practice, and has the potential for a range of diverse and serious complications. A combined care approach, with close attention to the various medical, neurological and psychiatric comorbidities, is required to ensure the best possible outcome. Given the potential for a poor outcome, and the array of treatments available to prevent and treat AWS and its complications, clear uniform management guidelines are needed as for other medical emergencies.

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