

Chapter 5 Alcohol withdrawal management

Alcohol Withdrawal Syndrome: Clinical Presentation

This section discusses the clinical signs and symptoms, onset and duration, and common complications of alcohol withdrawal.

Signs and symptoms of alcohol withdrawal

Alcohol withdrawal syndrome is characterised by central nervous system hyperactivity that occurs when an alcohol dependent individual abruptly stops or significantly reduces alcohol consumption. About 50% of alcohol-dependent patients develop clinically relevant symptoms of withdrawal, ranging from 13% to 71% (Victor and Adams 1953; Saitz et al. 1994; Degenhardt et al. 2000).

The signs and symptoms of alcohol withdrawal may be grouped into three major classes (autonomic, gastro-intestinal and cognitive and perceptual changes), and may be uncomplicated or complicated withdrawal (American Psychiatric Association 2000).

Table 5.1: Signs and symptoms of alcohol withdrawal

	<i>Autonomic hyperactivity</i>	<i>Gastrointestinal features</i>	<i>Cognitive and perceptual changes</i>
<i>Uncomplicated withdrawal features</i>	Sweating Tachycardia Hypertension Tremor Fever (generally <38°C)	Anorexia Nausea Vomiting Dyspepsia Diarrhoea	Poor concentration Anxiety Psychomotor agitation Disturbed sleep, vivid dreams
<i>Severe withdrawal complications</i>	Dehydration and electrolyte disturbances		Seizures Hallucinations or perceptual disturbances (visual, tactile, auditory) Delirium

Onset and duration of withdrawal symptoms

Onset of alcohol withdrawal is usually between six and 24 hours after the last drink or following significant reduction in alcohol consumption. In some individuals (usually relatively fit and healthy), the withdrawal syndrome is short-lived and inconsequential, with the acute phase resolving well within five days with minimal or no medical intervention. However, in others it increases in severity over the first 48 to 72 hours of abstinence (Saitz 1998; Shuckitt 2006; Prescrire 2007).

In some severely dependent drinkers, withdrawal can occur when the blood alcohol level (BAL) is decreasing, even if the patient is still intoxicated or has consumed

alcohol recently, with a significant proportion of dependent drinkers experiencing the onset of withdrawal symptoms before the BAL reaches zero (Victor and Brausch 1967).

Psychological symptoms of alcohol withdrawal, including dysphoria, sleep disturbance and anxiety often persist for 1-2 weeks after drinking cessation and can continue for months (Satel et al. 1993; Shuckitt 2006).

Severe withdrawal complications

Severe withdrawal complications include seizures, delirium and hallucinations.

Alcohol Withdrawal Seizures

Alcohol withdrawal seizures are usually generalised (tonic-clonic) seizures. Seizures may occur 6 to 48 hours after the last drink is consumed in alcohol dependent individuals, and can occur even if the blood alcohol level is high (e.g. greater than 0.10 g%) in severely dependent drinkers (Victor and Brausch 1967; Tartara et al 1983).

The prevalence of alcohol-withdrawal seizures is estimated at between 2 and 9% of alcohol dependent individuals (Chan 1985). Individuals who have experienced an alcohol withdrawal seizure are more likely to experience further seizures in subsequent alcohol withdrawal episodes (Trevisan et al. 1998). The risk of seizure recurrence within 6-12 hours is estimated at between 13% and 24% in untreated patients (Hillbom et al 2003).

Alcohol withdrawal delirium

The features of alcohol withdrawal delirium (also known as delirium tremens, DTs) are disturbance of consciousness and changes in cognition or perceptual disturbance (American Psychiatric Association 2002). The terms "alcohol withdrawal delirium" and "delirium tremens" can be used interchangeably.

The incidence of alcohol withdrawal delirium in un-medicated alcohol dependent patients averages at 5%, although the incidence is much lower with effective treatment of alcohol withdrawal. Early studies of delirium tremens reported mortality rates as high as 15%, however, mortality rates have fallen with advances in management to less than 1% (Mayo-Smith et al. 2004).

Alcohol withdrawal delirium usually occurs 48 to 96 hours after the last drink is consumed but may take up to seven days to appear. The delirium usually lasts for 2 to 3 days, although can persist for several days (Mayo-Smith et al. 2004).

Hallucinations

During any stage of the alcohol withdrawal, transient hallucinations either visual or tactile may occur in 3-10% of patients with severe withdrawal, however they have no prognostic significance (Trevisan et al. 1998). Some patients may also experience paranoia, psychomotor disturbances, abnormal affect and other delusions. Hallucinations may appear within the first 24 hours and in some cases last up to three days; however they can resolve within 24 to 48 hours.

Assessment and Treatment Matching

Assessment of patients undergoing alcohol withdrawal requires a comprehensive history, examination, investigations and collateral history and is described in detail in Chapter 3. This section discusses common predictors of alcohol withdrawal severity, withdrawal treatment services and their objectives, treatment matching and monitoring during withdrawal and the use of alcohol withdrawal scales are also discussed.

Predictors of withdrawal severity

Development of severe withdrawal in an individual patient is difficult to predict. However, a number of patient characteristics have been identified that are likely to be associated with more severe withdrawal symptoms or complications (Saitz 1998). These include: current drinking pattern, past withdrawal experience, concomitant substance use and coexisting medical and psychiatric conditions.

The severity of withdrawal is only moderately predicted by amounts of alcohol consumed. Large numbers of patients can be safely managed without medication (Benzer 1990; Whitfield et al. 1978). Severe withdrawal is more likely with the higher the levels of chronic alcohol consumption (e.g. 150 grams of alcohol per day), but individuals with lower levels can experience severe withdrawal and withdrawal complications. The minimal quantity and frequency of alcohol consumption that may lead to withdrawal is not known. In a recent review of alcohol withdrawal syndromes no studies identified the minimal level of alcohol consumption required to produce physical dependence (Prescrire 2007).

Duration of heavy alcohol use for 6 years or longer increases the odds of developing withdrawal symptoms 15 times (Ballenger and Post 1978).

Early morning drinking to alleviate withdrawal symptoms is a predictor of higher alcohol withdrawal severity (Benzer 1990; Essardas Darayanani et al. 1994; Prescrire 2007). Individuals with heavy but irregular (e.g. 2-3 days per week) alcohol consumption (sometimes referred to as 'binge' drinking) generally do not experience severe withdrawal, but are still at risk of such. Patients with a history of severe alcohol withdrawal syndrome (e.g. severe anxiety, seizures, delirium, hallucinations) are more likely to experience such complications in future withdrawal episodes (Essardas Darayanani et al. 1994; Trevisan et al. 1998; Saitz 1998).

Patients with heavy or regular use of other substances (e.g. benzodiazepines, stimulants, opiates) may experience more severe withdrawal features. In particular, withdrawal from both alcohol and benzodiazepines may increase the risk of withdrawal complications (Saitz 1998; Soyka et al. 1989).

Patients with concomitant medical (e.g. sepsis, epilepsy, severe hepatic disease, head injury, pain and nutritional depletion) or psychiatric conditions (e.g. anxiety, psychosis or depression) are more likely to experience severe withdrawal complications (Wetterling et al. 1994; Myrick and Anton 1998; Saitz 1998).

The presence of moderate to severe withdrawal symptoms (e.g. CIWA-Ar ≥ 15 , see discussion of alcohol withdrawal scales below) left untreated is one of the stronger predictors of seizures and confusion (Foy et al. 1988).

It is important to monitor all patients carefully during the alcohol withdrawal period, particularly those with heavy alcohol use and with a history of alcohol withdrawal.

Recommendation	Strength of recommendation	Level of evidence
5.1 The risk of severe alcohol withdrawal should be assessed based on current drinking patterns, past withdrawal experience, concomitant substance use, and concomitant medical or psychiatric conditions.	B	II

Objectives of alcohol withdrawal services

Research suggests that withdrawal treatment alone has little, if any, impact on long-term alcohol use (Vaillant 1988). All existing literature assessing efficacy of relapse prevention medication indicates high levels of relapse in the first 3 months after detoxification in placebo group. For example in the study by Kiefer et al. (2004) comparing acamprosate and naltrexone, 75% of placebo group relapsed at 12 weeks and 80% at 24 weeks post-withdrawal. Withdrawal management should not be seen as a stand-alone treatment that is likely to result in prolonged periods of abstinence, but instead as a transitional step on the long road to abstinence.

Many commentators have described objectives for alcohol and drug withdrawal services (e.g. Saitz and O'Malley 1997; Myrick and Anton 1998). A consensus approach developed for opiate withdrawal services in Australia (Lintzeris et al 2006) can also be applied to alcohol withdrawal services.

The realistic set of objectives adapted for alcohol withdrawal services is as follows:

1. *To interrupt a pattern of heavy and regular alcohol use.* Some individuals require the structure and support of withdrawal services in order to stop drinking. Whilst many have a longer term goal of achieving abstinence, some individuals may be seeking a temporary break from their alcohol use.
2. *To alleviate withdrawal symptoms.* Palliation of the discomfort of alcohol withdrawal symptoms is an important reason for patients presenting for treatment, and one of the primary aims of withdrawal services.
3. *To prevent severe withdrawal complications.* Management of alcohol withdrawal aims to prevent or manage potentially life threatening complications such as seizures, delirium and Wernicke's encephalopathy. Furthermore, alcohol withdrawal can complicate concomitant medical or psychiatric conditions.
4. *Facilitate linkages to ongoing treatment for alcohol dependence.* Withdrawal services are acute services with short-term outcomes. However alcohol dependence is a chronic relapsing condition and positive long-term outcomes are more often associated with participation in ongoing treatment such as counselling, self-help, residential rehabilitation and pharmacological approaches (see Chapter 7). Managed withdrawal provides an opportunity to plan and engage in post-withdrawal treatment services.
5. *To get help with any other problems.* While some people will be unwilling or unable to continue in ongoing drug treatment programs, they may benefit from

linkages with primary or specialist health services or welfare services (e.g. accommodation, employment services).

Recommendation	Strength of recommendation	Level of evidence
5.2 Successful completion of alcohol withdrawal does not prevent recurrent alcohol consumption and additional interventions are needed to achieve long-term reduction in alcohol consumption.	A	Ia
5.3 Realistic goals of clinicians, patients and their carers for withdrawal services include: interrupting a pattern of heavy and regular alcohol use, alleviating withdrawal symptoms, preventing severe withdrawal complications, facilitating links to ongoing treatment for alcohol dependence, providing help with any other problems (such as accommodation, employment services).	D	IV

Settings for alcohol withdrawal

Alcohol withdrawal management can occur in a variety of settings, ranging from hospital inpatient, community residential (e.g. specialised detoxification unit) to ambulatory services (outpatient or home-based detoxification services).

Outpatient withdrawal management is an effective, safe, and low-cost treatment for patients with mid-to-moderate symptoms of alcohol withdrawal. One randomised controlled study comparing inpatient and outpatient treatment of withdrawal found that the cost and duration of treatment were significantly lower in the outpatient group. The completion rates were higher in the inpatient group than in the outpatient (95% vs 72%) and abstinence rates were higher in the inpatient group at one month follow up. The abstinence rates were not different at 6 months. There were no serious medical complications in either group (Hayashida et al. 1989).

Soyka and Horak (2004) examined the effectiveness and safety of alcohol outpatient detoxification in an open prospective study. Patients were screened for relevant neuropsychiatric disorders and other exclusion criteria and then seen on a daily outpatient basis for 5-7 days. Psychotropic or symptomatic medications to alleviate withdrawal symptoms were prescribed if necessary (CIWA-A score >16). Psychotherapeutic interventions were conducted to motivate the patient for further alcohol therapy. Of 557 patients screened 331 entered the study. Ninety four percent (n = 312) of the study participants successfully completed treatment. Sixty percent of them required psychotropic medication. Ninety one percent of the initial sample patients entered a consecutive 3-month motivational treatment program. Forty six percent of patients successfully completed the 1-year consecutive outpatient treatment. The patients who were not included into the study required inpatient management of withdrawal for medical reasons. It should be noted that this study does not compare outpatient vs inpatient management. However, it provides evidence for safe and effective management of alcohol withdrawal in an outpatient setting.

Selecting withdrawal settings

The withdrawal setting should be carefully selected for each individual patient. Withdrawal can be managed in an ambulatory setting (i.e. outpatient, home-based detoxification), a community residential unit or in a hospital.

The choice of withdrawal setting requires a comprehensive clinical assessment and discussion with the patient (and where possible family or carers) regarding the advantages and disadvantages of each approach (Saitz and O'Malley 1997; Saitz 1998; Myrick and Anton 1998).

Factors to be considered in determining the most appropriate withdrawal setting for an individual include:

- likely severity of alcohol withdrawal and occurrence of severe withdrawal complications (seizures, delirium, hallucinations);
- use of other substances: individuals who report heavy use of other drugs (e.g. benzodiazepines, psychostimulants, opiates), may be at increased risk of withdrawal complications and generally require close monitoring and supervision (e.g. community residential unit);
- concomitant medical or psychiatric conditions: patients with significant comorbidity may require hospital admission until medically cleared. Patients may be able to be 'step-down' to less intensive withdrawal settings to complete withdrawal once medically stable.
- social circumstances, the availability of a safe environment and 'home' supports;
- outcome of prior withdrawal attempts: repeated failure at ambulatory withdrawal may be an indication for referral to a residential detox unit;
- patient preference and availability of resources;

Some patients wish to attempt ambulatory withdrawal despite multiple failed prior attempts. Further attempts at outpatient withdrawal may be appropriate, however clinicians should identify how this attempt will be different to previous attempts (e.g. increased home supports and monitoring), and negotiate with the patient mutually agreed criteria to be met in order to continue with the withdrawal attempt (e.g. no alcohol use in first 2 days).

Patients on waiting-lists for residential withdrawal units may require support in maintaining motivation and avoiding high risk activities until admission.

Prescribing benzodiazepines in an attempt to alleviate withdrawal prior to admission is not recommended, and may increase the risk of adverse events from the combination of alcohol and benzodiazepines.

Based on the assessment of these factors, patients with no history of severe withdrawal complications and without severe concomitant medical, psychiatric or other substance use disorders are likely to experience withdrawal of mild to moderate severity. They are suitable for ambulatory withdrawal setting, if they have a safe 'home' environment and good social support enabling daily monitoring by reliable support person and good access to health care services.

Patients with predicted moderate to severe withdrawal, who have a history of severe withdrawal complications (such as seizure, hallucinations) or withdrawing from multiple substances should be recommended withdrawal management in a community residential setting, if they have no severe medical or psychiatric comorbidity. Patients without safe home environment or social supports and those with repeated failed ambulatory withdrawal attempts would also benefit from residential withdrawal.

Inpatient hospital treatment should be recommended for those with severe withdrawal complications (such as delirium or seizures of unknown cause), and/or severe medical or psychiatric comorbidity. Hospital addiction medicine consultation liaison services should be accessible in hospitals to aid assessment, management and discharge planning.

Recommendation	Strength of recommendation	Level of evidence
5.4 Ambulatory withdrawal is appropriate for those with mild to moderate predicted withdrawal severity, a safe 'home' environment and social supports, no history of severe withdrawal complications, and no severe concomitant medical, psychiatric or other substance use disorders.	D	IV
5.5 Community residential withdrawal is appropriate for those with predicted moderate to severe withdrawal, a history of severe withdrawal complications, withdrawing from multiple substances, no safe environment or social supports, repeated failed ambulatory withdrawal attempts, and with no severe medical or psychiatric comorbidity.	D	IV
5.6 Inpatient hospital treatment is appropriate for those with severe withdrawal complications (such as delirium or seizures of unknown cause), and/or severe medical or psychiatric comorbidity.	S	
5.7 Hospital addiction medicine consultation liaison services should be accessible in hospitals to aid assessment, management and discharge planning.	S	

Monitoring during alcohol withdrawal

Patients with moderate to severe withdrawal symptoms left untreated are more likely to develop withdrawal complications (Foy et al. 1988). Other factors, such as patient's compliance with treatment, level of motivation and perception of treatment effectiveness may influence treatment outcome. It is important to carefully monitor patients during the alcohol withdrawal period paying particular attention to the following:

- *physical parameters*, including level of hydration, pulse rate, blood pressure, temperature, level of consciousness (especially if medicated);

- *severity of alcohol withdrawal.* It is beneficial to use an alcohol withdrawal rating scale to assess the severity of withdrawal, to guide treatment, and to assist clinicians in communicating more objectively about the severity and management of alcohol withdrawal. Alcohol withdrawal scales are described below.
- *general progress during withdrawal episode.* This includes ongoing level of motivation, alcohol and other drug use during ambulatory withdrawal (breathalyser readings and/or urine drug screens may be clinically indicated); response to any medication(s); and patient concerns or difficulties.

Clinical Institute Withdrawal Assessment for Alcohol Scale

The Clinical Institute Withdrawal Assessment for Alcohol revised CIWA-Ar is a 10-item, validated scale. CIWA-Ar scores below 10 are considered mild withdrawal; between 10 and 20 are moderate withdrawal, and above 20 are considered severe withdrawal. Patients with CIWA-Ar scores of >10 are at greater risk of developing withdrawal complications if not medicated (Sullivan et al. 1989).

Frequency of CIWA-Ar monitoring depends upon treatment setting and clinical condition of the patient. Patients with CIWA-Ar scores of >10 require more frequent monitoring (e.g. at least 4 hourly), and patients with severe withdrawal (CIWA-Ar>20) should be monitored every 2 hours (Saitz and O'Malley 1997; NSW Department of Health 2007).

Alcohol Withdrawal Symptoms – Rating Scale

An alternative scale is the Alcohol Withdrawal Symptoms - Rating Scale (AWS). The AWS has not been validated, however it has been widely used in Australian conditions and is considered acceptable for use (NSW Department of Health 1999).

Short Alcohol Withdrawal Scale

The *Short Alcohol Withdrawal Scale (SAWS)* is a self-completion scale used once a day, and is suited to ambulatory withdrawal settings (Gossop et al. 2002). Other validated scales may be used according to local preference.

Limitations of withdrawal scales

Alcohol withdrawal rating scales are not to be used as diagnostic tools, as many other medical conditions (e.g. sepsis, hepatic encephalopathy, severe pain), psychiatric conditions (e.g. anxiety disorder) or other drug withdrawal syndromes (e.g. benzodiazepine, stimulant or opiate withdrawal), will produce signs and symptoms that rate on these scales, and can lead to an inappropriate diagnosis of alcohol withdrawal (Foy et al. 1988).

These scales have not been validated for management of seriously ill patients. For example, there is evidence of inappropriate use of CIWA-Ar to guide treatment of alcohol withdrawal in hospitalised medical and surgical patients (Bostwick and Lapid 2004; Hecksel et al. 2008), particularly in patients with limited communication abilities.

Therefore, alcohol withdrawal scales should not be used to guide medication (e.g. symptom-triggered regimes) in patients with significant medical or psychiatric co-morbidity, or those withdrawing from other substances. Health professionals should consult a specialist drug and alcohol clinician about monitoring and management needs. Scoring is typically highly variable in clinical practice and often not reproducible. Clinicians should review scores before making management decisions.

Recommendation	Strength of recommendation	Level of evidence
5.8 Patients withdrawing from alcohol should be regularly monitored for physical signs, severity of alcohol withdrawal and general progress during withdrawal.	S	
5.9 Alcohol withdrawal scales (CIWA-Ar, AWS) can be used to assess withdrawal severity, to guide treatment (such as symptom-triggered medication regimes) and to aid objective communication between clinicians; but should not be used as diagnostic tools.	A	Ia
5.10 Alcohol withdrawal scales should not be used to guide treatment in patients concurrently withdrawing from other substances, or with significant medical or psychiatric comorbidity. Health professionals should consult a specialist drug and alcohol clinician about monitoring and management needs.	B	Ib
5.11 Scores on alcohol withdrawal scales are not always reproducible and should be checked before using them to make management decisions.	S	

Supportive Care

This section discusses strategies used to improve withdrawal outcomes, including patient information, environment and support, counselling, diet and rehydration, thiamine supplementation, sleep and relaxation and strategies to facilitate links with other services for further treatment and support.

Patient Information

Patients (and carers) generally benefit from information regarding the likely nature, severity and duration of symptoms during withdrawal, strategies for coping with symptoms and cravings, strategies to reduce high-risk situations and the role of medication (NSW Department of Health 2007).

Recommendation	Strength of recommendation	Level of evidence
5.12 Patients (and carers) should be provided with information about the likely nature and course of alcohol withdrawal, and strategies to cope with common symptoms and cravings.	C	III

Environment and support

Patients attempting alcohol withdrawal are vulnerable to psychological stress. Treatment is more effective in an environment that is quiet, non-stimulating, and non-threatening. Easy availability of alcohol and other drugs reduces the likelihood of treatment completion (Ozdemir et al. 1994; Myrick and Anton 1998).

Recommendation	Strength of recommendation	Level of evidence
5.13 Treatment environment should be quiet, non-stimulating, and non-threatening, and where alcohol and other drugs are not available.	S	

Supportive counselling

Counselling during the withdrawal episode should be aimed specifically at providing patient with strategies for coping with withdrawal symptoms, including cravings, maintaining motivation, and facilitating post-withdrawal links. While no studies directly assessed the effectiveness of these strategies in management of alcohol withdrawal, a recent meta-analysis of treatments for opioid dependence has shown that psychosocial interventions implemented during withdrawal management were effective in terms of completion of treatment, use of opioids, results at follow-up and compliance (Amato et al. 2008).

Recommendation	Strength of recommendation	Level of evidence
5.14 Supportive counselling should be provided to maintain motivation, provide strategies for coping with symptoms, and reduce high-risk situations.	D	III

Diet, nutrition and rehydration

Many patients experience nausea and/or diarrhoea during withdrawal. It appears that frequent, light meals are generally better tolerated in the first few days of withdrawal. Patients with such withdrawal symptoms as diarrhoea, nausea/vomiting or profuse sweating may develop dehydration. Dehydration can cause severe disturbances of fluid and electrolyte balance and provoke withdrawal complications and should be corrected with oral fluids or via intravenous infusion, if necessary. In patients with fluid retention water balance should be maintained by oral administration of fluids as intravenous infusion may cause fluid overload leading to heart failure (Myrick and Anton 1998).

Recommendation	Strength of recommendation	Level of evidence
5.15 Clinicians should ensure oral rehydration is adequate. Intravenous fluids may be necessary in severe dehydration and/or in those not tolerating oral fluids.	S	

Thiamine and other supplements

Thiamine deficiency is common in patients with alcohol dependence, particularly in those with poor nutritional status (Sgouros et al. 2004). Thiamine supplements are recommended for all individuals undergoing alcohol withdrawal (Cook 2000).

According to the recent Cochrane review there is insufficient evidence from randomised controlled trials to guide the clinician as to the optimum dose, frequency, route, or duration of thiamine treatment for prophylaxis or treatment of Wernicke's encephalopathy due to alcohol misuse (Day et al. 2004). There is one randomised, double-blind, multidose study of thiamine treatment in 107 subjects who were detoxifying from alcohol (Ambrose et al. 2001). The results did not reveal a simple dose-response relationship. However, the study has demonstrated that the dose of 200mg IM thiamine for two consecutive days was more effective than the 5mg dose in improving participants' performance in the test of working memory (a delayed alteration task).

The existing recommendations currently used in the UK and Australia (Thomson et al. 2002; Lingford-Hughes et al. 2004; NSW Department of Health 2007; Feeney and Connor 2008) are mostly based on studies by Cook et al. (e.g. 1998, 2000) and Thomson et al. (e.g. 2000; 2006). See also Sechi (2007) for review. In patients showing no clinical features of Wernicke's Encephalopathy or memory impairment, thiamine is recommended as a prophylactic measure (Cook et al. 1998).

The dose, route and duration of thiamine administration depend on patient's nutritional status.

Healthy patients with good dietary intake may be administered oral thiamine. The recommended dose is 300mg per day (e.g. 100mg tds) for 3 to 5 days, and maintained on 100mg oral thiamine for a further 4 to 9 days (total of 1-2 weeks of oral thiamine).

Intestinal absorption of oral thiamine supplements is slow and may be incomplete in patients with poor nutritional status (Thomson et al. 2000). Chronic drinkers with poor dietary intake and general poor nutritional state require parenteral thiamine doses.

The recommended dose of thiamine 300mg IM or IV per day for 3-5 days, with subsequent oral thiamine doses of 300mg per day for several weeks (Cook 2000). The intramuscular route should not be used for patients with coagulopathy as absorption of thiamine will be reduced.

Parenteral carbohydrates can cause rapid utilisation of thiamine in peripheral tissues and precipitate Wernicke's Encephalopathy. Therefore, thiamine (oral or intramuscular) should be given BEFORE any carbohydrate load (e.g. IV glucose) (Thomson et al. 2002).

Deficiencies of other B complex vitamins, vitamin C, folic acid, zinc and magnesium are not uncommon and an oral multi-vitamin preparation can be given for several days in nutritionally depleted individuals (Myrick and Anton 1998).

Thiamine supplementation should be continued indefinitely in an alcohol-dependent patient who continues to drink alcohol.

Recommendation	Strength of recommendation	Level of evidence
5.16 Thiamine should be provided to all patients undergoing alcohol withdrawal to prevent Wernicke's encephalopathy.	D	IV
5.17 Thiamine should be given before any carbohydrate load (such as intravenous glucose) as carbohydrates can cause rapid use or depletion of thiamine and precipitate Wernicke's encephalopathy.	D	III
5.18 Healthy patients with good dietary intake should be administered oral thiamine 300 mg per day for 3 to 5 days, and maintained on 100 mg oral thiamine for a further 4 to 9 days (total of 1 to 2 weeks of thiamine).	D	IV
5.19 Chronic drinkers with poor dietary intake and general poor nutritional state should be administered parenteral (intramuscular or intravenous) thiamine doses of 300 mg per day for 3 to 5 days, with subsequent oral thiamine doses of 300 mg per day for several weeks. The intramuscular route should not be used for patients with coagulopathy.	D	Ib
5.20 Thiamine supplementation should be continued indefinitely in an alcohol-dependent patient who continues to drink alcohol.	S	

Sleep and relaxation

Heavy drinkers commonly report sleep disturbances (Benca et al. 1992). Insomnia is a frequent symptom of alcohol withdrawal (Caetano et al. 1998) and a predictor of relapse during early recovery (Foster and Peters 1999; Brower et al. 2001; Malcolm et al. 2007).

However, there is no role for continuing treatment with long-term benzodiazepines or other sedatives to improve sleep following alcohol withdrawal (i.e. more than one week). Sleep hygiene practices should be encouraged. Patient literature should be provided regarding sleep and relaxation techniques.

Similarly, there is limited role for benzodiazepines or other sedatives for management of anxiety after alcohol withdrawal, and behavioural approaches to relaxation and anxiety management should be encouraged.

Recommendation	Strength of recommendation	Level of evidence
5.21 Sedatives (such as benzodiazepines) should not be continued beyond the first week of withdrawal. Behavioural approaches to management of anxiety and sleep problems should be encouraged.	D	IV

Facilitating links with other services for further treatment and support

It has long been recognised that effective management of patients' alcohol withdrawal symptoms presents a window of opportunity to initiate further treatment of their alcohol dependence (Saitz 1998). Post-withdrawal treatment options include counselling (e.g. relapse prevention), residential rehabilitation, self-help, and medications for relapse prevention. Medications such as naltrexone and acamprosate can be initiated during alcohol withdrawal treatment as a way of enhancing uptake, and indeed acamprosate may also reduce calcium mediated neuronal damage during the withdrawal process (Mann et al. 2008). These are generally commenced after at least three days of abstinence (see Chapter 7).

Based on the meta-analysis of studies investigating the effect psychosocial interventions during withdrawal from opioids (Amato et al. 2008), counselling strategies during alcohol withdrawal should focus on examining post-withdrawal treatment options, and facilitating engagement with these services (See section on Supportive counselling, above).

Recommendation	Strength of recommendation	Level of evidence
5.22 Clinicians should facilitate links to post-withdrawal treatment services during withdrawal treatment.	D	III

Medications for Managing Alcohol Withdrawal

The following describes the use of medications for managing alcohol withdrawal.

Benzodiazepines

Benzodiazepines are safe and effective for the treatment of alcohol withdrawal. In general, long acting benzodiazepines with a rapid onset of action are most commonly recommended. The recommendations are based on the evidence from earlier meta-analyses (Mayo-Smith 1997; Holbrook et al. 1999) and reviews (Lingford-Hughes et al. 2004; Mayo-Smith et al. 2004).

There is significant evidence that benzodiazepines are effective in reducing symptoms of alcohol withdrawal and in reducing the risk of seizures and alcohol withdrawal delirium when compared to placebo (Mayo-Smith 1997; Holbrook et al. 1999).

The most recent meta-analysis (Ntais et al. 2005) has also found that benzodiazepines are effective in reducing withdrawal symptoms and, in particular, in treatment and prevention of withdrawal seizures (see below).

Diazepam is the benzodiazepine of choice in many countries, including Australia. Chlordiazepoxide, a long acting and rapid onset benzodiazepine, is widely used internationally but is not registered in Australia.

The choice among different agents is guided by duration of action, rapidity of onset, and cost. Meta-analyses show no differences in relative efficacies of different benzodiazepines (Mayo-Smith 1997; Ntais et al. 2005). Earlier randomised controlled

trials have shown that lorazepam was more effective than placebo (Naranjo 1998) and as effective as diazepam in reducing symptoms of moderate alcohol withdrawal (Miller and McCurdy 1983). Long-acting benzodiazepines may be more effective in preventing seizures than short acting benzodiazepines (Mayo-Smith 1997).

Benzodiazepines with shorter duration of action, such as midazolam, lorazepam, oxazepam lorazepam are recommended when there is concern about prolonged sedation (e.g., in elderly, in patients with significant comorbidities or liver disease) (Saitz 1998; Mayo-Smith et al. 2004).

Benzodiazepines should not be continued beyond the first week for managing alcohol withdrawal due to the risk of rebound phenomenon and dependence (Saitz and O'Malley 1997).

Benzodiazepines: Recent Meta-analysis

A Cochrane review of the use of benzodiazepines for alcohol withdrawal was carried out in 2005 by Ntais et al (2005). Fifty-seven trials included a total of 4,051 people. There was a very large variety of outcomes and of different rating scales, and this limited the data analyses. It was found that benzodiazepines offered a large benefit against alcohol withdrawal seizures compared to placebo (relative risk [RR] 0.16; 95% confidence interval [CI] 0.04 to 0.69; p = 0.01). Benzodiazepines had similar success rates to other drugs (RR 1.02; 95% CI 0.92 to 1.12), particularly, anticonvulsants (RR 1.00; 95% CI 0.87 to 1.16) in reducing symptoms of alcohol withdrawal. Seizures were better prevented with benzodiazepines than with non-anticonvulsants (RR 0.23; 95% CI 0.07 to 0.75; p = 0.02). However, no differences in this outcome were found between benzodiazepines and anticonvulsants (RR 1.99; 95% CI 0.46 to 8.65). Thirteen trials with the total of 571 patients showed no difference in efficacy, adverse effects or drop-out rate among patients treated with the following benzodiazepines for 5-28 days: alprazolam, chlordiazepoxide, clobazam, diazepam, halazepam, loperazepam, lorazepam, and prazepam. Small sample sizes, inadequate reporting of patient status (inpatient or outpatient), or of randomisation techniques, limited the possibilities for further pooling of data. It was not possible to draw definite conclusions about the relative effectiveness and safety of benzodiazepines against other drugs (including carbamazepine, clonidine, propranolol, bromocriptine) in alcohol withdrawal, because of the large heterogeneity of the trials both in interventions and assessment of outcomes.

The main conclusion reached by the authors was that benzodiazepines were effective against alcohol withdrawal symptoms, in particular seizures, when compared to placebo. This conclusion is in concordance with previous meta-analyses and in general justifies the current status of benzodiazepines as first-line treatment for alcohol withdrawal, although clear superiority over other agents has not been demonstrated.

Recommendation	Strength of recommendation	Level of evidence
5.23 Benzodiazepines are the recommended medication in managing alcohol withdrawal. In Australia, diazepam is recommended as 'gold standard' and as first-line treatment because of its rapid onset of action, long half-life and evidence for effectiveness.	A	Ia

<p>5.24 Shorter-acting benzodiazepines (lorazepam, oxazepam, midazolam) may be indicated where the clinician is concerned about accumulation and over sedation from diazepam, such as in the elderly, severe liver disease, recent head injury, respiratory failure, in obese patients, or where the diagnosis is unclear.</p>	<p>D</p>	<p>III</p>
<p>5.25 Benzodiazepines should not be continued beyond the first week for managing alcohol withdrawal due to the risk of rebound phenomenon and dependence.</p>	<p>D</p>	<p>III</p>

Symptom-triggered therapy

Symptom-triggered medication regimen relies upon linking medication (e.g. diazepam doses) to scores on a frequently administered withdrawal scale (e.g. CIWA-Ar or AWS) (e.g. four times a day). Medication is administered only when the patient develops moderate alcohol withdrawal symptoms. Symptom-triggered regimens have the advantage of better tailoring medication to the needs of individuals, and have been shown to result in less benzodiazepine use than fixed-dose regimens in specialist residential detoxification settings (Saitz et al. 1994; Reoux and Miller 2000; Daeppen et al. 2002; Spies et al. 2003).

The meta-analysis described above (Ntais et al. 2005) included three of the above studies (Saitz et al. 1994; Daeppen et al. 2002; Spies et al. 2003) with the total of 262 patients. While there was a trend towards a higher effectiveness of symptom-triggered dosing schedules when compared to fixed-dose regimens, in terms of CIWA-Ar score at the end of treatment, therapeutic success and number of completed withdrawals per arm, the statistical significance was not reached.

This regimen is not suitable for ambulatory settings or for patients with a history of seizures (Saitz and O'Malley 1997).

It should be noted that the appropriateness of symptom-triggered regimen in seriously ill, medically or surgically unstable patients with an established drinking history is unproven. This is particularly the case for patients with limited communication abilities (Hecksel et al. 2008).

In the latter study (Hecksel et al. 2008) 25% of all hospital patients who received symptom-triggered therapy according to CIWA-Ar protocol were randomly selected (n=124) and assessed for appropriateness of treatment administered. It was found that although scoring with CIWA-Ar requires communication between the patient and nursing staff, 23% of cases involved patients unable to interact meaningfully. Furthermore, 44% of patients assessed with CIWA-Ar had no history of recent drinking. As a result, 64% of non-drinkers were treated as if they were experiencing alcohol withdrawal syndrome. All these patients could communicate appropriately with the nursing staff, but were not specifically asked about their current drinking status. The situation was especially problematic for patients who had a history of heavy drinking but who had since achieved sobriety. In this study, post-operative status was most likely to result in inappropriate initiation of the CIWA-Ar protocol, probably because the delirium common in the hours and days after surgery is more

likely to be mistaken for alcohol withdrawal syndrome. Patients with liver disease were more likely to receive appropriate treatment.

Similarly, the symptom-triggered schedule may not be appropriate for management of patients with psychiatric comorbidity or polysubstance dependence.

Recommendation	Strength of recommendation	Level of evidence
5.26 Diazepam should be administered in a symptom-triggered regimen in residential withdrawal settings for people with no concomitant medical, psychiatric or substance use disorders.	B	1a

Loading dose therapy

Loading dose regimens (also referred to as “front-loading”) administer high doses of benzodiazepines in the early stages of alcohol withdrawal. These regimens are used in managing patients with a prior history of severe withdrawal complications and in patients presenting in severe alcohol withdrawal and/or severe withdrawal complications (Saitz and O’Malley 1997). Diazepam is safe to administer in loading regime (Heinala et al. 1990). A common loading diazepam regime under these circumstances is 20mg orally every 2 hours until reaching 60 to 80mg or the patient is sedated (Saitz and O’Malley 1997).

Hillbom et al (2003) performed a meta-analysis of 22 randomised controlled studies investigating medications for treatment and prevention of alcohol withdrawal seizures (see below, in Anticonvulsants: Meta-analyses and reviews). They also recommend an administration of the loading dose of diazepam of 10-20mg orally or parenterally to all patients presenting in withdrawal seizures. They emphasised the importance of prevention and treatment of first seizures as every subsequent seizure increases the risk of status epilepticus and other life-threatening complications. Status epilepticus increases the risk of seizures in future withdrawal episodes (Hesdorffer 1998, cited in Hillbom et al. 2003).

Two small RCTs examined the effectiveness of diazepam loading dose (Sellers et al.1983, Manikant et al. 1993). Sellers et al (1983) showed that the loading dose regimen using 20mg diazepam was more effective than placebo. Manikant et al. (1993) compared conventional and loading doses. The total dose of diazepam in the conventional treatment and in the loading dose groups were 200 mg and 67 +/- 9.3 mg, respectively. Clinical response was comparable in both groups. None of the subjects developed diazepam related side effects.

Patients with a history of severe withdrawal complications (seizures, delirium) and those presenting in severe alcohol withdrawal with or without complications should be treated according to the loading dose regimen.

Recommendation	Strength of recommendation	Level of evidence
5.27 Diazepam should be administered in a loading regimen (20 mg 2 hourly until 60 to 80 mg or light sedation) in patients with a history of	B	1b

severe withdrawal complications (seizures, delirium); in patients presenting in severe alcohol withdrawal and/or severe withdrawal complications (delirium, hallucinations, following withdrawal seizure).

Fixed-schedule therapy

Benzodiazepines given at fixed dosing intervals are a common therapy for alcohol withdrawal management, and are well suited to ambulatory withdrawal, community residential and inpatient withdrawal settings (Saitz and O'Malley 1997; Saitz 1998).

Fixed schedule regimens may be supplemented with additional diazepam as needed for people with low tolerance of withdrawal discomfort (for example, 5 mg 6 hourly as needed, based on clinical observation or alcohol withdrawal scale scores) (Saitz and O'Malley 1997).

In general hospitals, patients with a history of alcohol dependence are the most likely to experience complications of alcohol withdrawal, such as delirium and seizures, when receiving symptom-triggered therapy according to the CIWA-Ar protocol. Such patients should be monitored more closely and may require more frequent doses of benzodiazepines than the CIWA-Ar protocol permits (Hecksel et al. 2008).

In patients with concomitant medical, psychiatric or substance use disorders a fixed-schedule therapy is more appropriate.

Recommendation	Strength of recommendation	Level of evidence
5.28 Diazepam should be administered in a fixed dose regimen in ambulatory settings, or for those with concomitant medical, psychiatric or substance use disorders.	C	Ib

Alternative, symptomatic and other medications

Alternative medications may need to be considered in patients who abuse benzodiazepines, particularly if they continue drinking. In minority of patients benzodiazepines cause paradoxical reactions (such as violence, agitation) or confusion and delirium and are not recommended for use in these patients. However, the alternative medications should be effective in preventing serious complications of alcohol withdrawal, such as seizures and delirium.

Anticonvulsant medications should be continued in patients who take them regularly (such as for epilepsy not related to withdrawal).

Anticonvulsants: Meta-analyses and reviews

A Cochrane review of clinical trials assessing safety and effectiveness of anticonvulsants in the treatment of alcohol withdrawal (Polycarpou et al. 2005), analysed forty-eight studies with the total number of 3610 patients. However,

because these studies assessed a large variety of outcomes and used different withdrawal rating scales, quantification of the data was limited. While certain trends were noted, no statistical significance was shown for the benefit of anticonvulsants in reducing severity of withdrawal symptoms (relative risk [RR] 1.32; 95% confidence interval [CI] 0.92 to 1.91) or preventing alcohol withdrawal seizures (RR 0.57; 95% CI 0.27 to 1.19) when compared to placebo. When anticonvulsants were compared to other drugs (such as oxazepam) no significant differences were found in CIWA-Ar scores at the end of treatment (weighted mean difference [WMD] -0.73; 95% CI -1.76 to 0.31). In a subgroup analysis of three studies, carbamazepine was found to be significantly more effective than a benzodiazepine (oxazepam and lorazepam), in reducing severity of some alcohol withdrawal symptoms (WMD -1.04; 95% CI -1.89 to -0.20; $p = 0.02$); however this result was based on only 260 participants. The incidence of alcohol withdrawal seizures post-treatment tended to be lower with anticonvulsants than with placebo or other drugs, but the difference did not reach significance. Phenytoin assessed alone was found to be ineffective in preventing seizures when compared to placebo (RR 0.78; 95% CI 0.35 to 1.77; $p = 0.56$). The side-effects tended to be less common in the anticonvulsant-group (RR 0.56; 95% CI 0.31 to 1.02). The authors state that it was not possible to draw definite conclusions about the effectiveness and safety of anticonvulsants in alcohol withdrawal in this review, due to the heterogeneity of the trials both in interventions and the assessment of outcomes.

An earlier review by Hillbom et al (2003) provides a meta-analysis of twenty two randomised controlled trials examining the efficacy of different drugs for the primary prevention of seizures. This study found that benzodiazepines significantly reduced the risk of seizures while antipsychotics significantly increased the risk seizures. Short-acting benzodiazepines (oxazepam and lorazepam) appeared less effective as tapering off the drugs caused additional seizures in some cases. Anticonvulsants were as effective as benzodiazepines in preventing primary alcohol withdrawal seizures but adding them to benzodiazepines did not further reduce the risk of seizures. A meta-analysis of three randomised controlled trials examining the efficacy of drugs for prevention of the secondary (recurrent) seizures, found phenytoin to be ineffective. The authors conclude that benzodiazepines should be the first line of treatment as they effectively prevent both first seizures and recurrent seizures during alcohol withdrawal episode. Non-sedative anticonvulsants are the second choice.

Ait-Daoud et al. (2006) provide an overview on a number of medications for treatment of alcohol dependence, including treatment of withdrawal. They examined the results of eight trials of valproate for treatment of withdrawal, including open-label, case-report and randomised controlled studies. They also reported in detail the results of a double-blind trial comparing carbamazepine with lorazepam (Malcolm et al. 2002). The authors concluded that 'valproate and carbamazepine have been shown to be safe and effective alternatives to benzodiazepines for treating alcohol withdrawal'. However, the effectiveness of these drugs for prevention of secondary seizures was not discussed.

Carbamazepine

Carbamazepine for treatment of alcohol withdrawal has been studied for many years and is widely used in Europe for this indication (Mayo-Smith 1997; Mayo-Smith 2004). It is a safe alternative to benzodiazepines, but it is usually is not recommended for use as the first line of treatment because it has significant side effects and may not prevent secondary seizures (Hillbom et al. 1989).

Prince and Turpin (2008) reviewed six randomised double-blind trials investigating carbamazepine, gabapentin and nitrous oxide as alternatives to symptom-triggered benzodiazepine administration for the treatment of alcohol withdrawal syndrome (Prince and Turpin 2008). The results of the review suggested that carbamazepine 200mg four times daily was as effective as 30 mg of lorazepam four times daily in reducing symptoms of alcohol withdrawal. It is therefore, may be useful for treatment of alcohol withdrawal, particularly in outpatient settings, although adverse effects and drug interactions may limit its usefulness. The role of gabapentin was unclear because of the lack of randomised, double-blind, controlled trials and the conflicting results of existing case series and open-label trials. Two trials of nitrous oxide were poorly designed and had conflicting results. The authors conclude that because of the limitations in evidence, the routine use of carbamazepine and gabapentin for the treatment of alcohol withdrawal cannot be recommended, and the use nitrous oxide should be avoided.

Valproate

One study looked at the role of valproic acid, conducting a literature review of controlled clinical trials (Lum et al. 2006). The results were inconclusive. Comparisons were made among various regimens of valproic acid and traditional therapy with benzodiazepine or non-benzodiazepine agents. Only 2 of 6 trials reported a statistically significant difference in favour of valproic acid on endpoints of alcohol withdrawal. However, these differences were of marginal clinical significance. The number of patients included in these studies did not allow for adequate evaluation of safety. The authors conclude that the existing limited efficacy and safety data suggest that valproic acid should not replace conventional therapy or be used as adjunct therapy for management of mild-to-moderate alcohol withdrawal syndrome.

Anticonvulsants: Randomised controlled trials

Oxcarbazepine

A pilot study of oxcarbazepine vs. carbamazepine was conducted in Germany (Schik, et al. 2005) with 29 patients. Results showed that the oxcarbazepine group had a significant decrease of withdrawal symptoms and reported significantly less 'craving for alcohol' compared to the carbamazepine group. Subjectively experienced side effects, normalisation of autonomic parameters and improvement in the cognitive processing speed did not differ between groups. Therefore, the authors suggest that oxcarbazepine might be an interesting alternative to carbamazepine, and having almost no addictive potential, no clinically relevant interaction with alcohol and no prominent sedatory effect, it might also offer an alternative to other drugs such as benzodiazepines or clomethiazole.

A study by Koethe et al examined the role of oxcarbazepine's efficacy and tolerability during alcohol withdrawal (Koethe et al. 2007), with limited results. The trial was conducted in 50 inpatients during a 6-day treatment of alcohol withdrawal in a 4-site, double-blind, randomised, placebo-controlled pilot study. The amount of rescue medication of clomethiazole capsules needed was chosen as the primary variable. Results showed no differences in the need for rescue medication clomethiazole, decrease of withdrawal symptoms, or craving for alcohol between the oxcarbazepine and the placebo group. Subjectively experienced side effects, normalisation of vegetative parameters, craving, or improvement of psychopathological parameters

were not different between the groups. The authors state that despite the negative finding, which may be attributable to the design of the study, oxcarbazepine still poses an interesting alternative to carbamazepine and other drugs because other studies have found it not only as efficient but also as having no addictive potential, while additionally possessing an anti-craving effect. They also suggests that it may have been better to trial it against benzodiazepine instead of placebo.

Gabapentin

A small trial was carried out comparing gabapentin and phenobarbital for the treatment of alcohol withdrawal (Mariani et al. 2006). A randomised, open-label, controlled trial had 27 inpatient participants. Results showed no significant differences in the proportion of treatment completers between treatment groups or the proportion of patients in each group requiring rescue medication for breakthrough signs and symptoms of alcohol withdrawal. There were no significant treatment differences in withdrawal symptoms or psychological distress, nor were there serious adverse events. The authors suggest that gabapentin may be as effective as phenobarbital in the treatment of alcohol withdrawal. However phenobarbital is no longer used in the management of alcohol withdrawal. The small sample size and the choice of a comparison drug, make it difficult to draw any firm conclusions from this study.

A recent double-blind study of 100 patients compared 2 doses of gabapentin (900 mg tapering to 600 mg or 1200 tapering to 800 mg) with lorazepam (6 mg tapering to 4 mg) for 4 days. They found that gabapentin was well tolerated and was clinically similar to lorazepam in reducing alcohol withdrawal symptoms, especially at the high dose. The gabapentin groups reported less craving, anxiety, and sedation compared to lorazepam (Myrick et al. 2009).

Topiramate

In a small study, Choi et al. (2005, cited in Ait-Daoud et al. 2006) found that topiramate 50 mg/day (N =25) was as efficacious as lorazepam up to 4 mg/day (N=27) at treating alcohol withdrawal symptoms in an inpatient setting.

Anticonvulsants: Summary

While some anticonvulsants, such as carbamazepine are effective in minimising alcohol withdrawal symptoms and in preventing primary withdrawal seizures, there is no clear evidence that anticonvulsants are effective in preventing secondary seizures or delirium. There is appears to be no advantage in adding anticonvulsants to benzodiazepines for preventing withdrawal seizures. Phenytoin and valproate are not effective in preventing the onset of alcohol withdrawal seizures. The role of newer anticonvulsants (e.g. gabapentin and topiramate) is yet to be demonstrated in controlled studies against gold standard treatment, such as diazepam. Anticonvulsant medications should be continued in patients who take them regularly (such as for epilepsy not related to withdrawal).

Recommendation	Strength of recommendation	Level of evidence
5.29 Carbamazepine is safe and effective as an alternative to benzodiazepines, although it is not effective in preventing further seizures in	A	1a

withdrawal episodes.

5.30 Phenytoin and valproate are not effective in preventing alcohol withdrawal seizures and are not recommended. A la

5.31 Newer anticonvulsant agents (such as gabapentin) are not recommended at this stage due to lack of clinical evidence. D IV

5.32 There is no benefit in adding anticonvulsants to benzodiazepines to manage alcohol withdrawal. A la

5.33 Anticonvulsant medications should be continued in patients who take them regularly (such as for epilepsy not related to withdrawal). S

Antipsychotic medications: Meta-analyses

Anti-psychotic medication when used alone may increase seizure risk (for example phenothiazines) and do not prevent the onset of delirium, as has been shown in the meta-analyses by Hillbom et al. (2003) (see above in Anticonvulsants) and Mayo-Smith et al. (2004) (see below, in Alcohol Withdrawal Delirium).

Antipsychotics should only be used in conjunction with benzodiazepines in the management of hallucinations or agitation associated with delirium that have not responded to adequate doses of benzodiazepines.

Antipsychotic medications: Randomised controlled studies

There are no placebo-controlled studies of neuroleptics or newer atypical antipsychotics (such as olanzapine and risperidon) for treatment of alcohol withdrawal. Nevertheless, neuroleptics, especially haloperidol, are commonly used (with sedative-hypnotic drugs) in patients with alcohol withdrawal delirium.

Studies reported below provide evidence for safety and effectiveness of some antipsychotic medications either alone or in combination with anticonvulsants in treatment of alcohol withdrawal. These studies, however, are relatively small and the results should be interpreted with caution.

Cyamemazine

Cyamemazine is a phenothiazine derivative with a pharmacological profile close to that of atypical antipsychotics and with some anxiolytic effect. It is not available in Australia. It has been shown to reduce convulsions in animal studies and there is one clinical trial of its efficacy and safety in alcohol-dependent patients (Favre et al. 2005). This was a small multicentre, randomised double-blind study investigating cyamemazine for its efficacy and tolerability in alcohol-dependent patients electing an alcohol withdrawal procedure, in comparison with diazepam. Eighty-nine alcohol dependent patients were randomised to receive cyamemazine or diazepam to compare it for efficacy and tolerability. On day 1, cyamemazine or diazepam (50 mg and 10 mg capsule, respectively) were administered at hourly intervals, with effects measured by reduction in CIWA-Ar (withdrawal scale) scores, up to a maximum of eight administrations. Starting from day 2, the compounds were given twice a day in progressively decreasing doses during a maximum period of 13 days. Similarity of

therapeutic effects and safety were confirmed in both medications. The authors' conclusions were that cyamemazine showed similar efficacy and tolerability to diazepam for the treatment of alcohol withdrawal symptoms at therapeutic doses in the range 100-300 mg. The incidence of delirium tremors or alcohol withdrawal seizures after initiation of treatment was 2.3% (one patient out of 44 for each). It is not clear from the protocol how many patients had a previous history of alcohol withdrawal seizures.

Tiapride/carbamazepine combination

Benzodiazepines can cause respiratory depression, especially in combination with alcohol. Administration of diazepam to patients with blood alcohol concentrations above 0.1% is usually discouraged. Because intoxicated patients quite often seek treatment for alcohol withdrawal, the search for alternative medications continues. Tiapride is an atypical neuroleptic with a dopamine receptor-antagonist activity, often used in treatment of hyperkinesias, including tremor. Tiapride does not prevent delirium or withdrawal seizures and has been studied in a combination with carbamazepine for treatment of alcohol withdrawal.

One small open-label study has compared four treatment conditions for alcohol withdrawal in intoxicated and non-intoxicated patients (Lucht al. 2003). Patients were assigned in blocks of 10 to one of the following: tiapride and carbamazepine (group A) vs clomethiazole (group B) vs diazepam (group C) in non-intoxicated patients and vs tiapride/carbamazepine in intoxicated patients (group D). Findings were that efficacy and safety were not different between groups (total group: delirium, 3.9%; seizure, 0.8%). While treatment could be initiated safely in intoxicated patients, in 18% of cases the tiapride/carbamazepine combination was ineffective in controlling withdrawal symptoms after the blood alcohol concentration fell below 0.1% and a change of medication was required. The authors' conclusions were that treatment with tiapride/carbamazepine can be used in alcohol-intoxicated and in non-intoxicated patients without delirium.

Soyka et al. (2006) used a retrospective study, pooling data from 540 patients to examine the efficacy, practicability and medical safety of a combination of tiapride and fast-acting formula of carbamazepine. Details of alcohol history and comorbid disorders were extracted from patient files. Patients had a long-term history of alcohol dependence and a significant alcohol intake before detoxification. Most patients were still intoxicated at the moment of hospitalisation (median respiratory alcohol 1.6g/l). Most patients had moderate-to-severe withdrawal (baseline CIWA-A-score 12.3). A pooled analysis of the results showed that, in general, medication safe and effective. Withdrawal symptomatology as indicated by CIWA-A scores decreased from baseline to 3.9 on day 5 and 2.6 on day 9). A total of 5 (0.9%) patients developed seizures, 5 on the initial, 2 on the second and 1 on the fourth day. Of the 151 patients who had a previous history of alcohol withdrawal seizures, only 4 developed seizures during treatment. Although a significant number of patients had a history of alcohol withdrawal delirium (103), only 5 of these patients developed delirium. Three patients had first episode of alcohol withdrawal delirium. Only 24 (4.4%) patients dropped out because of lack of efficacy or change of medication, and 15 (2.8%) because of side effects. No case of malignant neuroleptic syndrome was recorded. Severe withdrawal complications were more frequent in men compared to women and in patients with repeated inpatient treatment.

The authors conclude that, in line with previous research, the results from this study give further evidence that a combination of the anticonvulsant carbamazepine and tiapride is an effective and safe combination for the treatment of alcohol withdrawal.

Antipsychotic medications: Summary

Antipsychotic medications should not be a stand alone treatment of alcohol withdrawal but can be used in conjunction with benzodiazepines to treat hallucinations or agitation in patients who do not respond well to benzodiazepines alone. There is insufficient evidence at this stage to recommend cyamemazine or tiapride/carbamazepine combination for treatment of alcohol withdrawal.

Recommendation	Strength of recommendation	Level of evidence
5.34 Antipsychotic medications should only be used as an adjunct to adequate benzodiazepine therapy for hallucinations or agitated delirium. They should not be used as stand-alone medication for withdrawal.	A	Ia

Anti-hypertensive agents

Elevated blood pressure during alcohol withdrawal is usually well managed by adequate doses of benzodiazepines. In cases where blood pressure remains markedly elevated despite adequate benzodiazepine loading, a beta-blocker (e.g. atenolol or propranolol) is recommended. However, the use of propranolol in these patients is limited due to its association with hallucinations (Zilm et al. 1980; Saitz 1998).

Recommendation	Strength of recommendation	Level of evidence
5.35 Anti-hypertensive agents (beta-blockers) should be used for managing extreme hypertension that has not responded to adequate doses of diazepam for alcohol withdrawal.	D	IV

Symptomatic medication

Despite the absence of an empirical evidence base in alcohol withdrawal, symptomatic medications are commonly used in the management of alcohol withdrawal.

Recommendation	Strength of recommendation	Level of evidence
5.36 A range of symptomatic medications may be used for addressing specific symptoms (such as paracetamol for headache, anti-emetics, anti-diarrhoeal agents).	D	IV

Electrolyte disturbances

Hypokalaemia and hypomagnesaemia should be corrected using oral supplements (Saitz and O'Malley 1997; Myrick and Anton 1998). Hyponatraemia is usually self-limiting and should not be aggressively corrected because of the risk of central pontine myelinolysis (Laureno and Karp 1997; Leens et al. 2001).

Recommendation	Strength of recommendation	Level of evidence
5.37 Electrolyte replacement may be a necessary adjunctive treatment for patients with electrolyte abnormalities (such as hypomagnesaemia, hypokalaemia). Hyponatraemia should not be aggressively corrected due to the risk of central pontine myelinolysis.	S	

Other medications

Chlormethiazole (also spelled as clomethiazole) is a short-acting sedative and anticonvulsant medication that was historically widely used for treating alcohol withdrawal before the advent of benzodiazepines. It is no longer recommended for managing alcohol withdrawal due to its risk of respiratory depression and death in overdose or in combination with alcohol or other sedatives.

The use of barbiturates, clonidine and beta-blockers is not recommended for routine management of alcohol withdrawal, based on the meta-analysis by Mayo-Smith (1997). Alcohol (ethanol) (Mayo-Smith 1997; Saitz and O'Malley 1998; Weinberg et al. 2008) and GHB currently have no role in the treatment of alcohol withdrawal.

Studies on effectiveness of GHB in reducing alcohol withdrawal symptoms have been published, but there is no evidence to suggest that they are effective in preventing alcohol withdrawal seizures or delirium. Magnesium is used to correct hypomagnesaemia in patients with alcohol withdrawal, but is not a stand alone treatment (Mayo-Smith 1997).

Recommendation	Strength of recommendation	Level of evidence
5.38 Chlormethiazole, barbiturates, alcohol, beta-blockers, clonidine and gamma-hydroxybutyric acid (GHB) are not recommended in the routine management of alcohol withdrawal.	A	Ia

Treatment of Severe Withdrawal Complications

Severe complications of alcohol withdrawal include seizures, hallucinations and alcohol withdrawal delirium.

Alcohol Withdrawal Seizures

Alcohol acts on the brain through various mechanisms that influence seizure threshold, including calcium and chloride ion flow through glutamate (N-methyl-d-aspartate, NMDA) and gamma aminobutyric acid (GABA) receptors. Chronic alcohol use results in adaptive changes to the effects of alcohol, and the seizure threshold is lowered as a rebound phenomenon when alcohol intake is stopped.

Clinical presentation and prevalence

Alcohol withdrawal seizures (AWS) typically occur 6 to 48 hours after the last drink is consumed (50% between 13 and 24 hours, 90% within 48 hrs), and are usually generalised (tonic-clonic) seizures (Rueff 1995, cited in Prescrire 2007). New-onset alcohol withdrawal seizures are linked to heavy alcohol consumption (Hillbom et al. 2003).

Withdrawal seizures occur as blood alcohol levels fall, and in some severely dependent drinkers, seizures can occur even if the patient is still intoxicated or has consumed alcohol recently and the blood alcohol level is high (for example, greater than 0.10) (Victor and Brausch 1967).

Hillbom et al. (2003) reviewed the placebo arms of four studies of secondary prevention of seizures and estimated that the risk of seizure recurrence within 6-12 hours after a seizure was between 13% and 24%. Whilst the incidence of status epilepticus is low, alcohol withdrawal is major cause of status epilepticus.

The prevalence of alcohol-withdrawal seizures is estimated at between 2 and 9% of alcohol dependent individuals (8% in placebo arms in controlled studies of heavy drinkers in inpatient studies). Individuals who have experienced an alcohol withdrawal seizure are more likely to experience further seizures in subsequent alcohol withdrawal episodes (Hillbom et al. 2003).

The prevalence of seizures in alcohol dependent individuals when all causes are included is up to 15% (Chan 1985). This is at least three times higher than the general population. It is estimated that alcohol-related seizures account for one third of all seizure-related hospital admissions (Chan 1985; Bråthen et al. 2000).

Other causes of seizures in heavy drinkers

Heavy alcohol use can also contribute to seizures through other conditions including concurrent metabolic, infectious, traumatic, neoplastic or cerebrovascular conditions, or through concomitant use of other substances (particularly benzodiazepines). Furthermore, it has been suggested that long-term neurotoxic effects of alcohol may lead to epilepsy (Hauser et al. 1988). Seizures under these circumstances may be atypical of alcohol-withdrawal seizures in onset or type (e.g. partial-onset seizures).

However, other causes of seizures can present clinically as alcohol withdrawal seizures. In a series of 259 individuals with recent alcohol abuse and first onset seizures with no obvious cause other than alcohol withdrawal, 6% showed intracranial lesions on CT scan (Earnest et al. 1988).

Pharmacological approaches to prevention of seizures

Systematic reviews indicate that benzodiazepines effectively prevent alcohol withdrawal seizures, and are effective in preventing recurrent (further) seizures in a withdrawal episode (Mayo-Smith 1997; Hillbom et al. 2003).

In patients with prior seizure history, or in severe alcohol withdrawal diazepam loading is recommended. Carbamazepine effectively prevents alcohol withdrawal seizures, but is not effective in preventing recurrent (further) seizures in a withdrawal episode (Hillbom et al. 2003).

There appears to be no advantage in adding anticonvulsants to benzodiazepines for preventing alcohol withdrawal seizures (Hillbom et al. 2003).

Phenytoin and valproate do not effectively prevent the onset of alcohol withdrawal seizures and are not recommended (Hillbom et al. 2003). The role of other anticonvulsants (such as gabapentin, topiramate) is yet to be demonstrated, and while their GABA-ergic actions suggest they may be useful, they are not recommended at this stage.

See 'Medications for managing alcohol withdrawal' above for more detail.

Assessing and managing seizures in heavy drinkers

Many heavy drinkers present to services (e.g. hospital, paramedic) following a seizure, and can pose a diagnostic dilemma for clinicians. The diagnosis of alcohol withdrawal seizures is one of exclusion of other causes of seizures, such as epilepsy, seizures due to head injury, subdural hematoma or metabolic, neoplastic, infectious, cardiovascular and other causes (Saitz 1998; Rathlev 2002, cited in Hughs 2008; Hillbom et al. 2003; Bråthen et al. 2005).

Studies investigating the diagnosis and management of alcohol withdrawal seizures have been reviewed by Hillbom et al. (2003) and the European Federation of Neurological Societies task force (Bråthen et al. 2005).

An alcohol withdrawal seizure can be diagnosed if none of the following criteria are present:

- clinical features or suspicion of other causes of seizures (such as head injury, metabolic, infectious, neoplastic, cerebrovascular disorders)
- no previous seizure history
- the patient experiences two or more seizures in succession
- partial-onset (focal) seizures
- seizure occurring more than 48 hours after last drink

- no recent heavy alcohol use or other features of alcohol withdrawal.
- If any of the above criteria are present, alcohol withdrawal seizures should not be assumed. (Hillbom et al. 2003; Bråthen et al. 2005)
- The patient should be admitted into hospital, assessed for other causes of seizures, and monitored for at least 24 hours. Careful collateral history should be taken where possible (Bråthen et al. 2005).
- Clinical examination should focus on differentiation between epileptic and alcohol withdrawal seizures.
- Table 5.2 identifies common differences between alcohol withdrawal seizures and epileptic seizures.

Table 5.2 Post-ictal signs and symptoms: comparing epilepsy and alcohol withdrawal seizures

	Epilepsy	Alcohol withdrawal seizures
Consciousness level	Post-ictal sleep/drowsy	Sleeplessness
Mood	Calm	Anxiety, agitated
Tremor	No	Yes
Sweating	No	Yes
BP, PR	Normal	Elevated
Temperature	Normal/slight fever	Fever (lower than 38.5°C)
Arterial bloods	Normal	Respiratory alkalosis
EEG	Pathology	Normal, low-amplitude

Notes: EEG – electroencephalogram; BP, PR – blood pressure, pulse rate

Source: EFNS guideline on the diagnosis and management of alcohol-related seizures: Report of the European Federation of Neurological Societies task force (2005) .available at

<http://www.guideline.gov/summary/summary.aspx?doc_id=9648>

Where the likely diagnosis is alcohol withdrawal seizures, patients should be administered benzodiazepines to prevent further (secondary) seizures (see Loading-dose therapy above).

Where the diagnosis of alcohol withdrawal seizures can be established against criteria (above), the patients should be admitted into a supervised withdrawal setting for at least 48 to 72 hours and monitored for vital signs, alcohol withdrawal symptoms and neurological symptoms. Thiamine administration (100 mg three times daily intramuscular or intravenous) before carbohydrate is recommended as prophylaxis of Wernicke's encephalopathy. Supportive management, including nursing in a quiet environment away from excessive sensory stimuli and rehydration should be provided. Diazepam loading to prevent further alcohol withdrawal seizures is recommended as described above, in Loading-dose therapy.

Recommendation	Strength of recommendation	Level of evidence
5.39 Alcohol withdrawal seizure should only be	B	II

assumed if the clinical presentation is typical of an alcohol withdrawal seizure, no other causes of seizure are suspected, and the patient has a history of previous alcohol withdrawal seizures. All other cases need full investigation.

5.40 Heavy drinkers with a seizure of unknown cause should be admitted to hospital and monitored for at least 24 hours. Investigations include biochemical tests and neuro-imaging, and possibly EEG.	C	III
5.41 Loading with benzodiazepines (diazepam, lorazepam) and close monitoring for at least 24 hours is recommended after an alcohol withdrawal seizure.	A	Ia
5.42 Anticonvulsants are not effective in preventing further seizures in the withdrawal episode.	A	Ia

Role of long-term anticonvulsants for patients with alcohol withdrawal seizures

Patients should not be initiated on long-term anticonvulsants unless there are other causes of seizure activity. Alcohol withdrawal seizures will not recur if the patient remains abstinent, and most patients have very poor adherence with anticonvulsants if they recommence alcohol use, and indeed may even increase the risk of seizures due to erratic anticonvulsant use (Hillbom et al. 2003).

Recommendation	Strength of recommendation	Level of evidence
5.43 Long-term anticonvulsant treatment is not recommended to prevent further alcohol withdrawal seizures.	D	IV

Hallucinations

Patients may experience hallucinations or other perceptual disturbances (e.g. misperceptions) at any stage of the alcohol withdrawal phase and are not a predictor of alcohol withdrawal delirium (Holloway 1984, cited in Turner et al. 1989). Hallucinations may be visual, tactile or auditory. Visual hallucinations commonly reported by patients include bugs crawling on the walls or patient’s bed. Auditory hallucinations are often voices that are accusatory in nature and patients appear frightened and paranoid. Visual and auditory hallucinations may occur simultaneously. Hallucinations occur on the background of clear sensorium in contrast with the clouded consciousness characteristic of alcohol withdrawal delirium (Turner et al. 1989). The autonomic symptoms of withdrawal may be absent.

Assessment and monitoring

Thorough psychiatric evaluation is required in order to exclude concomitant medical or psychiatric conditions.

Medication

There are no controlled trials demonstrating the superiority of different antipsychotic medications, and practitioners should use medications with which they are most familiar.

Antipsychotic medication should not be used in isolation (i.e. without adequate benzodiazepine loading) as they do not adequately prevent the onset of alcohol withdrawal delirium and may lower seizure threshold.

Alcoholic hallucinosis

Chronic alcohol use can result in an organic psychotic disorder, most commonly with hallucinatory features (alcoholic hallucinosis), that can be difficult to differentiate from other causes of psychosis, such as paranoid schizophrenia (Soyka 1990; Glass 1989a). Hallucinations (usually auditory) occur whilst patients are drinking, although may persist during withdrawal, and can be mistaken for alcohol withdrawal hallucinations.

Alcoholic hallucinosis is a rare syndrome, compared to alcohol withdrawal delirium, with estimated prevalence of 0.6% (Soyka 2008).

Treatment with antipsychotic medications is recommended until long-term abstinence is achieved and symptoms ameliorate. The prognosis is usually good if long-term abstinence is maintained, although a minority (10-20%) will develop a chronic schizophrenia-like syndrome (Glass 1989b).

Treatment of alcoholic hallucinosis with sodium valproate has been investigated in a double-blind placebo-controlled study (Aliyev and Aliyev 2008). The results of the study suggest that valproate reduces auditory hallucinations in patients with alcoholic hallucinosis.

Alcohol Withdrawal Delirium

Alcohol withdrawal delirium is also referred to as delirium tremens or DTs and the terms can be used interchangeably.

Clinical presentation and prevalence

The features of alcohol withdrawal delirium are disturbance of consciousness and changes in cognition or perceptual disturbance developing in a short period of time during or shortly after alcohol withdrawal syndrome (American Psychiatric Association 2000). It is accompanied by other symptoms of withdrawal, such as high fever, tachycardia, hypertension and diaphoresis (Mayo-Smith et al. 2004).

The incidence of alcohol withdrawal delirium in placebo-treated alcohol dependent patients entered into inpatient clinical trials averages at 5% (Mayo-Smith 1997). Early studies reported mortality rates as high as 15%, however, mortality rates have fallen with advances in management to less than 1% (Mayo-Smith et al. 2004),

Concomitant medical conditions are common and may include dehydration, electrolyte abnormalities, renal failure, unrecognised head trauma, infections (including meningitis), gastrointestinal haemorrhage, pancreatitis, liver failure,

Management

The initial treatment goal in patients with AWD is control of agitation. Rapid control of agitation reduces the incidence of subsequent adverse events. Hospitalisation is recommended.

Mayo-Smith et al. (2004) have reviewed 49 studies investigating treatment of alcohol withdrawal delirium and conducted a meta-analysis of nine randomised clinical trials. Sedative hypnotics were found more effective than neuroleptics in reducing mortality from alcohol withdrawal delirium (relative risk of mortality with neuroleptic treatment compared with sedative-hypnotic treatment was 6.6 (95% confidence interval, 1.2-34.7). Sedative-hypnotic agents were superior to neuroleptic agents in reducing the duration of alcohol withdrawal delirium. The authors recommend that control of agitation should be achieved using parenteral rapid-acting sedative-hypnotic agents. Adequate doses should be used to maintain light somnolence for the duration of delirium. Coupled with comprehensive supportive medical care, this approach is highly effective in preventing morbidity and mortality.

Monitoring and assessment

There are no controlled studies assessing these issues, the literature includes recommendations from clinical experts and case reports reviewed by Mayo-Smith et al. (2004). Thorough medical evaluation is required in order to identify complications of alcohol withdrawal delirium (such as electrolyte disturbances) and concomitant medical conditions.

Close monitoring and supervision (preferably one-to-one) may be needed to ensure safety of the patient from harm to self or others. Vital signs (including pulse, blood pressure, temperature) should be monitored frequently. Patient should be managed in a quiet room with minimal sensory stimulation.

Recommendation	Strength of recommendation	Level of evidence
5.44 Alcohol withdrawal delirium requires hospitalisation, medical assessment, and close monitoring.	A	I
5.45 Patient should be managed in a quiet environment with minimal sensory stimulation.	C	III

IV fluids and nutritional supplements

Electrolyte abnormalities should be corrected. In particular, hypomagnesaemia is often reported in patients with AWD, and magnesium administration may help reduce neuromuscular activity and agitation (Saitz and O'Malley 1997).

Recommendation	Strength of recommendation	Level of evidence
5.46 Dehydration and electrolyte imbalance should be corrected.	S	

Medication

Benzodiazepines are recommended as the primary medication in managing AWD, reducing mortality, duration of delirium and with fewer complications than with neuroleptics in controlled trials (Mayo-Smith et al. 2004).

Controlled studies are lacking with regards to the most effective benzodiazepine, or route of administration.

Antipsychotic medications should be used as second-line medication in controlling agitation of AWD, as an adjunct to (not instead of) adequate benzodiazepine doses (Mayo-Smith et al. 2004). There are no controlled trials demonstrating the superiority of different antipsychotic medications, and practitioners should use medications with which they are most familiar.

The newer antipsychotic agents (e.g. risperidone, olanzapine, quetiapine) have a better safety profile.

Recommendation	Strength of recommendation	Level of evidence
5.47 Benzodiazepines should be used to achieve light sedation. Oral diazepam or lorazepam loading until desired effect is the treatment of choice. Intravenous diazepam or midazolam is appropriate if rapid sedation is needed.	A	1a
5.48 Antipsychotic medications should be used to control agitation of alcohol withdrawal as an adjunct to (not instead of) adequate benzodiazepine doses.	A	1a

Wernicke's Korsakoff's Syndrome

Wernicke's encephalopathy is a form of acute brain injury resulting from a lack of thiamine (vitamin B1) that most commonly occurs in chronically alcohol dependent individuals (Victor et al. 1989). In alcohol dependent patients thiamine deficiency occurs due to poor dietary intake and due to intestinal malabsorption. It is estimated that healthy subjects absorb 4.5% of an oral dose of thiamine, compared to 1.5% in alcohol-dependent patients (Thomson et al. 2002). The condition is initially reversible, but if untreated or inadequately treated can lead to Korsakoff's syndrome, a chronic and disabling condition characterised by severe anterograde amnesia and often presents with confabulation. Korsakoff's is not associated with dementia or delirium.

Approximately one quarter of patients with Wernicke's encephalopathy recover completely, a quarter show significant improvement, a quarter only partially recover, and one quarter no improvement with time. Approximately one quarter require long-term institutional care (Cook et al. 1998).

There is no effective treatment of Korsakoff's Syndrome.

Clinical presentation and diagnosis

The initial diagnosis of Wernicke's encephalopathy remains clinical. The classic triad of signs of Wernicke's encephalopathy syndrome are:

- Confusion or mental impairment (estimated to occur in 80% of cases)
- Ataxia (approximately 20-25% of cases)
- Eye signs - nystagmus, ophthalmoplegia (approximately 30% of cases) (Harper 1986).

Only a minority of patients with Wernicke's encephalopathy (estimated at 10%) exhibit all three signs. In rare cases, untreated Wernicke's encephalopathy may result in hypothermia, hypotension, coma and death (Harper et al. 1986).

Wernicke's encephalopathy is grossly under-diagnosed (Thomson et al. 2002). Post-mortem studies reveal changes diagnostic for Wernicke's encephalopathy in 12.5% of heavy drinkers (compared to 1.5% of general population). Fewer than 80% of these cases are diagnosed before post-mortem (Harper et al. 1986; Cook et al. 1998).

Clinical features of Wernicke's encephalopathy may be misinterpreted as alcohol intoxication, alcohol withdrawal, head injury, or other causes of confusion in heavy drinkers. Whilst there are no specific routine diagnostic tests for Wernicke's encephalopathy, magnetic resonance imaging (MRI) remains a valuable technique (Sechi and Serra 2007). It can usually detect symmetric alterations in the mamillary bodies, medial thalami, tectal plate, and periaqueductal area (Chung et al. 2003; Estruch et al. 1998; Sechi and Serra 2007). In patients with a history of alcohol abuse, contrast media and other methods of enhanced MRI can often identify mamillary body lesions typical for Wernicke's encephalopathy, even in the presence of normal unenhanced MR images. MRI has low sensitivity (53%) but high specificity (93%) for Wernicke's encephalopathy (Antunez et al. 1998). Valuable adjuncts for an early diagnosis of Wernicke's encephalopathy are MR fluid-attenuated inversion recovery (FLAIR) sequence and diffusion-weighted MRI (Sullivan and Pfefferbaum 2009).

Diagnosis of Wernicke's encephalopathy requires a high index of suspicion in heavy or chronic drinkers, especially if there are any clinical features consistent with Wernicke's encephalopathy or Korsakoff syndrome (e.g. memory impairment).

Recommendation

Strength of recommendation

Level of evidence

5.49 Clinicians should consider MR contrast neuro-imaging where the diagnosis of Wernicke's encephalopathy is not clinically established.

D

III

Preventing and treating Wernicke's encephalopathy

The most recent meta-analysis of studies examining efficacy of thiamine in preventing and treating Wernicke's encephalopathy in patients with alcohol dependence (Day et al. 2009) found insufficient evidence to guide clinicians in the

choice of thiamine dose, frequency and route of administration or duration of treatment. Only two randomised controlled studies were identified and only one contained data sufficient for quantitative analysis. The current approach described in this section, is based on uncontrolled trials and expert opinion (e.g. Thomson et al. 2002; Lingford-Hughes et al. 2004; Thomson and Marshall 2006; Feeney and Connor. 2008).

Is recommended that:

- all heavy or chronic drinkers should be considered at risk of Wernicke's encephalopathy
- all patients undergoing alcohol withdrawal should be treated with thiamine to prevent Wernicke's encephalopathy and
- all patients with any features of WE should be treated as though Wernicke's encephalopathy is established.

Prophylaxis

In patients showing no clinical features of WE or memory impairment, thiamine is recommended as a prophylactic measure. See Section on Thiamine and other supplements in this chapter.

Treatment

All heavy drinkers with any features of WE (e.g. confusion, ataxia, eye signs), coma, memory impairment, hypothermia with hypotension, or delirium tremens should be treated as though WE is established (even if intoxicated). Thiamine should be given BEFORE any carbohydrate load (e.g. IV glucose). Parenteral doses of at least 500mg per day thiamine (IM or IV diluted in saline over 30 minutes) should be administered daily for at least 3 to 5 days, with subsequent doses of at least 300mg (oral or parenteral) per day for 1 to 2 weeks. Any electrolyte disturbances, including hypomagnesaemia, should be corrected.

Recommendation	Strength of recommendation	Level of evidence
5.50 All patients exhibiting any features of Wernicke's encephalopathy should be treated as though Wernicke's encephalopathy is established.	D	III
5.51 All patients suspected of Wernicke's encephalopathy should be treated with high-dose parenteral thiamine (at least 500 mg daily) for at least 3 to 5 days. The intramuscular route should not be used for patients with coagulopathy. Subsequent oral thiamine doses of 300 mg per day for several weeks.	D	III
5.52 Patients suspected of Wernicke's encephalopathy should have hypomagnesaemia corrected in order for thiamine supplements to be effective.	D	III

Long-term thiamine use in persistent drinkers

Oral thiamine (e.g. 100mg daily) should be maintained until long term abstinence has been achieved. Persistent drinkers should be maintained on oral thiamine supplements.

References

- Ait-Daoud, N, Malcolm RJ, Jr. and BA Johnson 2006, An overview of medications for the treatment of alcohol withdrawal and alcohol dependence with an emphasis on the use of older and newer anticonvulsants. *Addict Behav* 31(9): 1628-1649.
- Aliyev, ZN and NA Aliev 2008, Valproate treatment of acute alcohol hallucinosis: a double-blind, placebo-controlled study. *Alcohol Alcohol* 43(4): 456-459.
- Amato, L, Minozzi S, Davoli M et al. 2008, Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev.* (4):CD005031.
- Ambrose, ML, Bowden SC and G Whelan 2001, Working memory impairments in alcohol-dependent participants without clinical amnesia. *Alcohol Clin Exp Res.* 25(2): 185-191.
- American Psychiatric Association 2000, Diagnostic and Statistical manual of Mental Disorders, Fourth Edition, Text Revision. Washington DC: American Psychiatric Association.
- Antunez, E, Estruch R, Cardenal C et al. 1998, Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. *AJR AM J Roentgenol* 171(4): 1131-1137.
- Ballenger, JC and RM Post 1978, Kindling as a model for alcohol withdrawal syndromes. *Br J Psychiatry* 133: 1-14.
- Benca, RM, Obermeyer WH, Thisted RA et al. 1992, Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry* 49(8): 651-668;
- Benzer, DG 1990, Quantification of the alcohol withdrawal syndrome in 487 alcoholic patients. *J Subst Abuse Treat* 7(2): 117-123.
- Bostwick, JM and MI Lapid 2004, False positives on the Clinical Institute Withdrawal Assessment for Alcohol - Revised: is this scale appropriate for use in the medically ill? *Psychosomatics* 45(3): 256-261.
- Bråthen, G, Ben-Menachem E, Brodtkorb E et al. 2005, EFNS guideline on the diagnosis and management of alcohol-related seizures: report of an EFNS task force. *Eur J Neurol* 12(8): 575-581.
- Brower, KJ, Aldrich MS, Robinson EA et al. 2001, Insomnia, self-medication, and relapse to alcoholism. *Am J Psychiatry* 158(3): 399-404.
- Caetano, R, Clark CL and TK Greenfield 1998, Prevalence, trends, and incidence of alcohol withdrawal symptoms: analysis of general population and clinical samples. *Alcohol Health Res World* 22: 73-79.
- Chan, AW 1985, Alcoholism and epilepsy. *Epilepsia* 26(4): 323-333.
- Chung, SP, Kim SW, Yoo IS et al. 2003, Magnetic resonance imaging as a diagnostic adjunct to Wernicke's encephalopathy in the ED. *Am J Emerg Med* 21(6): 497-502.

- Cook, CCH, Hallwood PM and AD Thomson 1998, B-vitamin deficiency and neuro-psychiatric syndromes in alcohol misuse, *Alcohol Alcohol Suppl* 33 (4): 317–336.
- Cook, CC 2000, Prevention and treatment of Wernicke-Korsakoff Syndrome, *Alcohol Alcohol Suppl* 35(1): 19–20.
- Daepfen, JB, Gache P, Laundry U et al. 2002, Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. *Arch Intern Med.* 162(10): 1117-1121.
- Day, E, Benthon P, Callaghan R et al. 2004, Thiamine for Wernicke-Korsakoff syndrome in people at risk from alcohol abuse. *Cochrane Database Syst Rev* 1, CD004003.
- Degenhardt, L, Hall W, Teesson M et al. 2000, *Alcohol use disorders in Australia: findings from the National Survey of Mental Health and Well-Being*. Technical Report no. 97. Sydney: National Drug and Alcohol Research Centre.
- Earnest, MP, Feldman H, Marx JA et al. 1998, Intracranial lesions shown by CT scans in 259 cases of first alcohol-related seizures. *Neurology* 38(10): 1561-1565.
- Essardas Daryanani, H, Santolaria FJ, Reimers EG et al. 1994, Alcoholic withdrawal syndrome and seizures. *Alcohol Alcohol* 29(3): 323-328.
- Estruch, R, Bono G, Laine P et al. 1998, Brain imaging in alcoholism. *Eur J Neurol* 5(2): 119-135.
- Favre, J-D, Allain H, Aubin H-J et al. 2005, Double-blind study of cyamemazine and diazepam in the alcohol withdrawal syndrome. *Hum Psychopharmacol* 20(7): 511-519.
- Feeney, GF and JP Connor 2008, Wernicke-Korsakoff syndrome (WKS) in Australia: no room for complacency. *Drug Alcohol Rev* 27(4): 388-392.
- Foster JH and TJ Peters 1999, Impaired sleep in alcohol misusers and dependent alcoholics and the impact upon outcome. *Alcohol Clin Exp Res* 23 (6): 1044–1051.
- Foy, A, March S and V Drinkwater 1988, Use of an objective clinical scale in the assessment and management of alcohol withdrawal in a large general hospital. *Alcohol Clin Exp Res* 12(3): 360-364.
- Glass, IB 1989a, Alcoholic hallucinosis: a psychiatric enigma, 1, the development of an idea. *Br J Addiction* 84: 29-41.
- Glass, IB 1989b, Alcoholic hallucinosis: a psychiatric enigma, 2, Follow-up studies. *Br J Addiction* 84: 151-164.
- Gossop, M, Keaney F, Stewart D et al. 2002, Short Alcohol Withdrawal Scale (SAWS) development and psychometric properties. *Addict Biol* 7(1): 37–43.
- Harper, CG, M Gilesn and R Finlay-Jones 1986, Clinical signs in the Wernicke-Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. *J Neurol Neurosurg Psychiatry* 49(4): 341-345.

- Hauser, WA, SK Ng and JC Brust 1988, Alcohol, seizures, and epilepsy. *Epilepsia* 29 Suppl 2: S66-78.
- Hayashida, M, Alterman AI, McLellan AT et al. 1989, Comparative effectiveness and costs of inpatient and outpatient detoxification of patients with mild-to-moderate alcohol withdrawal syndrome. *N Engl J Med* 320(6): 358-365.
- Hecksel, KA, Bostwick JM, Jaeger TM et al. 2008, Inappropriate Use of Symptom-Triggered Therapy for Alcohol Withdrawal in the General Hospital. *Mayo Clin Proc* 83(3):274-279.
- Heinälä P, Piepponen T and H Heikkinen 1990, Diazepam loading in alcohol withdrawal: clinical pharmacokinetics. *Int J Clin Pharmacol Ther Toxicol* 28(5): 211-7.
- Hillbom, M, Tokola R, Kuusela V et al. 1989, Prevention of alcohol withdrawal seizures with carbamazepine and valproic acid. *Alcohol*, 6: 223-226.
- Hillbom, M, I Pieninkeroinen and M Leone 2003, Seizures in alcohol-dependent patients: epidemiology, pathophysiology and management. *CNS Drugs* 17(14): 1013-1030.
- Holbrook AM, Crowther R, Lotter A, et al. 1999, Diagnosis and management of acute alcohol withdrawal. *CMAJ* 160(5): 675-80.
- Hughes, JR (2008) Alcohol withdrawal seizures. *Epilepsy and Behavior* 15: 92-97
- Kiefer, F, Andersohn C, Otte K, et al. 2004, Long-term effects of pharmacotherapy on relapse prevention in alcohol dependence. *Acta Neuropsychiatr.* 16: 233–238.
- Koethe, D, Juelicher A, Nolden BM et al. 2007, Oxcarbazepine--efficacy and tolerability during treatment of alcohol withdrawal: a double-blind, randomized, placebo-controlled multicenter pilot study. *Alcohol Clin Exp Res* 31(7): 1188-1194.
- Leens C, Mukendi R, Forêt F et al. 2001, Central and extrapontine myelinolysis in a patient in spite of a careful correction of hyponatremia. *Clin Nephrol* 55(3): 248-253.
- Lingford-Hughes, AR, S Welch and DJ Nutt 2004, Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology British Association for Psychopharmacology. *J Psychopharmacol* 18(3): 293-335.
- Lintzeris N, Clark N, Winstok A et al. 2006, *National clinical guidelines and procedures for the use of buprenorphine in the treatment of opioid dependence*. Canberra: Australian Government Department of Health and Ageing.
- Laureno, R and BI Karp 1997, Myelinosis after correction of hyponatremia. *Ann Intern Med* 126(1): 57-62.
- Lucht, M, Kuehn KU, Armbruster J et al. 2003, Alcohol withdrawal treatment in intoxicated vs. non-intoxicated patients: a controlled open-label study with tiapride/carbamazepine, clomethiazole and diazepam. *Alcohol Alcohol* 38(2): 168-175.
- Lum, E, SK Gorman and RS Slavik 2006, Valproic Acid Management of Acute Alcohol Withdrawal. *Ann Pharmacother* 40(3): 441-448.

- Malcolm, R, Myrick H, Roberts J et al. 2002, The differential effects of medication on mood, sleep disturbance, and work ability in outpatient alcohol detoxification. *Am J Addict* 11(2): 141-150.
- Malcolm, R, Myrick LH, Veatch LM et al. 2007, Self-reported sleep, sleepiness, and repeated alcohol withdrawals: a randomized, double blind, controlled comparison of lorazepam vs gabapentin. *J Clin Sleep Med* 3(1): 24-32.
- Manikant, S, BM Tripathi and BS Chavan 1993, Loading dose diazepam therapy for alcohol withdrawal state. *Indian J Med Res* 98: 170-173.
- Mann, K, F Kiefer, R Spanagel, et al. 2008, Acamprosate: recent findings and future research directions *Alcohol Clin Exp Res* 32(7): 1105-1110.
- Mariani, JJ, Rosenthal RN, Tross S et al. 2006, A randomized, open-label, controlled trial of gabapentin and phenobarbital in the treatment of alcohol withdrawal. *Am J Addict* 15(1): 76-84.
- Mayo-Smith, MF 1997, Pharmacological management of alcohol withdrawal. *JAMA* 278 (2): 144-151
- Mayo-Smith, MF, Beecher LH, Fischer TL, et al. 2004, Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med* 164: 1405-1412.
- Miller, WC Jr and L McCurdy 1984, A double-blind comparison of the efficacy and safety of lorazepam and diazepam in the treatment of the acute alcohol withdrawal syndrome. *Clin Ther* 6(3): 364-371.
- Myrick, H and RF Anton 1998, Treatment of Alcohol Withdrawal. *Alcohol Health Res World* 22(1):38-43
- Myrick, H, Malcolm R, Randall PK, et al. 2009, A double-blind trial of gabapentin versus lorazepam in the treatment of alcohol withdrawal. *Alcohol Clin Exp Res* 33(9): 1582-1588.
- Naranjo, CA, Sellers EM, Chater K et al. 1983, Nonpharmacologic intervention in acute alcohol withdrawal. *Clin Pharmacol Ther* 34: 214-219
- NSW Department of Health 2007, NSW drug and alcohol withdrawal clinical practice guidelines. Mental Health and Drug and Alcohol Office, NSW Department of Health.
- NSW Health Department 1999, *New South Wales Detoxification Clinical Practice Guidelines*, NSW Health Department
- Ntais, C, Pakos E, Kyzas P et al. 2005, Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev.* (3):CD005063.
- Ozdemir, V, KE Bremner and CA Naranjo 1994, Treatment of alcohol withdrawal syndrome. *Ann.Med* 26(2): 101-105.
- EFNS 2005, *EFNS guideline on the diagnosis and management of alcohol-related seizures: Report of the European Federation of Neurological Societies task force*. available at <http://www.guideline.gov/summary/summary.aspx?doc_id=9648>

- Polycarpou, A, Papanikolaou P, Ioannidis JPA et al. 2005, Anticonvulsants for alcohol withdrawal. *Cochrane Database Syst Rev* (3): CD005064.
- Prescrire 2007, Alcohol withdrawal syndrome: how to predict, prevent, diagnose and treat it. *Prescrire International* 16(87): 24-31.
- Prince, V and KR Turpin 2008, Treatment of alcohol withdrawal syndrome with carbamazepine, gabapentin, and nitrous oxide. *Am J Health Syst Pharm* 65(11): 1039-1047.
- Reoux, JP and K Miller 2000, Routine hospital alcohol detoxification practice compared to symptom triggered management with an Objective Withdrawal Scale (CIWA-Ar). *Am J Addict* 9(2): 135-144.
- Saitz, R, Mayo-Smith MF, Roberts MS et al. 1994, Individualized treatment for alcohol withdrawal: a randomized double-blind controlled trial. *JAMA* 272(7): 519-23.
- Saitz, R and SS O'Malley 1997, Pharmacotherapies for Alcohol Abuse: Withdrawal and Treatment. In: Samet. JH, Stein. MD and O'Connor. PG (eds) *The Medical Clinics of North America: Alcohol and Other Substance Abuse*. 81(4), pp 881-907, WB Saunders Company Pennsylvania.
- Saitz, R 1998, Introduction to alcohol withdrawal. *Alcohol Health Res World* 22(1): 5-12.
- Satel, SL, Kosten TR, Schuckit MA et al. 1993, Should protracted withdrawal from drugs be included in the DSM-IV? *Am J Psych* 150: 695-704.
- Schik, G, Wedegaertner FR, Liersch J et al. 2005, Oxcarbazepine versus carbamazepine in the treatment of alcohol withdrawal. *Addict Biol* 10(3): 283-288.
- Schuckitt, MA 2006, *Drug and alcohol abuse: a clinical guide to diagnosis and treatment* (6th edn.) New York: Springer.
- Sechi, G and A Serra 2007, Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 6: 442-455.
- Sellers, EM, Naranjo CA, Harrison M et al. 1983, Diazepam loading: simplified treatment of alcohol withdrawal. *Clin Pharmacol Ther* 34(6): 822-826.
- Sgouros, X, Baines M, Bloor RN et al. 2004, Evaluation of a clinical screening instrument to identify states of thiamine deficiency in inpatients with severe alcohol dependence syndrome. *Alcohol Alcohol* 39(3): 227-232.
- Soyka, M, Lutz W, Kauert G et al. 1989, Epileptic seizures and alcohol withdrawal: Significance of additional use (and misuse) of drugs and electroencephalographic findings. *J Epilepsy* 2(2): 109-113.
- Soyka, M 1990, Psychopathological characteristics in alcohol hallucinosis and paranoid schizophrenia. *Acta Psychiatrica* 81:255-259.
- Soyka, M and M Horak 2004, Outpatient alcohol detoxification: implementation efficacy and outcome effectiveness of a model project. *Eur Addict Res*. 10(4): 180-187.

- Soyka, M, Schmidt P, Franz M et al. 2006, Treatment of alcohol withdrawal syndrome with a combination of tiapride/carbamazepine: results of a pooled analysis in 540 patients. *Eur Arch Psychiatry Clin Neurosci* 256(7): 395-401.
- Soyka, M 2008, Prevalence of alcohol-induced psychotic disorders. *Eur Arch Psychiatry Clin Neurosci* 258(5): 317-318.
- Spies, CD, Otter HE, Hüske B et al. 2003, Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. *Intensive Care Med.* 29(12): 2230-2238.
- Sullivan, J, Sykora K, Schneiderman J et al. 1989, Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar), *Br J Addiction* 84 (11): 1353-1357.
- Sullivan, EV and A Pfefferbaum 2009, Neuroimaging of the Wernicke–Korsakoff Syndrome *Alcohol Alcohol* 44(2): 155-165.
- Tartara, A, Manni, R and Mazella, G. 1983, Epileptic seizures and alcoholism: clinical and pathogenetic aspects. *Acta Neurol. Belg.* 83(2): 88-94.
- Thomson, AD 2000, Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke–Korsakoff syndrome. *Alcohol Alcohol Suppl* 35(1): 2–7.
- Thomson, AD, Cook CCH, Touquet R et al. 2002, The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department, *Alcohol Alcohol Suppl* 37(6): 513–521.
- Thomson, AD and EJ Marshall 2006, The treatment of patients at risk of developing Wernicke's Encephalopathy in the community, *Alcohol Alcohol Suppl* 41(2): 159–167.
- Trevisan, LA, Boutros N, Petrakis IL et al. 1998, Complications of Alcohol Withdrawal: Pathophysiological insights. *Alcohol Health Res World* 22(1): 61-66.
- Turner, RC, Lichsyein P, Peden JG et al. 1989, Alcohol withdrawal syndromes: A review of pathophysiology, clinical presentation and treatment. *J Gen Int Med* 4(5): 432-444.
- Valliant, GE 1988, What can long-term follow up teach us about relapse and prevention of relapse in addiction? *Br J Addict* 83(10): 1147-1157.
- Victor, M and RD Adams 1953, The effect of alcohol on the nervous system. *Research Publications of the Association for Research on Nervous and Mental Disorders* 32: 526-573.
- Victor, M and C Brausch 1967, The role of abstinence in genesis of alcoholic epilepsy. *Epilepsia* 8(1): 1-20.
- Victor, M, RD Adams and GH Collins 1989, *The Wernicke-Korsakoff Syndrome and related Neurological disorders due to alcoholism and malnutrition*. Philadelphia: F A Davis Company.
- Wetterling, T, Kanitz RD, Veltrup C et al. 1994, Clinical predictors of alcohol withdrawal delirium. *Alcohol Clin Exp Res* 18(5): 1100-1102.
- Whitfield, CL, Thompson G, Lamb A et al. 1978, Detoxification in 1024 alcoholic patients without psychoactive drugs. *JAMA* 239(14): 1409-1410.

Weinberg, JA, Magnotti LJ, Fischer PE, et al. 2008, Comparison of intravenous ethanol versus diazepam for alcohol withdrawal prophylaxis in the trauma ICU: results of a randomized trial. *J Trauma*. 64(1): 99-104.

Zilm, DH, Jacob MS, MacLeod SM et al. 1980, Propranolol and chlordiazepoxide effects on cardiac arrhythmias during alcohol withdrawal. *Alcohol Clin Exp Res* 4(4): 400-405.