



PSYCHOPHARMACOLOGICAL MANAGEMENT OF ACUTE ALCOHOL WITHDRAWAL SYMPTOMS. A REVIEW

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Various health organizations advise integration of training for alcohol withdrawal management.

ABSTRACT

Evidence based medicine suggest that implementations of a clinical protocol for the management of acute alcohol withdrawal symptoms improves patient's outcome. Clinical guidelines were developed by several institutions mainly to ensure high quality, person centered, and safe management of alcohol withdrawal symptoms with a large variation in the local practice especially in the management of unplanned alcohol withdrawal with regards to the regime, choice of benzodiazepines and appropriate vitamin supplementation. Various health organizations advise integration of training for alcohol withdrawal management. Timely assessments and staff education increase patient monitoring, create a safer and caring environment, reduce the risks including agitation to staff and other patients and enhance the quality of care. This review looked at the various National Health Services Hospitals with guidelines and protocols providing a comprehensive review for the acute management of alcohol withdrawal symptoms

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INTRODUCTION

Alcohol withdrawal symptoms could be elicited when patients are referred for admission late at night or over the weekends, consequently it may be inevitable to implement alcohol withdrawal management to avoid morbidity and possible mortality after ruling out other disorders¹Patients should be treated in a Medical ward especially if the symptoms are severe as it will be safer²

Detoxification is the treatment of symptoms and complications occurring after a period of heavy and sustained alcohol misuse³. The Goals of detoxification includes providing a safe withdrawal from alcohol enabling the patient to become drug free, providing relief of subjective symptoms, prevention of withdrawal complications such as Delirium Tremens (DT) and Korsakov's encephalopathy, providing a humane withdrawal protecting the patient's dignity and preparing for management of alcohol dependency^{4, 5}. This is a review of alcohol withdrawal treatment including for high risk patients such as the elderly or patients suffering from co-morbid hepatic impairment.

Alcohol Withdrawal Symptoms

Significant symptoms can be associated with the abrupt cessation of alcohol intake in individuals that suffer from alcohol dependence.

The Diagnostic and Statistical Manual (DSM 5)⁶ Criteria for alcohol withdrawal requires the cessation of (or reduction in) heavy and prolonged alcohol use and two or more of the following developing within hours to a few days; automatic hyperactivity (ex; sweating or pulse greater than 100 beats per minute), increased hand tremors, Insomnia, Nausea or Vomiting, Transient visual, tactile or auditory hallucinations or illusions, psychomotor agitation, anxiety, grand mal seizures. The symptoms cause clinically significant distress or impairment in social or occupational or other important areas of functioning. Symptoms should not be due to a general medical condition and are not better accounted for by another mental illness.

The US Preventive Services task force recommends screening patients for problem drinking through a careful history or standardized screening questionnaire for example, The Alcohol Used Disorders Identification, known as AUDIT is one assessment tool used in identification of alcohol misusers

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with a minimum score of zero and a maximum score of 40. A score of 8 or more is suggestive of hazardous or harmful alcohol consumption⁷

Alcohol withdrawal symptoms can range from mild to severe symptoms: Mild symptoms may include tension, irritability, poor concentration, anxiety, tremors, mood and sleep disturbances^{8,9}. Moderate symptoms may include nausea, tremors, sweating, headache, vomiting, flu-like symptoms, anxiety, tachycardia, and transient auditory hallucination⁹; while severe symptoms may include confusion, vomiting, visual and auditory hallucinations, delusions, aggressive behaviors, ataxia, seizures, altered consciousness, sweating, fever, tremors and dehydration⁹.

What is Alcoholic Hallucinosi s?

Alcoholic hallucinosis may develop 12 to 24 hours after cessation of Alcohol use. Alcoholic hallucinosis can be visual (for example bugs crawling on the bed), auditory (frequently derogatory or accusatory voices) or tactile but otherwise a clear sensorium, compared to Delirium Tremens where the sensorium is impaired^{2,10,11}.

What is Alcohol withdrawal Delirium or Delirium Tremens (DT)?

Alcohol Withdrawal Delirium or DT may develop 48 to 72 hours after cessation of Alcohol use. DT have a mortality rate of 1 to 5 % and can increase to 15 to 20 % usually due to cardiovascular and respiratory collapse especially if inappropriately managed^{3,8,10,11}.

Patients with DT can present with fear, hallucinations, predominantly visual but may be tactile or auditory. These hallucinations often evoke severe fear, agitation, restlessness, confusion, disorientation, reversal of sleep pattern, delusions, paranoid ideas, increased Startle reaction, tremors in the hands and body, sweating, dehydration, tachycardia, increased blood pressure while fever (Temperature more than 38.3 C) is common and could be with or without infection. DT usually occur in heavy drinkers who reduced their consumption or withdraw unexpectedly or have been inadequately treated during withdrawal^{3,4,10-14}.

What are the risk factors for progression from mild to severe Alcohol withdrawal Symptoms and DT?

Some factors increase the risk of progression from mild to severe withdrawal symptoms and DT such as fever, high anxiety, tachycardia especially if the heart rate is more than 100, hypoglycemia, insomnia, sweating, hypomagnesaemia, hypocalcaemia, comorbid psychiatric disorders, use of other psychotropic drugs, marked withdrawal symptoms on presentation, older Age, comorbid medical illness such as concurrent urinary or chest infection, abnormal liver functions, dehydration, hypokalemia (especially with respiratory alkalosis), past history of severe alcohol withdrawal, seizures and/or DTs, and high alcohol intake > 15 units per day^{8,11,14}.

Alcohol Related Seizures

Alcohol Related Seizures are more common in patients with a history of multiple episodes of detoxifications and may develop 24 to 48 hours after cessation of alcohol use and rarely beyond 48 hours following cessation. They are usually generalized and may precede or accompany DT. Alcohol Related Seizures are characterized by major tonic motor

seizures occurring during withdrawal in patients who normally have normal EEGs or no seizures. Fits can be single or generalized and 30 % are followed by DT^{8,10,14}.

Wernicke's encephalopathy (WE) and Korsakoff's syndrome

WE is characterized by a triad of confusion, ataxia (muscle incoordination) and ophthalmoplegia (paralysis of the ocular muscle). Other findings are nystagmus, hypothermia, hypotension and memory disturbance. High level of suspicion is important because not all symptoms may be present as the presence of only one symptom could be highly suggestive. WE is a complication caused by Thiamine (Vitamin B1) deficiency and detoxification is a risk factor. Untreated WE can lead to permanent brain damage, Korsakoff's syndrome (characterized by antegrade amnesia, confabulation with relative preservation of intellectual functions)^{2,10,12,15}.

Hypoglycemia

Hypoglycaemia could lead to the development of acute confusion especially in the early stages of detoxification. The treatment of hypoglycemia is by administering parental Thiamine and glucose to prevent the precipitation of Acute Wernicke's Encephalopathy, ideally done in a Medical ward or Emergency department^{2,16}.

Patients that should be admitted or referred urgently to a medical rather than a psychiatry ward for detox are those with suspected DT or past history of DT, WE, severe symptoms, suspected seizures or past history of seizures related to alcohol withdrawal, history of detox in a medical ward for severe alcohol withdrawal, organic complications of alcohol dependence such as evidence of alcoholic liver disease, malnutrition or nil by mouth, respiratory disease or evidence of other acute Medical disorder on presentation, pregnancy or elderly patients above 70 years or above 60 years with frailty^{2,11,13,17,18}.

Laboratory Investigations for Alcohol withdrawal patients

The following tests should be carried as part of the screening of any suspected alcohol dependency or withdrawal; alcohol breath test, FBC, U&E, LFT, GGT, Amylase, B12, folate, glucose, magnesium, TFT, INR, ECG, abdominal ultrasound^{10,11,19}.

Pharmacological Management of Alcohol withdrawal

Psychopharmacology decision should be initiated depending on the history and objective evidence as not all patients will have serious withdrawal symptoms. Most inpatient alcohol detox should be completed in 7 to 10 days¹⁵. The psychopharmacology management in alcohol withdrawal should ensure the suitable medication in the right dose, in the correct time to control the symptoms and keep the patient comfortable without the risk of sedation^{4,20}.

Benzodiazepines

There is evidence that benzodiazepines are the treatment of choice to reduce alcohol withdrawal signs and symptoms, prevent alcohol related seizures and reduce DT^{1,8,15,21}. Oral Drugs are recommended for the routine management of Alcohol withdrawal¹⁹.

In the absence of hepatic impairment, long acting benzodiazepines such as chlordiazepoxide and Diazepam are recommended with chlordiazepoxide the treatment of choice in uncomplicated detoxification due to its reduced potential for dependency compared to Diazepam^{11,14,22}. A fixed dose of

chlordiazepoxide withdrawal regime should be prescribed in patients where it is difficult to rate their alcohol dependence¹⁴. Diazepam may be an alternative in patients requiring very high doses due to its longer half-life.

It is recommended to use one benzodiazepine and avoid using multiple benzodiazepines¹³. Overdose of benzodiazepine can cause respiratory depression and mortality, while undertreating alcohol withdrawals could lead to DT, seizures and mortality^{13, 15}.

During the first 24 hours; mild symptoms that are not causing distress may not require medications. For mild symptoms, chlordiazepoxide can be prescribed when required only if symptoms developed but this requires more experienced staff for monitoring the symptoms¹¹, alternatively it could be prescribed on a fixed but reducing regime based on the clinical judgment.

In moderate to severe withdrawal symptoms, a reducing regime of chlordiazepoxide over 5 to 7 days is recommended. Longer period of reducing regime may be needed in severe symptoms and up to 10 days¹¹.

The dose is estimated by initial assessment of the predicted withdrawal intensity, for example, Stat Dose of chlordiazepoxide 20 to 50 mgs followed by 20-30 mgs QDS. (Lower doses could be used in mild symptoms and higher in moderate to severe symptoms). Additional when required chlordiazepoxide 10 -20 mgs QDS must be available and doses may be increased in more severely dependent drinkers^{9, 13, 19}.

From the second to the fifth day, consider subsequent reduction regime by approximately 20% of the chlordiazepoxide dose every day. Doses of 30mg qds or above should only be prescribed when severe withdrawal symptoms expected and the patient's response to treatment must be regularly and closely monitored¹.

Example of a reducing regime for chlordiazepoxide¹¹

Day	Dose of chlordiazepoxide
1	20 mgs QDS
2	15 mgs QDS
3	10 mgs QDS
4	10 mgs BD
5	10 mgs OD

The level of observation should Initially be every 15 minutes monitoring of BP, pulse, respiratory rate, pulse oximetry and orientation¹¹ for three days because of the risk of seizures and DT then twice daily and more frequent if needed^{14, 17, 23}.

Respiratory rate should not be less than 10 /min and pulse oximetry should not be less than 90%. Doses of chlordiazepoxide in excess of 100mg daily can be prescribed in selected cases and in case of over sedation, benzodiazepines next dose could be missed and the regime reviewed¹³.

Patients with Severe Hepatic Impairment

Patients with deranged liver function tests and clinical signs of hepatic disease should be referred to a medical unit³. The metabolism of chlordiazepoxide is impaired in liver disease, but could be used cautiously in mild to moderate hepatic impairment (reduce the dose by 50%). Shorter acting benzodiazepines such as oxazepam or lorazepam should be considered as their metabolism is not impaired in liver disease^{8, 10, 14, 19}.

Lorazepam 0.5 mg is equivalent to chlordiazepoxide 10 mg, which is equivalent to diazepam 5 mgs is equivalent to Oxazepam 15 mgs^{3, 24}.

Elderly patients

To minimize the side effects of benzodiazepines in the elderly, start very slow and go very slow as a rule. It is recommended that half the dose of benzodiazepines can eventually be used¹⁴. Oxazepam has a shorter half-life and less prone to toxicity and could be considered as an alternative to chlordiazepoxide in the elderly^{13, 24}.

What if Benzodiazepines are not suitable for the patient?

Carbamazepine is an appropriate alternative to benzodiazepines in the treatment of alcohol withdrawal symptoms. It does not show significant difference in the adverse effects compared to benzodiazepines and its dropout rates are generally lower compared to benzodiazepines. Carbamazepine also showed a reduction in alcohol craving after withdrawal, is non-sedating and has less potential for abuse in studies up to 800 mgs of carbamazepine given in the first day with the dose tapered to 200 mgs by the fifth day^{3, 8, 25}.

Clomethiazide can be used in acute alcohol withdrawal if both benzodiazepines and carbamazepine are contraindicated. Gabapentin was also shown to be effective in the treatment of alcohol withdrawal in small studies⁸.

Vitamin Supplement

Oral supplementation may not be sufficient because there is significant impairment in the absorption of vitamins¹⁰. Parental Thiamine is given in form of Intramuscular Pabrinex. The dose is one pair of ampoules daily for 3 to 5 days intramuscularly^{13, 26}. Pabrinex needs to be injected slowly in the upper lateral quadrant into the gluteal muscle, while varying the site of injection with repeated injections¹⁹. Parenteral thiamine is associated with a low risk of anaphylaxis; 1 per 5 million pairs of IM ampoules used, consequently patients given IM Pabrinex should be closely monitored for 30 minutes following injection and equipment for anaphylaxis management should be readily available¹¹.

Parental thiamine administration should be followed by oral Thiamine 100 mgs TDS, vitamin B Compound Strong Two tablets TDS if clinically indicated and multivitamins once daily^{11, 13, 26}. Oral Thiamine should be continued on discharge for 6 months if abstinence is achieved or indefinitely if heavy alcohol drinking continued. The daily dose of Oral Thiamine could be divided to optimize absorption^{16, 26}.

Treatment of Wernicke's consists of 2 to 3 ampoules of Pabrinex IV administered three times daily for at least two days followed by one pair for 3 to 5 days or as long as clinical improvement continues and it must be administered in a specialized medical ward after reviewing the local formulary¹³.

Alcohol Related Seizures

Prophylaxis

Anticonvulsant prophylaxis is not recommended routinely for alcohol withdrawal and remains a matter of clinical judgment depending on the balance of risks and benefits²⁷. Carbamazepine may be the anticonvulsant of choice when used as a prophylaxis 5. Phenytoin must not be prescribed to prevent or treat alcohol withdrawal seizures^{13, 16, 20, 26}.

Treatment

The National Institute of Clinical Excellence in the UK (NICE) recommends the use of buccal Midazolam or rectal Diazepam¹⁷. Some Mental Health Units use Rectal Diazepam 10 mgs for emergency seizure control and can be repeated after ten minutes if the seizure continues¹⁷. Diazepam is also advocated as a benzodiazepine of choice for medically assisted alcohol withdrawal in those with a previous history of seizures^{13, 24}, while other Mental health units advocate the use of buccal midazolam 10 mgs, repeated after ten minutes if necessary for the treatment of alcohol related withdrawal seizures^{17, 26}. Continuing treatment with an anticonvulsant that has been used to treat alcohol withdrawal seizures is not recommended²⁶.

Acamprosate

Treating alcohol dependence after the treatment of withdrawal is good practice and acamprosate is used to maintain abstinence in alcohol dependence^{11, 13}. Treatment can be initiated at the time of detoxification as it may exert a neuroprotective effect³. It is advised that initial prescribing and monitoring is arranged in secondary care for 12 weeks after which can be prescribed in primary care³.

Acamprosate is usually prescribed at a dose of 666 mgs three times daily. If the patient's weight is less than 60 kg, the maximum daily dose is 1332 mgs, (666 mgs twice daily can be prescribed). Acamprosate should be continued for up to 12 months or longer for those benefiting as evidence suggests that the benefit from Acamprosate is maintained for over one year¹¹.

Acamprosate should be stopped if drinking persists for 4 to 6 weeks while taking the medication and it should be avoided in severe hepatic impairment or if the creatinine level is > 120 micromole/L¹³.

Role for other Medications

Naltrexone and Nalmefene are opioid antagonists that may have a role in some patients in maintaining abstinence and depending on the formularies available in some countries. However Naltrexone requires liver function tests before and during treatment. Nalmefene could have a role for those who have a high drinking risk level; ie 7.5 units of alcohol per day or more in men or 5 units per day or more in women. 3, 13 Disulfiram interact with Alcohol to produce increased levels of acetaldehyde, the accumulation of which leads to unpleasant symptoms such as flushing, Nausea, Vomiting, vertigo, headache, and abdominal pain. Consequently may not always be favorable by patients and may require a special consent. 3, 13

CONCLUSION

Acute alcohol withdrawal symptoms can be unexpected and happens shortly after patients being admitted to the hospital and pharmacological management may be needed to ensure the safety of patients and staff. Benzodiazepines, and Thiamine remain the main treatment options to control the symptoms and prevent complications and in most cases will not be needed for more than 5 to 7 days. Complications of alcohol withdrawal include delirium, seizures, Wernicke's encephalopathy and Korsakov's. Good practice involves the treatment of Alcohol dependence after treating alcohol

withdrawal with acamprosate shown to reduce craving with good safety profile.

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