

Invited State-Of-The-Art Review

Controversies on the treatment of alcohol withdrawal symptoms

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Dan Med J 2026;73(9):A03260192. doi: 10.61409/A03260192

ABSTRACT

Alcohol withdrawal symptoms (AWS) are serious and seen in patients with severe alcohol problems reducing their alcohol intake. AWS is associated with a high morbidity and mortality, and – if untreated – with delirium, seizures, and increased severity of subsequent withdrawals. Benzodiazepines are the drugs of choice for treating AWS, and the dosage should be sufficient, preferably according to symptom scores. Experiencing AWS has no positive effects, and early detection and adequate treatment are crucial to the outcome. Medicine-free treatment of AWS is a thing of the past.

KEY POINTS

- Alcohol withdrawal symptoms are a serious medical condition.
- Withdrawal treatment prevents the development of seizures, delirium tremens and prevents future withdrawal symptoms from worsening.
- Sufficient medical treatment with benzodiazepines, according to symptoms, is imperative, safe and well documented.
- Experiencing untreated withdrawal symptoms is a thing of the past.

Despite existing guidelines and research, we constantly meet clinical staff who are reluctant to treat alcohol withdrawal symptoms (AWS), either for moral reasons (“it’s the patient’s own fault”) or for lack of knowledge (“it may be dangerous to treat the patient if he is not completely sober or may take too many pills”).

An ongoing clinical controversy has thus been whether patients with AWS should be treated medically or whether it is safe to observe patients with withdrawal with or without low medication

doses.

In addition, there is ongoing debate about how withdrawal medication should be dosed, and if treatment should be initiated before the blood alcohol level is zero. Furthermore, qualitative and implementation studies demonstrated a number of additional barriers for the implementation of evidence-based practices [1]. Patients with alcohol problems are a particularly stigmatised patient group that is perceived as having negative characteristics and is subject to stereotyping [2]. This has not changed for a number of years [3], and stigma is one of the most important barriers to seeking treatment [4]. In the present paper, we will demonstrate 1) that AWS is a serious medical condition, 2) that treatment for AWS should be initiated even in the case of mild symptoms and at every stage of the detoxification period and 3) that it is out of place to undertreat AWS. We also present recent knowledge about how to best administer AWS treatment, including dosage.

What is alcohol withdrawal?

When patients seek treatment for alcohol use disorders, the treatment offered in the phase when the alcohol level is decreasing is called detoxification. During and after this phase, withdrawal symptoms may well occur. Most patients can be detoxified and observed on an outpatient basis, but it is important to follow the development of withdrawal symptoms as they are potentially life-threatening. Alcohol withdrawal (ICD-10 code F10.3) is defined as a reduction or cessation of heavy alcohol use and two or more symptoms developed within hours or days (autonomic hyperreactivity (pulse > 100 beats/min.); hand tremor; sleep disturbances; nausea or vomiting; transient visual, tactile or auditory hallucinations; psychomotoric agitation; anxiety; convulsions).

85% of patients in alcohol treatment are alcohol dependent (ICD-10 code F10.2), defined as ≥ 3 symptoms within the past 12 months (craving; loss of control; withdrawal symptoms; tolerance; neglect of other interests; drinking despite clear evidence of harmful consequences) [5]. Three in four of these have relapses that include experiencing withdrawal syndrome, where symptoms such as sweating, shaking and sleep disturbances prevent them from stopping the relapse. Withdrawal symptoms are unpleasant, potentially dangerous and not least undignified, and the fear of these symptoms alone makes some patients relapse [6]. Abstinence treatment makes the decision to abstain easier, prevents the development of delirium tremens and seizures [7] and prevents future withdrawal symptoms from worsening.

In patients with withdrawal symptoms, it is important to clarify how long the current period of heavy drinking has lasted, whether the patient has experienced previous withdrawal symptoms and/or delirium tremens and whether previous seizures have been recorded. In addition, it is important to assess other substance abuse, psychiatric and somatic co-morbidities. This, along with the severity of the withdrawal symptoms, helps determine whether the patient can be treated as an outpatient or needs inpatient care [6].

The diagnosis

The psychological symptoms consist of inner unrest and restlessness, anxiety, disturbed attention function, insomnia and confusion. The physical symptoms consist of a tendency to sweat, tremors in the hands or the whole body, an increase in heart rate to $> 100/\text{min.}$, and an increase in temperature. The most serious form of withdrawal may include visual/auditory hallucinations and/or seizures and involves the risk of developing actual persistent withdrawal seizures and/or delirium tremens. Many of the symptoms can resemble symptoms of a wide range of other diseases. Therefore, it is important to ensure that the symptoms are not caused by, e.g., infections, blood poisoning, hepatic coma, poisoning, head trauma, brain damage, neurological disease or hypoglycaemia.

The symptoms usually develop within the first 6-24 hours after the last alcohol intake and, in most cases, last 1-3 days. If the symptoms occur after > 72 hours, they may be due to something else. It is important to be aware that alcohol withdrawal can also develop solely due to a reduction in alcohol consumption and that symptoms are present and should be treated even before the blood alcohol level reaches zero [8, 9].

Most AWS symptoms will only last up to a week, but a limited proportion of patients may experience anxiety, depressive symptoms, irritability, cognitive dysfunction, sleep disturbances and fatigue for up to ≥ 6 months – a syndrome called post-acute alcohol withdrawal (PAWS) [10, 11].

The neurobiological background for alcohol withdrawal symptoms

Alcohol stimulates the brain's primary inhibitory neurotransmitter (gamma-aminobutyric acid (GABA)) and inhibits the brain's primary excitatory system (glutamate). With prolonged exposure, the brain's signalling systems adapt to the ongoing effects of alcohol, resulting in an imbalance between the two and other signalling substances in a complex interaction between alcohol and the brain [12]. Longstanding heavy drinking induces disturbances in brain signalling, leading to symptoms of addiction, e.g., alcohol tolerance and positive as well as negative reinforcement behaviour [12]. When the alcohol intake is reduced, the addicted brain reveals the imbalance between the GABA and glutamate signalling, resulting in hyperexcitability, anxiety, insomnia and dysphoria [12-14]. Thus, AWS is a sign of a serious and long-standing alcohol use disorder. The stimulating system becomes predominant without sufficient compensatory activation of the inhibitory system, and this neurobiological disturbance is directly related to the development of AWS [13, 15, 16]. Additional neurobiological disturbances also seem to be the cause of protracted symptoms in PAWS [11].

How many people develop withdrawal symptoms?

In general populations, the prevalence of AWS symptoms varies from 1% to 5%, whereas the

prevalence of individual symptoms in patients in alcohol treatment varies from 8% to 86% [17]. The likelihood of experiencing withdrawal symptoms increases with increasing alcohol intake. Approximately half of patients with moderate to severe alcohol use disorder will develop AWS when reducing their alcohol intake [18, 19].

In a primary care population, the incidence of hospital admission with alcohol withdrawal is 169 per 100.000 person years and constitutes overall 2.3% of all hospitalisations – rates that are comparable to frequent chronic diseases such as COPD, hypertension, heart failure and diabetes [20]. Not surprisingly, the proportional incidence rate relative to all-cause hospitalisation is highest in patients diagnosed with alcohol use disorder (AUD) (39%) and patients with high scores on the short Alcohol Use Disorder Identification Test (AUDIT-C) (23%) [20].

Are alcohol withdrawal symptoms dangerous?

Delirium tremens – the most serious complication of withdrawal – is seen in 3-5% of inpatients with withdrawal. Among hospitalised patients with AWS, 13% were treated in an ICU, and 23% had a diagnosis of delirium tremens [21]. Previous suicide attempts are common (43%) in inpatients with AWS and are observed in 12% in the following two years [22]. Significant predictors were depression, female gender, sense of hopelessness and severity of AWS [22].

Mortality among hospitalised patients with AWS ranges from 2% [23] to 7% [24] and depends on the severity of AWS at admission and during the first three days [25]. Delirium presenting at admission is associated with an increased risk of death as well as comorbidity (liver, heart, lung, diabetes, epilepsy), multiple diagnoses, previous ICU admission for AWS is predictive of higher mortality [23-25]. AWS is associated with increased morbidity from several diseases [26-29]. Furthermore, AWS increases postoperative medical and surgical complications, length of hospital stay and costs [30].

Repeated withdrawal episodes lead to worsening of withdrawal symptoms (Kindling effect) [31], and changes in sensitivity and excitability thresholds may increase the severity of AWS and the risk of complications, such as seizures, delirium tremens and death [24, 32-34]. Furthermore, repeated episodes of AWS may constitute a negative motivational factor [34]. Additionally, a recent study showed that a kindling mechanism is important for the development of complicated withdrawal [35], so adequate treatment of AWS is important to reduce the risk of kindling and more serious complications of AWS.

Can alcohol withdrawal symptoms function as a motivator and reinforce a positive treatment outcome?

Historically, many programmes (especially older 12step-based detox centres) used “social detox”, which may be described as care without medication. There is, however, absolutely no evidence to support the idea that experiencing AWS would have any positive effect on long-term alcohol-

related outcomes in patients with addiction. Neither trials nor cohort studies support this hypothesis. On the contrary, research consistently shows the opposite.

As mentioned above, a history of AWS is a strong predictor of suicide [22], repeated AWS increase brain excitability [13], and AWS is associated with a high prevalence of hospitalisation and increased morbidity [36]. All major clinical guidelines emphasise that untreated AWS – apart from clinically insignificant symptoms – can be difficult to predict, is dangerous and increases morbidity and mortality [37-39]. Experiencing untreated withdrawal symptoms (“cold turkey”) should, in other words, be a thing of the past.

Benzodiazepines are the drug of choice for treatment

Treatment of AWS and prescribing medication is a health-professional task. Patients must be assessed by a nurse or doctor according to health authority guidelines. The aim of AWS is to calm the patient, reduce seizure frequency, and minimise the risk of developing delirium tremens.

More than 100 pharmacological agents have been tried for withdrawal treatment, and meta-analyses have reviewed > 60 randomised controlled trials with > 40 different drugs. GABA stimulation is appropriate from a neurobiological point of view, and there is overwhelming evidence that treatment with these agents is the most effective, i.e. thereby restoring the balance between GABA and glutamate in the brain.

Benzodiazepines are by far the most frequently used drug for the treatment of AWS. 93% of patients in a cohort of > 245,000 patients with AWS, received benzodiazepines [21]. The NICE clinical guideline 100 [37] and other international guidelines conclude that benzodiazepines are more effective than placebo in preventing withdrawal seizures whereas the effects in terms of therapeutic success, mortality or side effects are less documented.

No differences in effectiveness on several different endpoints have been found when comparing different benzodiazepines, although some advocate for the use of lorazepam, which, due to more predictable pharmacokinetics, is potentially better as treatment for withdrawal seizures and delirium tremens.

Several systematic reviews have unanimously concluded that benzodiazepines have a significant effect on withdrawal symptoms, withdrawal seizures and delirium tremens and that outpatient treatment is safe and effective for mild and moderate symptoms. A recent meta-analysis included 149 RCTs of various pharmacological treatments for withdrawal [40] and found that chlordiazepoxide significantly reduced the incidence of seizures (OR = 0.21; 95% CI: 0.08-0.53). The same was true for lorazepam, diazepam, chlormethiazole and divalproex. Diazepam was the only drug shown to reduce the incidence of delirium tremens. There is insufficient evidence for the effect of auricular acupuncture for treating AWS [41-43].

The adverse effects of benzodiazepines are few and well known. Paradoxical reactions such as

confusion, excitement and dysphoria can occur after treatment with benzodiazepines (especially in the elderly), and the most serious side effect is respiratory depression, but even ten times the normal daily dose rarely leads to serious complications. Nevertheless, careful observation should always be ensured. The exact incidence of side effects, including respiratory depression, remains unknown, but a review showed that benzodiazepines were responsible for approximately 3.8% of all deaths caused by a single drug in England [44]. A retrospective Danish study showed that respiratory depression was the most common cause of ICU admission [45]. Benzodiazepines are potentially addictive [46] and should be used with caution.

However, this should not mean that patients in need of withdrawal treatment are not adequately treated, since AWS and alcohol use disorders are far more serious conditions.

AWS is not a harmless condition to treat. A study of 436 patients admitted with withdrawal symptoms showed that 6.6% died [24], and 37.8% were transferred to an intensive care unit, including 188 patients with delirium tremens. The most important predictive factors for death were the severity of withdrawal symptoms, liver disease and other comorbidities. A recent study found that, in an intensive care unit, patients with alcohol withdrawal demonstrated a lack of correlation between doses, plasma concentrations and clinical effects [47] – a finding warranting careful observation of these patients. In severe inpatient cases where the effect of benzodiazepines may be insufficient and inappropriate, barbiturates and ultimately propofol are alternatives under careful monitoring [36, 48].

Dosage according to symptom scoring is better than a fixed dosage for hospitalised patients

The Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-Ar), is a widely used scoring system for assessing withdrawal internationally. The scale is well validated [49-51] and can detect even mild withdrawal symptoms [51]. During hospitalisation, the Withdrawal Syndrome Scale for Alcohol (WSA) [52], or an adjusted version thereof, has been used and has demonstrated its value in both specialised detoxification departments and psychiatric departments, even for outpatient use [53]. Patients monitor their own symptoms, and medication is dosed based on symptom severity and progression [54, 55].

Maximum AWS score within the first three days of treatment is associated with length of stay and mortality, and those with the highest scores have a > 2 fold increased risk of death [25]. Controlling dosage based on symptom severity is more effective than fixed dosing schedules in hospitalised patients. Early identification and treatment are important to prevent more severe withdrawal syndromes [32, 33] and if treatment is delayed, the risk of, e.g., admission, seizures and delirium increases [36].

Studies investigating whether there is a difference between fixed-dose and symptom-controlled dosing and symptom-controlled treatment resulted in shorter treatment courses and smaller doses of benzodiazepines, but no difference in the severity of withdrawal symptoms during treatment [56, 57]. It was concluded that symptom-controlled treatment should be used in withdrawal

treatment during hospitalisation or in other settings where 24-hour monitoring is possible [37].

The dosage needs to be sufficient for symptom relief at initiation and during the first days to calm patients, preferably to induce sleep. Guidelines describe wide dosage ranges and encourage clinicians not to aim for the lowest dosage, but rather to recognise that different severities of AWS require different dosages, often high, for relatively few days, until the balance in the brain is restored.

Concluding remarks

Withdrawal symptoms are unpleasant and undignified, and the fear of these symptoms alone can cause some patients to continue drinking alcohol. Typically, the first withdrawal symptoms develop within the first 6-24 hours after the last alcohol intake and typically last 1-3 days. Most patients with AWS are alcohol dependent, and many experience AWS symptoms such as sweating, shaking and sleep disturbances, preventing them from stopping drinking. Abstinence treatment makes the decision to abstain easier, prevents the development of delirium tremens and seizures and prevents future withdrawal symptoms from worsening. Medical treatment with benzodiazepines is safe and well documented. Experiencing untreated withdrawal symptoms is a thing of the past.

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Accepted 17 June 2026

Published 18 August 2026

Conflicts of interest IB reports financial support from or interest in the Specialist Training Programme in General Practice and I-Course in the Region of South Denmark. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2026;73(9):A03260192

doi 10.61409/A03260192

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