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Day, Ed; Daly, Chris

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Ed Day[1] | Chris Daly[2]

[1]Addiction Psychiatry, Institute for Mental Health, School of Psychology, University of Birmingham, Edgbaston, Birmingham, UK

[2]Addiction Psychiatry, Greater Manchester Mental Health FT, Chapman Barker Unit, Prestwich Hospital, Manchester, UK

Correspondence
Ed Day, Clinical Reader in Addiction Psychiatry, Institute for Mental Health, School of Psychology, University of Birmingham, 52 Pritchatts Road, Edgbaston, Birmingham B15 2TT, UK.
Email: e.j.day@bham.ac.uk

Abstract

Up to half of individuals with a history of long-term, heavy alcohol consumption will experience the alcohol withdrawal syndrome (AWS) when consumption is significantly decreased or stopped. In its most severe form, AWS can be life-threatening. Medically assisted withdrawal (MAW) often forms the first part of a treatment pathway. This clinical review discusses key elements of the clinical management of MAW, necessary adjustments for pregnancy and older adults, likely outcome of an episode of MAW, factors that might prevent completion of the MAW process and ways of overcoming barriers to ongoing treatment of alcohol use disorder. The review also discusses the use of benzodiazepines in MAW. Although there is clear evidence for their use, benzodiazepines have been associated with abuse liability, blunting of cognition, interactions with depressant drugs, craving, delirium, dementia and disrupted sleep patterns. Because glutamatergic activation and glutamate receptor upregulation contribute to alcohol withdrawal, anti-glutamatergic strategies for MAW and other potential treatment innovations are also considered.

KEYWORDS
Alcohol, benzodiazepine, delirium tremens, detoxification, pharmacological, psychosocial, seizure, treatment, withdrawal

INTRODUCTION

The intended audience of this narrative review is primarily clinicians working in specialist addiction treatment settings, with a focus on planned medically assisted alcohol withdrawal (MAW) as a part of a longer treatment journey. Although consideration will be given to the management of unplanned withdrawal in hospital settings, severe complications of the alcohol withdrawal syndrome (AWS) such as seizures and delirium tremens are medical emergencies and detailed reviews of treatment regimens are available elsewhere [1–8]. Both authors have been part of the Public Health England expert group to develop the United Kingdom's (UK) first national treatment guidelines for alcohol use disorders, which in turn was supported by evidence from the UK National Institute for Health and Care Excellence (NICE) guidance [9,10]. This was supplemented by a Web of Science review using the key words 'alcohol', 'withdrawal' and 'management'.

THE CHARACTERISTICS OF ALCOHOL DEPENDENCE AND WITHDRAWAL STATES

Symptoms of withdrawal and their physiological counterpart tolerance make up two of the 11 features of Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-5) alcohol use disorder (AUD) [11]. Up to 50% of individuals with a history of long-term, heavy alcohol consumption will experience the AWS (see Table 1) to some degree when alcohol use is reduced or stopped [7,12]. Symptoms and signs usually appear within 8 to 24 hours of a drop in blood alcohol levels caused by initiation of abstinence or a significant reduction in consumption [13]. Transient visual, auditory or tactile hallucinations occur in 2% to 8% of individuals [14]. In many cases the symptoms resolve without treatment, but in some they can progress to a more serious, potentially life-threatening condition. Approximately 10% of symptomatic individuals experience withdrawal-related seizures [15] and if left untreated up to one-third of patients in hospital with severe

TABLE 1 DSM-5 diagnostic criteria for alcohol withdrawal [11].

All 4 criteria must be present to diagnose alcohol withdrawal
A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged
B. Two (or more) of the following, developing within several hours to a few days after cessation of (or reduction in) alcohol use described in criterion A:
1. autonomic hyperactivity (e.g. sweating or pulse rate greater than 100 b.p.m)
2. increased hand tremor
3. insomnia
4. nausea or vomiting
5. transient visual, tactile or auditory hallucinations or illusions
6. psychomotor agitation
7. anxiety
8. generalized tonic–clonic seizures
C. The signs and symptoms in criterion B cause clinically significant distress or impairment in social, occupational or other important areas of functioning
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another medical disorder, including intoxication, or withdrawal from another substance
Alcohol withdrawal seizure
Typically the generalized tonic–clonic type, characterized by rhythmic, yet jerking movement, especially of the limbs
Delirium
The DSM-5 criteria for delirium are:
A. A disturbance in attention (i.e. reduced ability to direct, focus, sustain and shift attention) and awareness (reduced orientation to the environment)
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of day
C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language visuospatial ability or perception)
D. The disturbances in criteria A and C are not better explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of severely reduced level of arousal, such as coma
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. because of a drug of abuse or to a medication), or exposure to a toxin, or is because of multiple aetiologies

withdrawal symptoms will progress to delirium (known as delirium tremens) [16], although delirium tremens may also occur without preceding seizures.

PATHOPHYSIOLOGY

Alcohol acts as a central nervous system depressant by rapidly increasing the release of γ-aminobutyric acid (GABA) in the brain, with prominent effects on GABA-type A ($GABA_A$) receptors [17]. At the same time it inhibits postsynaptic N-methyl-d-aspartate (NMDA) glutamate receptor activity [18]. An extended period of alcohol use at higher levels produces a downregulation of $GABA_A$ receptors, and a corresponding upregulation of NMDA receptors and the glutamatergic system. An abrupt drop in blood levels of alcohol unmasks glutamate-mediated excitation, and the resulting autonomic overactivity produces delirium. Seizure activity is driven largely in the brainstem by removal of the tonic inhibitory effect of the GABA system [19]. Epileptiform activity is rarely detected in the electroencephalogram (EEG) after alcohol withdrawal seizures, possibly because of a different trigger zone than is normal in the context of epilepsy. Alcohol withdrawal also produces an increase in the neurotransmitter dopamine, which in turn contributes to the clinical manifestations of autonomic hyperarousal and hallucinations [20].

Historically, a slow reduction in alcohol consumption to abstinence was the only method available to reduce the discomfort and harms of the AWS and mild cases may only require supportive care [15]. However, planned and early intervention with medication reduces the likelihood of severe complications. Pharmacological stimulation of the ligand-gated $GABA_A$ receptor produces membrane hyperpolarization by enhancing chloride ion influx, resulting in a global slowing of neurotransmission, anxiolysis, sedation and anticonvulsant activity. Agents that target the $GABA_A$ receptor can, therefore, be used to support 'detoxification' (e.g. benzodiazepines, barbiturates and propofol).

OBJECTIVES OF CLINICAL MANAGEMENT OF ALCOHOL WITHDRAWAL

Detoxification or MAW is a part of an overall treatment pathway, and failure to consider ongoing treatment for the newly abstinent drinker often leads to relapse. The goals of the MAW episode are to safely achieve physical withdrawal from alcohol, prevent (or treat) severe withdrawal phenomena such as seizures or delirium tremens, and optimise physical and mental health. Knowledge of the usual level of drinking and the time of the last alcoholic drink helps to gauge the extent and severity of the AWS. Patients may under-report their consumption (quantity and/or frequency), and so validation by other reliable sources is helpful. It is also important to enquire about the outcome of past attempts to stop and the use of other psychoactive substances. A history of delirium tremens (likelihood ratio [LR] = 2.9, 95% CI = 1.7–5.2) and baseline systolic blood pressure 140 mmHg or higher (LR = 1.7, 95% CI = 1.3–2.3) are associated with an increased likelihood of delirium tremens or withdrawal seizure [13]. The Prediction of Alcohol Withdrawal Severity Scale (PAWSS, Supporting information Data S1) [21] is useful in predicting a severe AWS (LR = 174, 95% CI = 43–696) when scoring 4 or more and LR = 0.07 (95% CI = 0.02–0.26, when scoring 3 or less) (see Supporting information Data S1). The use of a breathalyser is also important in considering when to commence MAW and identifying high-risk withdrawal. However, the clinician should be directed by emergent withdrawal symptoms rather than waiting for the breath alcohol concentration (BrAC) to return to zero before commencing MAW.

BEST PRACTICE TO ACHIEVE EFFECTIVE CLINICAL MANAGEMENT OF WITHDRAWAL

Setting

Non-residential/community ('home' or 'ambulatory')

MAW can be undertaken at home, in outpatient clinics, day hospitals or specialist residential settings, with the intensity of supervision matching the severity of the AUD and the likely medical risks associated with withdrawal [22]. A community setting is the default position in most UK specialist alcohol treatment services unless the criteria for inpatient admission (below) are met. Such an approach can lead to cost-savings [23], although there is some randomized controlled trial (RCT) evidence that patients assigned to inpatient detoxification are more likely to complete than a group receiving the same MAW in an outpatient setting [24].

MAW in a community setting usually involves daily monitoring of the signs and symptoms of the AWS by a specialist nurse, with the medication prescribed by a general practitioner (GP) or a specialist service [25]. A recent review of community MAW for alcohol dependence concluded that such programs are characterised by 'clearly defined eligibility criteria, non-ambiguous medication protocols based on objective measurement of withdrawal symptoms, at least daily structured monitoring of the patient's progress and linkage with continuing psychosocial care after completion of detoxification' [25]. The review of 20 studies found benzodiazepines were the primary medication prescribed, and that community detoxification was safe with high completion rates. When compared to inpatient treatment, MAW in the community had better drinking outcomes, good acceptability and was 10 to 23 times cheaper [25].

Hospital

A planned episode of MAW for alcohol and/or other drugs in a specialist inpatient setting should be prioritised in the following circumstances [25,26]:

1. previous history of severe AWS, especially with delirium tremens and withdrawal seizures;
2. current presentation of severe withdrawal, especially with high breathalyser alcohol reading;
3. co-morbid physical health problems (e.g. significant liver disease [cirrhosis, alcoholic hepatitis], epilepsy, cardiac disease, or mobility issues because of cerebellar damage, severe myopathy or neuropathy);
4. pregnancy;
5. co-morbid mental health problems (e.g. cognitive impairment including dementia, Wernicke-Korsakoff syndrome, psychosis, bipolar disorder, personality disorder, and/or high suicide risk);
6. complex social circumstances (e.g. homelessness, domestic violence or safeguarding concerns); and
7. frequent previous unsuccessful community MAW episodes, especially with evidence of increasing severity of AWS.

There is also emerging evidence for the benefit of providing timely MAW following admission to hospital with a presentation of alcohol-related physical or mental health problems [27]. Literature exists to guide clinicians working in intensive care units who are managing cases with severe withdrawal and other physical comorbidity [2,4,8]. Healthcare professionals treating people during MAW should be skilled in the assessment and monitoring of withdrawal symptoms and signs [9], follow local protocols and use validated assessment tools to support the process (e.g. CIWA-Ar, see below).

Timeframe

MAW in inpatient or outpatient settings is usually completed within 3 to 10 days depending on complexity and the emergence of severe withdrawal symptoms. The crucial period for the development of delirium tremens and seizures is the first 48 to 72 hours after cessation or significant reduction in alcohol consumption and careful monitoring and active treatment is important during this period. The treatment duration will depend on individual factors (severity of AWS,

physical and mental health), treatment factors (fixed dose or symptom-triggered MAW) and setting (acute hospital, mental health unit or specialist detoxification unit).

Pre-detoxification preparation

Patients with high use of inpatient alcohol withdrawal services are a small, but costly population with poor follow-on rates to subsequent treatment [28] and may benefit from targeted services to address their complex clinical and social needs [29,30]. MAW should be embedded within a wider treatment program that supports lifestyle changes to increase the likelihood of long-term alternations in drinking behaviour [31]. Retrospective reviews of hospital records show that a history of previous withdrawal episodes is associated with more severe and medically complicated withdrawal [32]. Kindling is a phenomenon whereby the repeated administration of weak electrical or chemical stimuli, which initially cause no overt behavioural response, result in the appearance of a behavioural effect such as a seizure [33]. Both clinical and experimental evidence support the existence of such a kindling mechanism, whereby AWS severity progressively increases with each episode [34,35]. One model suggests that limbic system hyperirritability accompanying each withdrawal episode kindles increasingly widespread subcortical structures, leading to a progression from tremor to seizures and delirium tremens over time.

Human studies also show that repeated withdrawal episodes are associated with cognitive impairments, as well as changes in affect, increased craving and impairment in behavioural control [36]. The risks and benefits of undertaking MAW should therefore be assessed, and the chances of longer-term success optimized through preparation and aftercare planning [37,38]. This may involve developing partial control over drinking as an interim step toward abstinence, combined with individual and social lifestyle changes before MAW. Both brief (3-hour) motivation-oriented therapy [39] and a psychoeducational intervention related to stress and trauma [40] have shown potential in increasing the likelihood of completing MAW when compared with treatment as usual, but require definitive evaluation. Treatment with benzodiazepines is not likely to produce sufficient attenuation of the hyperglutamatergic state produced by withdrawal, and acamprosate is known to reduce glutamate in the brain [41,42]. Adding acamprosate to benzodiazepines does not appear to reduce withdrawal symptoms, but may support a longer period of post-withdrawal abstinence [43].

Medication of choice

The pharmacological management of alcohol withdrawal has been systematically reviewed on behalf of the UK NICE [26,44], the Cochrane collaboration [45,46], and the British Association for Psychopharmacology [31]. The evidence base is strongest for long acting benzodiazepines such as chlordiazepoxide [31,44]. Diazepam may be preferred in patients with a history of delirium tremens, repeated seizures or seizures in a previous MAW episode, and those requiring additional detoxification from benzodiazepines. Shorter acting benzodiazepines with a different metabolism pathway (e.g. oxazepam or lorazepam) may be preferred in those with known or suspected liver function impairment. Lorazepam is recommended (in addition to diazepam) in the treatment of delirium tremens, but can also be used in patients with significant liver disease, including those in which it has taken over 24 hours for the blood alcohol concentration (BAC) to fall below zero. Clomethiazole should be reserved for inpatient settings [9,31].

Because reducing glutamate overactivity is thought to be important in reducing the risk of brain toxicity during withdrawal, alternatives to benzodiazepines such as carbamazepine may be considered. NICE has recommended using carbamazepine or benzodiazepines [9], but a Cochrane review acknowledging potential benefits found 'insufficient evidence in favour of anticonvulsants for treatment of alcohol withdrawal' [46]. Reviews of prescribing practice in the United Kingdom suggest that benzodiazepines are overwhelmingly preferred [47].

Fixed-dose versus symptom-triggered regimens

A fixed-dose regimen uses a predetermined dosing schedule with a slowly reducing daily dose. As shown in Table 2 (and Supporting information Data S1), such regimens may be guided by an initial assessment of the severity of dependence [49] and supplemented with 'as needed' doses to titrate to effect. Fully 'symptom-triggered' regimens can produce rapid symptom control with reduced total benzodiazepine dose (Fig. 1). A trained observer assesses the withdrawal symptoms using a standardized scale at fixed regular intervals, and a predetermined dose of benzodiazepine is administered when a preset score is obtained. The most commonly recommended scale is the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) [50]. It has 10 items producing a total score between 0 (no withdrawal) and 67 (severe withdrawal and delirium tremens) [50]. Scores <8 represent mild AWS not requiring medication, 8 to 15 represent moderate AWS and >15 represents severe AWS and an increased risk of seizures and/or delirium.

A systematic review [51] found moderate strength evidence for symptom-triggered therapy reducing the duration of MAW and total benzodiazepine dose. However, this mainly applies to lower risk patients in specialized settings, and it is less clear that the process is useful in general hospital settings. There is insufficient evidence to support symptom-triggered therapy producing better outcomes in terms of mortality, seizure control or delirium in any setting [51]. NICE guidance recommends a fixed-dose regimen for community-based withdrawal [26], a fixed-dose regimen with 'as needed' medication in specialist services and a 'symptom-triggered' regimen within a general medical inpatient setting [9].

In the acute hospital, the patient with AWS often has co-morbid conditions and nursing staff may be regularly diverted by other

TABLE 2 Sample fixed dose regimens of chlordiazepoxide, titrated to effect.

Indicative daily alcohol consumption	15–25 units		30–49 units		50–60 units
Severity of alcohol dependence	Moderate SADQ score 15–29		Severe SADQ score 30–39		Very severe SADQ score 40–60
Day 1 (starting dose)	15 mg qid	25 mg qid	30 mg qid	40 mg qid[a]	50 mg qid[b]
Day 2	10 mg qid	20 mg qid	25 mg qid	35 mg qid[a]	45 mg qid[b]
Day 3	10 mg tid	15 mg qid	20 mg qid	30 mg qid	40 mg qid[a]
Day 4	5 mg tid	10 mg qid	15 mg qid	25 mg qid	35 mg qid[a]
Day 5	5 mg bid	10 mg tid	10 mg qid	20 mg qid	30 mg qid
Day 6	5 mg qhs	5 mg tid	10 mg tid	15 mg qid	25 mg qid
Day 7		5 mg bid	5 mg tid	10 mg qid	20 mg qid
Day 8		5 mg qhs	5 mg bid	10 mg tid	15 mg qid
Day 9			5 mg qhs	5 mg tid	10 mg qid
Day 10				5 mg bid	10 mg tid
Day 11				5 mg qhs	5 mg tid
Day 12					5 mg bid
Day 13					5 mg qhs

Taken from NICE Guidelines 100 and 115 [48]. SADQ = Severity of Alcohol Dependence Questionnaire.

[a]Doses of chlordiazepoxide in excess of 30 mg qid should be prescribed only in severe alcohol dependence and the response to treatment should be monitored regularly and closely.

[b]Doses of chlordiazepoxide in excess of 40 mg qid should be prescribed only in very severe alcohol dependence. Such doses are rarely necessary in women and children and never in older people or in cases of liver impairment.

Administer Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) and breathalyser on admission

If breathalyser reading elevated (i.e. >Breath Alcohol Content (BrAC) 87 mcg% or Blood Alcohol Content (BAC) 200 mg/100 mL) repeat in 1 hour and monitor CIWA-Ar

If CIWA-Ar >10 at second reading give chlordiazepoxide 20 mg PRN and commence chlordiazepoxide 25 mg qds regime (or higher if appropriate)

NB: The BAC is for guidance only. Some patients will need to start chlordiazepoxide with BAC >200 mg % if withdrawal symptoms are severe.

Continue CIWA-Ar readings hourly for first 24–48 hours:

CIWA-Ar scores >10 should trigger as needed (PRN) prescribing of chlordiazepoxide 20 mg on each occasion

If >5 doses of PRN required in 48 hours this should prompt a review of the withdrawal regime

All regimes to be reviewed at 48 hours, adjusting upward (or downward if over sedated) as necessary. The doses should be a reflection of the frequency of PRN medication dispensed and physical assessment of the patient.

The British National Formulary recommends a maximum dose of chlordiazpoxide of 250 mg/day, but this can be exceeded if titrating to effect (i.e. mild sedation) using regular (minimum every 4 hours) assessment with CIWA-Ar. The lowest dose needed to achieve the effect should always be used, and the dose reduced and stopped as soon as possible.

severely ill patients. CIWA-Ar involves a mixture of subjective and objective items and has not been validated for use in severely ill patients (who may be unconscious). In this setting symptom-triggered MAW may be unreliable, encouraging use in cases with non-alcohol-related delirium where benzodiazepines have made the problem worse [52]. A review of 18 AWS rating scales found a lack of agreement about what constituted the most important markers of withdrawal, with 30 separate signs and symptoms used [53]. Several hospital-based rating scales have been incorporated into a complete symptom-triggered package of care (e.g. Glasgow Modified Alcohol Withdrawal Scale [54], Minnesota Detoxification Scale (MINDS) [2]), although at present these lack multi-centre RCT evaluation.

Delirium tremens

Delirium tremens usually emerges after 2 to 3 days of withdrawal and should be treated as a medical emergency. It is characterised by severe tremor, hallucinations (auditory, olfactory and classically visual) and confusion, alongside associated paranoid delusions, agitation, insomnia, tachycardia, hyperthermia, hypertension, and tachypnoea. It is estimated that 3% to 5% of patients hospitalised with AWS meet the criteria for delirium [8]. Risk factors significantly correlated with the development of alcohol withdrawal delirium include current infectious disease, tachycardia (heart rate above 120 b.p.m at admission), signs of alcohol withdrawal with a BAC of more than 1 g/L of body fluid, a history of epileptic seizures, and a history of delirium [55]. Electrolyte abnormalities, for example, low levels of potassium and/or magnesium, low platelet count, and cardiac, respiratory or gastrointestinal disease also predict delirium during alcohol withdrawal [8]. Death occurs in up to 4% of hospitalized patients with delirium tremens, and hyperthermia, persistent tachycardia and the use of physical restraints predict mortality [56].

The onset of delirium tremens can be prevented by prompt initiation of treatment, alongside identification and management of co-morbid medical problems [57]. Key treatment goals are to control

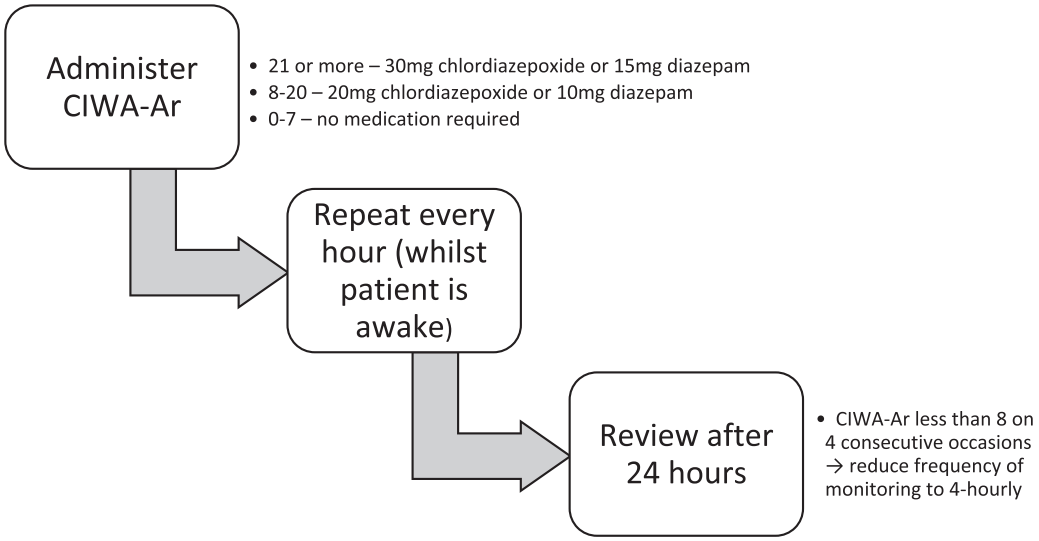

FIGURE 1 A sample symptom-triggered medically assisted withdrawal process using Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar). Stop process when CIWA-Ar consistently <10 for 12 hours. Oxazepam (30 mg orally) may be used in cases of liver impairment (raised International Normalised Ratio (INR) or reduced albumin)

agitation, reduce the risk of seizures and decrease the risk of injury and death [8]. Management of established delirium tremens should involve nursing in a well-lit, quiet room with reorientation chart and infrequent nursing changes. A fluid balance chart is essential to ensure intake of at least 3 L/day, but avoiding over hydration, and vital signs should be measured every 15 to 30 minutes until the patient is stable. Other emerging causes of confusion such as infection must be monitored, alongside daily blood tests for urea and electrolytes, blood glucose and full blood count. Electrolyte imbalances such as hypokalaemia and hypomagnesemia should be corrected. A review of treatment regimens recommends diazepam 10 to 20 mg intravenously or orally every 1 to 4 hours as needed for 5 days or until delirium settles [8]. Parenteral administration of lorazepam may be required to produce light sedation (1–4 mg 6-hourly intramuscularly), and prominent psychotic symptoms treated with haloperidol 1 to 5 mg oral 8-hourly (Supporting information Data S1).

Seizures

Grand mal epileptiform seizures can occur 12 to 48 hours after cessation or significant reduction in consumption. They are more likely in individuals with previous history of withdrawal seizures or epilepsy and in severe dependence can occur even if the breathalyser reading has not reached zero. There may be multiple seizures, but rarely status epilepticus. Consideration should be given to correcting low magnesium levels and other electrolyte disturbance. Benzodiazepines prevent de novo seizures, and although anticonvulsants are equally efficacious there is no advantage in combining the two [31]. If the risk of seizures is known to be high, diazepam may be the first choice medication with doses as high as 40 mg 6-hourly. If the patient is already taking an anticonvulsant medication this should be continued and the blood levels monitored. Lorazepam (1-4 mg intramuscularly) has been shown to prevent a second seizure in the same withdrawal episode and should be used in preference to starting anticonvulsants [9].

Wernicke's encephalopathy

Wernicke's encephalopathy (WE) is an abrupt onset confusional state characterised by impairment in consciousness, ophthalmoplegia and ataxia. Cases are often missed and a high index of suspicion should be maintained [58], with every patient with delirium tremens treated as if they have incipient WE [57]. It is caused by a deficit in vitamin B1 (thiamine) brought on by poor diet and the negative impact of alcohol on its intestinal absorption [59] and is more common in people with co-existing malnutrition and poor physical health. Because the biologically active form of thiamine (thiamine pyrophosphate) is an essential coenzyme in biochemical pathways in the brain, thiamine must be given before (or concomitantly with) intravenous administration of glucose to prevent the precipitation of WE in thiamine-deficient individuals [60].

Although the pathophysiology of WE is reasonably clear and the role of thiamine in treating patients with WE is well established [61], recommendations about dosage and duration of treatment are acknowledged to be arbitrary [58]. The British Association for Psychopharmacology guidelines recommend that WE requires immediate treatment with 2 pairs of Pabrinex ampoules (equivalent 500 mg thiamine) every 8 hours by intravenous infusion for 3 days, followed by 1 pair of Pabrinex ampoules (250 mg thiamine) once daily intramuscularly for 3 to 5 days or until clinical improvement ceases. Patients with significant weight loss, poor diet, signs of

malnutrition, memory disturbance, previous history of WE or a suspicion of Korsakoff psychosis represent an 'at-risk' group that may benefit from prophylaxis with 1 pair of Pabrinex ampoules intramuscularly for 3–5 days. Lower risk groups require only oral thiamine (50 mg every 6 hours) [31].

SPECIAL CONSIDERATIONS

Neuropsychological impairment

People with alcohol dependence often show mild to moderate neuropsychological impairment. Memory, executive function and visuospatial ability may be affected, with general intelligence, declarative memory, language skills and motor and perceptual abilities less impaired [62]. Withdrawal from alcohol has been associated with cognitive impairments, which in turn are associated with an increased risk of relapse [63]. Although there is evidence of cognitive recovery in IQ, verbal skills and recent memory following 7 to 14 days of abstinence, sustained impairments in problem-solving visuospatial ability and perceptual motor skills have been found after 28 days, with some deficits lasting beyond a year of abstinence [64].

Pregnancy

MAW can be undertaken at any stage in pregnancy [65], although AWS may lead to placental abruption, preterm delivery and foetal distress or death [66]. An inpatient setting is therefore recommended, with frequent monitoring of the mother and of foetal movements and heart rate [67]. Benzodiazepine use during pregnancy does not increase the risk of major foetal malformations, and chlordiazepoxide and diazepam appear to be safer than clonazepam, alprazolam and lorazepam [68]. However, benzodiazepines in the third trimester have been associated with floppy baby syndrome, failure to feed, and temperature dysregulation. Some clinicians recommend lorazepam as the preferred benzodiazepine in the third trimester, because its short onset and offset of action reduces neonatal benzodiazepine withdrawal [67].

Older adults

Instruments such as PAWSS can be helpful to screen for those requiring MAW [69]. A hospital setting is required for older adults in poor general health with multiple co-morbidities, dementia or a requirement for constant one-to-one monitoring. Benzodiazepines with a longer half-life (diazepam, chlordiazepoxide) can produce oversedation, and so consider reducing the dose or using shorter-acting benzodiazepines such as oxazepam or lorazepam. Careful monitoring with an objective scale (e.g. CIWA-Ar) may help to prevent falls or respiratory depression. There is evidence to support the use of thiamine, magnesium, multivitamins and supportive care [69].

POST-DETOXIFICATION PROGNOSIS

Failure to complete MAW can be a barrier to ongoing treatment [70], reducing confidence in achieving long-term abstinent recovery. Systematic reviews of both community and residential MAW report completion rates of 45% to 100% [25,71]. In specialist residential settings increased odds of completing MAW are associated with: greater length of time in education; stable accommodation; referral from professional agencies; and absence of co-existing drug use or psychiatric conditions [72]. Programs that address barriers to completion such as previous trauma achieve better outcomes [73]. A return to alcohol consumption is the norm for people with severe AUD who complete MAW, with more than half having their first drink within 2 weeks [74] and 85% of patients eventually relapsing [75]. Impairment in the prefrontal cortex associated with repeated episodes of withdrawal may impair conflict resolution and increase sensitivity to stress, both of which can contribute to relapse. Withdrawal may also exacerbate craving, further increasing the likelihood of relapse [37].

Transition to treatment

Although MAW is an opportunity to link patients to specialist treatment or mutual aid groups, this does not happen for the majority. In a national United States (US) data set, 66% of MAW episodes were completed, but only 11% of discharges were followed by transfer to ongoing treatment [71]. One UK service reported 60% of patients completing a planned MAW engaging in ongoing aftercare [76], improving to 82% through the use of an abstinence preparation group [38]. People are more likely to access further treatment if they are educated, white and have previously attended addiction treatment [71]. Building positive perceptions about ongoing treatment through a specific treatment plan promotes greater post-MAW treatment uptake [77]. Patients with little mutual-help experience benefit from a motivational intervention as part of the referral method [78,79], and including more mutual-help components is associated with higher rates of treatment entry or mutual-help group attendance within 7 days of MAW completion [80]. In short-term, standalone inpatient MAW, providing a staff escort to attend the assessment for the next stage of treatment and an incentive for attending are associated with an increased likelihood of completing intake procedures [81]. The provision of individual counselling that extends beyond the MAW period [82] and use of peer-led interventions have been associated with increased rates of 12-step meeting attendance in the longer term [83]. Brief family treatment has also been shown to facilitate ongoing treatment post-detoxification [84]

Post-MAW treatment

A plan for ongoing relapse prevention including medication, psychosocial and mutual-aid components should be built into the MAW program [26,31]. Greater time spent in addiction treatment and mutual

aid groups post-detoxification is associated with sustained abstinence [85,86]. Receiving any treatment within the first month after MAW is also associated with significantly less chance of readmission [87]. Simple, telephone-based contact can be used to monitor treatment and mutual aid group participation [88], and telehealth interventions have the potential to deter repeated MAW episodes and improve outcomes [89]. Computerized cognitive bias modification training during MAW helps to prevent relapse during the high-risk early period following discharge from treatment [90].

Psychosocial treatments are the mainstay of ongoing care and have small, but significant relapse prevention effects [91,92]. Excellent reviews of relapse prevention medication are available [93]. Naltrexone and acamprosate reduce relapse rates by 5% to 8% up to 1 year after treatment [94] and both are offered as first-line treatment post-MAW in the United Kingdom [26]. There are no specific contraindications for their use in patients with comorbid psychiatric conditions [95]. Acamprosate has the better evidence for supporting abstinence (NNT = 12), whereas naltrexone may be more effective in preventing a return to heavy drinking in people who occasionally lapse. Both oral and injectable formulations of naltrexone can be initiated before hospital discharge [96].

Disulfiram produces a rapid increase in concentration of acetaldehyde on drinking alcohol. The fear of the resulting physical reaction (flushing, nausea and vomiting, sweating, hypotension and palpitations) prevents patients from drinking alcohol post-MAW. Drowsiness is the most common side effect (10%), and the reported severe effects of optic neuritis, neuropathy, hepatitis and psychosis appear to be rare [95]. Disulfiram is associated with a higher success rate than control conditions, but only in open-label studies [97]. It is most appropriate in motivated patients with a network of family or friends willing to supervise its administration in a supportive manner.

INNOVATIVE APPROACHES OR TREATMENTS IN DEVELOPMENT

Although there is clear scientific and practical evidence for the use of benzodiazepines for AWS, their use has been associated with abuse liability, blunting of cognition, interactions with depressant drugs, craving, delirium, dementia and disrupted sleep patterns [5]. Because glutamatergic activation and glutamate receptor upregulation contribute to alcohol withdrawal, anti-glutamatergic strategies for MAW have been proposed. The glutamate release inhibitor lamotrigine, the NMDA glutamate receptor antagonist memantine, and the AMPA/kainite receptor inhibitor topiramate [98] significantly reduce observer-rated and self-rated withdrawal severity, dysphoric mood and supplementary diazepam administration compared with placebo. Benzodiazepine-sparing protocols for the prophylaxis and treatment of AWS have been proposed [5].

The optimum medication regimen would maximise AWS control, reduce the risk of complications, and prevent neuroinflammation and brain damage [31]. Medications that may be useful in treating withdrawal, but also in reducing the risk of complications and preventing relapse during early abstinence, include baclofen, some anticonvulsants (e.g. topiramate) and gamma-hydroxybutyric acid (GHB or sodium oxybate), but evidence of benefit is inconclusive. Baclofen is a GABA-B receptor agonist approved to reduce spasticity associated with neurological disorders and is relatively safe with medical co-morbidity. However, in a meta-analysis of 14 RCTs baclofen showed no statistically significant superiority over placebo [99], and it remains an experimental option.

DECLARATION OF INTERESTS

None.

ORCID

Ed Day https://orcid.org/0000-0002-7106-7013

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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