REVIEW

The pharmacologic treatment of alcohol withdrawal syndrome in the ICU

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Abstract

Alcohol withdrawal syndrome (AWS) presents a significant problem among new admissions to the intensive care unit. In patients with a history of alcohol abuse, AWS manifests itself with symptoms of autonomic hyperactivity, tremors, hallucinations, agitation, anxiety, and seizures. Progression of AWS, called delirium tremens (DT), is associated with increased mortality. Traditionally, AWS is treated with benzodiazepines which have a well-established record for reducing symptoms of withdrawal and provide adequate control of both seizures and DT. However, the side-effects of benzodiazepines have prompted the introduction of alternative agents. Anticonvulsants and gamma-hydroxybutyrate do suppress symptoms of AWS, but their effectiveness in the prevention of seizures and DT is doubtful. Ethanol results in less sedation than benzodiazepines, although the evidence for its role in AWS remains limited. Alpha-2 agonists are potent against symptoms of noradrenergic overdrive and are suitable as adjuvants to benzodiazepines. Antipsychotics have no demonstrable effectiveness in AWS and may even be harmful.

Introduction

The incidence of alcohol dependence and associated disorders is high amongst ICU patients. Although there are no epidemiological data for the Netherlands, in the United States between 10% and 33% of patients admitted to the ICU suffer from alcohol dependence[1]. According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) alcohol dependence is formally defined as a maladaptive pattern of alcohol use resulting in clinical impairment or stress as manifested by the development of tolerance and withdrawal, unsuccessful efforts to abstain, consumption of ever greater quantities and the involvement of a considerable amount of time that limits other activities[2]. Symptoms of alcohol withdrawal may occur in up to 91% of alcohol-dependent patients after acute abstinence[3,4]. The syndrome of alcoholic withdrawal consists of signs and symptoms (see *table 1*[2]) developing in alcohol-dependent individuals within 6 to 48 hours after their last intake of alcohol or reduction in intake[5,6]. Although these symptoms are usually mild, 5-10% of alcohol-dependent patients[7] develop a severe dysautonomic and encephalopathic state known as 'delirium tremens' (DT) after 48-72 hours of abstinence[8,9]. In this progression of alcohol withdrawal syndrome (AWS) the autonomic disarray is further exacerbated and the patient's cognition and level of consciousness can change within a short period of time. DT is associated with a mortality rate of 5% which is attributable to complications of its clinical symptomatology like coronary spasms, arrhythmias and myocardial infarction[8].

The natural course of AWS is a gradual lessening of symptoms 72 hours after its onset[9,10]. However, given the high mortality and morbidity, early treatment of AWS is warranted. Since the first clinical descriptions of the syndrome in the nineteenth century, many pharmacologic and therapeutic treatments have been published in medical journals[11]. Reviews of this body of literature are few and inconsistent. The objective of this review is to examine the evidence supporting the popular pharmacologic treatment options for AWS. The subsequent discussion is based on a systematic search of the electronic literature database MEDLINE (PubMed). For each

Table 1. DSM-IV-TR Alcohol withdrawal – diagnostic criteria[2]

A.	Cessation of (or reduction in) alcohol use that has been heavy and prolonged
B.	Two (or more) of the following, developing within several hours to a few days after Criterion A
	- Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100)
	- Increased hand tremor
	- Insomnia
	- Nausea or vomiting
	- Transient visual, tactile, or auditory hallucinations or illusions
	- Psychomotor agitation
	- Anxiety
	- Grand mal seizures
C.	Clinically significant distress or impairment in social, occupational, or other important areas of functioning
D.	The symptoms are not due to a general medical condition and are not better accounted for another mental disorder

pharmacologic agent a search query was composed of synonyms for the respective agent in combination with 'alcoholwithdrawal', 'AWS', 'delirium tremens' and 'DT'. The search results were filtered for relevant meta- analyses, trials, cohort studies and case series. Previous reviews describing a segment of the literature were also consulted.

The resulting review is structured as follows. First, the pathophysiology of alcohol dependency and withdrawal is elucidated. Second, the method of diagnosing AWS is discussed. Third, the evidence supporting the popular pharmacotherapies is presented. The fourth and final section summarizes and concludes.

Pathophysiology

Alcohol or ethanol influences multiple stages of the neurotransmission cascade in the central nervous system. Genetic, pharmacological and electrophysiological studies have demonstrated that alcohol modifies synaptic transmission by altering neuronal excitability through an interaction with ligand and voltage-gated ion channels. The sedative effects of alcohol are principally thought to be the result of its interference with two neurotransmission systems. At low concentrations (< 100 mg/dl) alcohol enhances transmission of gamma-aminobutyric acid (GABA), by promoting chloride conductance through the GABAA-receptor. At higher concentrations (> 250 mg/dl) alcohol works directly on the GABAA-receptor and causes a prolonged opening of its chloride channel that is independent of the neurotransmitter GABA. This second mechanism makes alcohol toxic in overdose. A prolonged opening of the chloride channel causes excessive influx of chloride into neurons of the respiratory system resulting in respiratory depression[10,12]. Continued exposure to alcohol leads to tolerance with downregulation of GABAA-receptors. Besides reinforcing the inhibitory effects of GABA, alcohol tempers excitatory neurotransmission mediated by glutamate. This neurotransmitter binds N-methyl-D-aspartate (NMDA)-receptors resulting in a calcium influx depolarizing the neuron. One of the results of NMDA stimulation is an enhancement of signal transmission between neurons called long-term potentiation which underlies learning and the development of memory. Alcohol serves as a blocker of the NMDA-receptors inhibiting this process and contributing to amnesia and depression of cerebral function. Over time the brain's reaction is to increase the number of NMDA-receptors which allow normal functioning in the presence of alcohol, the formation of tolerance[10,12].

In AWS, GABA neurotransmission is decreased while glutamatergic neurotransmission is increased resulting in a state of heightened excitability. Furthermore, the increased sympathetic activity is due to an overstimulation of noradrenergic neurons following increased glutamate function and the loss of noradrenergic autoinhibition[12]. The hallucinations experienced during withdrawal are caused by an enhanced dopaminergic transmission following disinhibition of dopaminergic neurons through reduced GABAergic activity[10]. Research has shown that the increased susceptibility to seizures seen in patients is likely to have its origin in the deep layers of the superior colliculus where NMDA-receptor mediated excitation is no longer chronically suppressed by alcohol[13].

Diagnosis

AWS should be considered as a diagnosis of exclusion. If the patient's history and physical findings prompt clinical suspicion then alternative etiologies must be ruled out, such as infection (meningitis), head trauma (intracerebral hemorrhage), epilepsy, electrolyte or metabolic disturbances, hepatic failure, intoxication or withdrawal from other substances. The formal diagnostic criteria are listed in *table 1*. The clinical spectrum varies from uncomplicated withdrawal syndrome with patients having a clear sensorium with signs of autonomic hyperactivity and increased sympathetic stimulation. Worsening of the symptoms can result in hallucinations and progression to DT with or without seizures. When the history on alcohol consumption is unavailable or unreliable, biomarkers such as gammaglutamyl transferase (GGT) and carbohydrate-deficient transferrin (CDT) may provide clues for chronic alcohol overuse with combined sensitivities of 81-90% and specificities of 63-95%[14]. Ethanol levels on admission have no predictive value for AWS[15].

After the diagnosis of AWS hs been made, the severity of symptoms can be quantified by the Clinical Institute Withdrawal Assessment Scale for Alcohol (CIWA-Ar)[16,19].

Treatment

Without therapy the symptoms of alcohol withdrawal are expected to reach their peak 72 hours after the last ingestion of alcohol and generally resolve within four days after this moment[9,12]. In most cases the symptoms are relatively mild and no pharmaco-therapeutic management is required. However, in manifest AWS treatment is indicated to avoid DT or seizures. The pharmaco-therapeutic management of AWS entails the substitution of a long-acting agent for alcohol and subsequently to taper its dosage over time[17]. Historically, many different classes of drugs have been tried in the management of AWS. This section provides an overview of the primary pharmacologic agents. The discussion of supportive measures is beyond the scope of this article.

Benzodiazepines

Benzodiazepines have been the mainstay of pharmacotherapeutic treatment of AWS and the prevention of secondary seizures since 1969[18]. Benzodiazepines produce their effect by increasing the affinity of GABAA-receptors for the neurotransmitter GABA. This results in a greater influx of calcium into the neuron which inhibits neurotransmission. In this way benzodiazepines serve as a direct substitute for the GABA-modulating effects of alcohol[7].

The evidence supporting the use of benzodiazepines in AWS is relatively solid with three good quality meta-analyses independently concluding benzodiazepines to be the preferred treatment. Mayo-Smith[19] conducted a meta-analysis of six prospective, placebo-controlled trials from the 1960s to 1980s involving three

different benzodiazepines and concluded that benzodiazepines are more effective than placebo in reducing the occurrence of DT (risk reduction of 4.9 cases of delirium per 100 patients, P=0.04) and in seizure prophylaxis (risk reduction of 7.7 seizures per 100 patients treated, P<0.001). A second meta-analysis was authored by Holbrook et al.[20] and included three randomized, placebo-controlled trials from the 1980s with a total of 112 patients and three benzodiazepines[21-23]. Benzodiazepines were superior to placebo in reducing the signs and symptoms of AWS as measured with the CIWA-Ar score two days after the initiation of therapy (OR 3.28, 95% CI 1.30-8.28). The authors also analyzed eight other randomized, placebo- controlled trials in which benzodiazepines were compared with alternative control drugs. The heterogeneity of the studies prevented pooling but there was no manifest superiority of any alternative agent over benzodiazepines. Benzodiazepines were not appreciably safer when compared with a dopamine-agonist, an anticonvulsant and a tri-cyclic antidepressant (OR 0.67, 95% CI 0.34-1.32). In a more recent meta-analysis, Amato et al.[24] included three randomized, placebo- controlled trials from the 1970s and 1980s with a total of 324 patients in which benzodiazepines were compared with placebo[18,21,23]. Their analysis showed that benzodiazepines perform significantly better in seizure prophylaxis with a relative risk of 0.16 (95% CI 0.04-0.69). When compared with alternative drugs, benzodiazepines demonstrate a non-significant tendency to deliver better seizure and delirium control, fewer adverse effects and a lower dropout rate[24].

The class of benzodiazepines comprises several drugs with varying properties concerning speed of onset, half-life and route of metabolism. Trials comparing different benzodiazepines have failed to produce evidence in favour of the distinct superiority of one benzodiazepine over any other in the treatment of AWS[19,20,24]. There are, nonetheless, several considerations which may guide the choice of benzodiazepine. The longer-acting drugs in this class may provide a smoother course of withdrawal and even be more effective in seizure control. In a meta-analysis of three prospective, controlled trials, a non-significant trend was found towards improved seizure control with longer- acting agents (6.7 fewer cases of seizures per 100 patients, P=0.07)[19,25-27]. Another issue influencing the choice of benzodiazepine is the safety in patients with cirrhotic and other liver diseases. Both diazepam and chlordiazepoxide have a complex metabolism in the liver with active metabolites prolonging the half-lives of both drugs. Decreased liver function enhances and lengthens their sedative effects. In contrast, the shorter acting lorazepam has a simpler metabolism, is less influenced by cirrhosis of the liver and has only inactive metabolites. Consequently, the behaviour of lorazepam is more predictable in patients with hepatic dysfunction. Another potential risk with diazepam is the fact that it is more lipophilic than lorazepam and chlordiazepoxide. This characteristic results in a rapid onset of action because of a swift distribution into the brain. Yet it also causes a rapid redistribution to peripheral fat which may quickly reverse this effect. Given that peripheral fat becomes saturated at an uncertain pace, this effect may lead to oversedation when high doses of diazepam are administered[6].

Anticonvulsants

The sedative side-effects of benzodiazepines and their potential for addiction prompted a search for alternative agents in the treatment of AWS. The beneficial effects of anticonvulsants in the prevention of epileptic seizures resulted in trials examining their use in AWS. The best evidence is available for carbamazepine, an anticonvulsant whose mechanism of action in AWS may be explained by its GABAergic activity[28] and blockade of NMDA-receptors[29]. A recent review by Barrons & Roberts[30] identified three randomized double blinded trials[31-33] in which carbamazepine was compared to a benzodiazepine. In each trial carbamazepine and the benzodiazepine proved equally effective at reducing symptoms of alcohol withdrawal. Moreover, in two trials[31,33] carbamazepine demonstrated significantly greater reduction of symptoms on days 6-7 after the start of treatment. This result remained present in a meta-analysis of the trials by the Cochrane Collaboration[34]. A seizure was observed in just one of the studies[42]. Carbamazepine has also been compared to placebo in a double blinded randomized trial with 105 patients with mild AWS in an outpatient setting. In the group receiving carbamazepine, withdrawal symptoms diminished significantly faster on the second day of treatment with a non-significant tendency continuing on days 4-7[35]. Oxcarbazepine was studied in a single blinded randomized trial in which it demonstrated similar effectiveness to carbamazepine in controlling symptoms of withdrawal[36]. However, when compared to placebo in a group of patients with severe AWS in a double blinded randomized trial, oxcarbazepine was not superior neither in suppressing symptoms, nor in seizure prevention[37].

The effectiveness of the GABA-activity enhancing anticonvulsant valproic acid in AWS has been studied in several small trials[38]. In a double blinded placebo-controlled study of 43 patients with moderate withdrawal symptoms, the group randomized to valproic acid needed significantly less oxazepam for symptom control[39]. In comparison to benzodiazepines, two trials showed that valproic acid is just as effective in reducing symptoms in patients with mild, uncomplicated AWS[40,41].

The potential of the antiglutamergic anticonvulsants topiramate and lamotrigine in treating AWS was assessed in a single blinded randomized trial of 127 patients with significant symptoms[42]. Compared to placebo, both medications were able to significantly reduce withdrawal severity, dysphoric mood and supplementary diazepam administration. However, their performance was no different from that of the control-drug diazepam. Among the older anticonvulsants, phenytoine has not shown to be effective in the treatment of AWS and DT[43], while phenobarbital has demonstrated comparable performance to benzodiazepines[44] but has an unattractive side-effect profile.

In summary, anticonvulsants seem efficacious in the treatment of mild AWS. Nonetheless, their capability for preventing DT or seizures in severe AWS remains unknown.

Ethanol

The use of ethanol in the prophylaxis and treatment of AWS has mostly been limited to surgical wards and intensive care units and is controversial[45,46]. A nation-wide survey in the Netherlands published a decade ago showed that 16% of intensive care units occasionally used ethanol in the context of AWS[47]. In the surgical specialties, ethanol is perceived to possess several advantages over other agents. First, compared with benzodiazepines ethanol does not readily cause drowsiness which may hamper the evaluation of a patient, for example, in a trauma setting. The lack of drowsiness also allows for rapid mobilization of patients in the postoperative period. Second, in comparison with benzodiazepines ethanol is seen to carry less risk of respiratory depression which facilitates weaning and participation in pulmonary toilet. In non-surgical specialties ethanol is not as popular due to a short duration of action, a narrow margin of safety and possible tissue damage at the infusion site[9,48].

Research into the employment of ethanol for the treatment of AWS generally consists of small case series with varying quality of methodology[46]. Two randomized controlled trials have been published. Spies et al.[49] randomized 197 alcohol-dependent surgical patients to four prophylactic regimens started on admission to the ICU: 50 patients received intravenous ethanol, 48 flunitrazepam-clonidine, 49 chlormethiazole-haloperidol and 50 patients were given flunitrazepam- haloperidol. No differences were found between the groups with respect to symptoms of AWS as measured by the CIWA-Ar scale, length of stay in the intensive care and major cardiovascular and pulmonary complications. Weinberg et al.[48] randomized 49 trauma patients with a history of severe alcohol abuse into two groups on admission to the intensive care unit. 26 patients were administered ethanol (5%, max 200 ml/hour) intravenously while 24 patients received diazepam by intravenous or enteral route (max 20 mg/4 hours). The ethanol group proved to be significantly more difficult to keep in a calm and cooperative state when measured with the Riker Sedation- Agitation Scale. All patients managed to wean from therapy 96 hours after initiation with no appreciable difference between the two groups. Note that in both trials ethanol was given intravenously. The enteric administration of ethanol is not recommended because of its narrow margin of safety and the dependency of its intestinal absorption on the presence and composition of gastric contents, smoking habits, medications (ranitidine, erythromycin) and inter- and intra- individual differences in the gastric emptying rate[50]. Moreover, the oral administration of ethanol has been reported to expose patients to taste and behavioural clues promoting relapse into past drinking behaviour[51].

Gamma-hydroxybutyrate (GHB)

Gamma-hydroxybutyrate or GHB is a metabolite of GABA, to which it is structurally similar. GHB is naturally present in the human brain and is involved in the regulation of sleep cycles, temperature regulation, cerebral glucose metabolism and blood flow, memory, and emotional control[52]. Regarding its use in the treatment of AWS, GHB has the interesting characteristic of being a weak agonist of GABAB-receptors and the fact that exogenous GHB is converted to GABA which results in an indirect activation of GABAA-receptors. Consequently, GHB partly mimics the actions of alcohol in the brain and may therefore act as a substitute drug[53]. Compared with placebo, GHB is effective in the treatment of AWS as demonstrated by the results of a single published trial. Gallimberti et al.[54] randomized 23 patients with AWS to placebo or GHB (50 mg/kg) and scored their symptoms on a 30- point scale during seven consecutive hours. At the end of the observation period the withdrawal symptoms in the GHB-group had virtually disappeared while in the placebo group the level of agitation had increased. In two similar trials, GHB has been compared with diazepam[51,55]. A total of 102 alcohol-dependent patients were randomized to either GHB (50 mg/kg) or diazepam (0.5-0.75 mg/kg) and for periods of up to three weeks their symptoms were measured with the CIWA-Ar scale. In both trials GHB performed at least as well as diazepam in treating AWS. In sub scores of the CIWA-Ar scale, GHB proved to be faster in suppressing symptoms of anxiety and agitation.

Concerns for the use of GHB are possible side-effects and its addiction potential. In a review by the Cochrane Collaboration of 13 trials of GHB for the treatment of alcohol related disorders 20% of patients developed transitory vertigo or dizziness at a dose of 50 mg/kg, while 0.6 to 2.5% reported diarrhea, headache, rhinitis or nausea[56]. No serious adverse events occurred. Craving was only seen in the treatment of alcohol dependence in up to 10% of patients.

α2-agonists

The symptoms of AWS are partly the product of noradrenergic overdrive. One of the prime receptors for noradrenergic transmission in the brain is the α2-receptor. Normally this receptor inhibits the firing of the presynaptic norepinephrine neuron, but during AWS its sensitivity is impaired which results in augmented noradrenergic transmission. Accordingly, an exogenous high affinity α2-agonist could potentially reinforce noradrenergic auto-inhibition and be of use in the treatment of AWS[61]. Three small trials[57-59] investigated the application of the α2-agonist clonidine in the prophylaxis for withdrawal in alcohol-dependent patients. Compared with either the sedative chlormethiazole, or the benzodiazepine chlordiazepoxide, no significant difference was found in observer rated symptoms of AWS. However, the groups treated with clonidine had significantly lower blood pressure and heart rate. In another trial, Robinson et al.[60] randomized 32 patients with symptoms of acute alcohol withdrawal to clonidine or chlormethiazole. In the clonidine group eight patients dropped out of treatment due to orthostatic hypotension, seizures or hallucinations. These symptoms were not observed in the chlormethiazole group. Adinoff et al.[61] examined the loading doses required to control symptoms of withdrawal in 25 alcohol-dependent males for diazepam, alprazolam, diazepam and placebo. In contrast to both benzodiazepines, clonidine proved to be no more effective than placebo but did decrease systolic blood pressure significantly. Spies et al. reported that lower median doses of flunitrazepam were required to control symptoms of AWS when

this was combined with clonidine rather than haloperidol[49]. All in all, the above-mentioned research shows that clonidine is effective in the treatment of symptoms of AWS related to noradrenergic overdrive, but does not support clonidine monotherapy for preventing delirium or seizures[62].

Dexmedetomidine, a derivative of the veterinary sedative and analgesic medetomidine, has eight times the affinity of clonidine for the α2-receptor[61]. In the context of AWS, a limited number of case reports demonstrate successful employment of dexmedetomidine for controlling symptoms of noradrenergic overdrive, mainly as an adjunct to benzodiazepines[63-67].

Antipsychotics

Although antipsychotic or neuroleptic drugs, especially haloperidol, are routinely employed in the treatment of AWS[9] no randomized, placebo-controlled trials have ever been published demonstrating their effectiveness. The evidence is limited to predominantly non-randomized benzodiazepine controlled studies and only for the older category of atypical antipsychotic drugs (phenothiazines, haloperidol). In the context of AWS, no human studies have been conducted with the newer atypical antipsychotics (clozapine, olanzapine, risperidone)[68]. Mayo-Smith performed a meta-analysis[19] of four prospective trials in which phenothiazines (chlorpromazine and promazine) were compared with benzodiazepines (diazepam or chlordiazepoxide) or placebo. Phenothiazines were no more effective than placebo in preventing delirium and less effective than benzodiazepines (6.6 more cases of delirium per 100 patients, P=0.002). Moreover, in comparison with benzodiazepines, treatment with phenothiazines increased the incidence of seizures (+ 11.4 cases per 100 patients, P<0.001). This finding is compatible with the clinical experience that chlorpromazine lowers the threshold for seizures[69,70]. Haloperidol was compared to chlordiazepoxide in a double blinded randomized trial[71] including 49 patients with symptoms of acute withdrawal. After four hours of treatment haloperidol was able to suppress symptoms in 70% of patients, whereas chlordiazepoxide controlled symptoms in just 44% of patients. No statistical analysis was presented.

All studies considered there is insufficient evidence to suggest a prime role for antipsychotics in the treatment of AWS. Moreover, the typical antipsychotics are known for their sometimes severe side-effects including the extra-pyramidal syndrome, the neuroleptic malignant syndrome and the possibility of ventricular tachyarrhythmias induced by a prolongation of the QTc interval[9].

Conclusion

In ICU patients, AWS is a major problem associated with significant morbidity and mortality. Treatment is aimed at reducing symptoms of withdrawal and at preventing seizures and the development of DT. Benzodiazepines have proven to be effective for all these objectives and remain the gold standard in treatment. Anticonvulsants and GHB have both demonstrated to diminish symptoms of withdrawal, but their adequacy in preventing seizures and DT is not known.

Ethanol may result in less sedation than benzodiazepines, but good quality evidence supporting its role in AWS is scant. There is no indication for antipsychotics in the treatment of AWS. Finally, α2-agonists could serve as adjuvant agents to benzodiazepines in order to suppress noradrenergic overdrive.

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