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Pharmacotherapy of alcohol withdrawal syndromes – Recommendations of the Polish Psychiatric Association and the Pharmacotherapy Section of the Polish Society for Addiction Research

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Summary

Alcohol addiction is one of the most common health problems. Long-term consumption of high doses of ethanol leads to numerous adaptive changes in the central and peripheral nervous systems, most notably a decrease in the activity of inhibitory GABAergic pathways and an increase in the activity of excitatory glutamatergic pathways. Up to half of patients may develop alcohol withdrawal syndrome (AWS) when they stop drinking alcohol.

This article contains the recommendations of the Polish Psychiatric Association and the Pharmacotherapy Section of the Polish Society for Addiction Research for the pharmacotherapy of AWS. This paper presents the aetiopathogenesis, neurotransmitter and receptor mechanisms, symptoms and diagnostic criteria of AWS, medications used in the treatment of alcohol withdrawal syndromes, management of uncomplicated and complicated alcohol withdrawal syndromes, and discusses the management of special populations. First-line drugs in the management of AWS are benzodiazepines (BDZ). Most studies have not shown a superiority of any BDZ in the treatment of AWS. The decision to choose a formulation should be based on its pharmacokinetic properties, comorbidities, and the patient's current condition. The most commonly used BDZs are diazepam, lorazepam, oxazepam, and clorazepate.

Key words: alcohol withdrawal syndrome (AWS), treatment, recommendations, benzodiazepines

Introduction

In 2013, the recommendations of the Pharmacotherapy Section of the Polish Society for Addiction Research and the Psychopharmacology Section of the Polish Psychiatric Association (PTP) for pharmacotherapy of alcohol dependence were published [1]. An update of these recommendations was published in 2019 [2]. This article contains the recommendations of the Polish Psychiatric Association and the Pharmacotherapy Section of the Polish Society for Addiction Research for the pharmacotherapy of alcohol withdrawal syndromes, and it is a very important supplement to the previous documents.

Alcohol addiction is one of the most common health problems [3]. Up to half of addicted patients may develop alcohol withdrawal syndrome (AWS) when they discontinue or reduce their regular alcohol intake [4-8]. Virtually all medical professionals encounter the problem of AWS. Symptoms of this syndrome often occur in hospitalised patients who have discontinued drinking because of their hospital stay, in emergency room patients, and in those attended at emergency departments or managed by emergency medical teams.

The recommendations presented in this paper are intended to support physicians in making therapeutic decisions; however, they do not replace the need for accurate diagnosis of a patient combined with individual choice of therapy. The aim of the study is to present current guidelines for pharmacotherapy of symptoms of alcohol withdrawal syndrome. It is important to remember that treatment of AWS symptoms should be accompanied by continued treatment of alcohol dependence. Any patient with symptoms of AWS should be referred for rehab therapy, and the inclusion of pharmacotherapy for addiction should also be considered for each patient [2].

The intention of the authors of this paper was to present recommendations that are supported by research results in accordance with the principles of evidence-based medicine (EBM), but also to give them a practical dimension, so that they are easy to understand and apply in everyday medical practice. These recommendations are intended for both psychiatrists and physicians of all other specialties, especially those who treat patients with AWS symptoms in their daily work.

The recommendations in this paper are based on a review of guidelines and recommendations from other scientific societies and expert groups and the literature, with particular emphasis on the results of clinical trials and meta-analyses of such studies. The presented recommendations are the result of subsequent consensus among the authors.

Alcohol withdrawal syndrome – aetiopathogenesis, neurotransmitter and receptor mechanisms

Long-term consumption of high doses of ethanol leads to numerous adaptive changes in the central and peripheral nervous systems [9]. Abrupt cessation of drinking or significant reduction in alcohol intake leads to the manifestation of neuroadaptation with a direction essentially opposite to the effects of alcohol. In addition, the brain, when responding to strong, chronic pharmacological stimuli, such as alcohol, that interfere with its functioning, is supported by a kind of neuroadaptive memory that occurs more quickly and with greater intensity with the next relapse of drinking. Tolerance to alcohol increases, and kindling of repeated withdrawal syndromes may occur [10, 11].

The most important central adaptations that develop as a consequence of chronic drinking include: (1) decreased activity of neurotransmitter pathways with typical inhibitory effects on cortical and subcortical structures and (2) increased activity of excitatory pathways [10]. Decreased activity of inhibitory GABAergic pathways and increased activity of excitatory glutamatergic pathways leads, among other things, to increased muscle tone, exaggerated reflexes, lowered convulsive threshold, and, in extreme cases, to grand mal seizures. These same adaptive changes may account for the abnormal sleep architecture, decreased threshold for sensory stimuli, and confusion seen in severe AWS. Drugs with GABAergic inhibitory effects on the central nervous system (benzodiazepines, barbiturates) attenuate the symptoms of AWS [11, 12].

High doses of alcohol suppress sympathetic nervous system activity, most likely by a central mechanism, provoking the occurrence of neuroadaptations of the opposite direction [9, 10]. Thus, alcohol withdrawal leads to overactivity of the sympathetic system with excessive norepinephrine release and dysregulation of basic vital signs (increased blood pressure, tachycardia, excessive sweating, hyperthermia, increased muscle tone) [11]. Drugs that decrease sympathetic system activity by a central (dexmedetomidine, clonidine) or peripheral (β-blockers) mechanism may relieve some of the symptoms of AWS. Nicotine and noradrenergic psychostimulants more potent than nicotine may exacerbate some AWS symptoms by increasing sympathetic activity [11, 12].

Alcohol-related neuroadaptive changes may also affect central neurons that produce serotonin and dopamine [10]. Stimulation of dopaminergic and serotonergic pathways by alcohol appears to lead to adaptive changes of the opposite direction seen after alcohol withdrawal. Weakening of the activity of serotonergic and dopaminergic neurons after cessation of drinking, at least in some patients, may provoke the occurrence of AWS symptoms affecting the drive and emotional sphere (anergy, anxiety, anhedonia, depressed mood). These latter adaptations and symptoms may last longer

than sympathetic overactivity or lowering of the seizure threshold, increasing the risk of drinking relapse [11, 12].

Alcohol withdrawal syndrome

Alcohol withdrawal syndrome refers to a cluster of symptoms that appear in an alcohol-dependent person during a period of sudden withdrawal or significant reduction in the amount of regularly consumed alcohol. The diagnostic criteria for AWS in the disease classifications (ICD-10, ICD-11, and DSM-5) are similar and include an analogous set of symptoms [13-15], which are listed in Table 1.

Table 1. **Criteria for the diagnosis of alcohol withdrawal syndrome according to the ICD-10 classification (F10.3) [13]**

1) Recent cessation or reduction of alcohol consumption after repeated, and usually prolonged and/or high-dose use
2) Any 3 of the following symptoms:
a) tremor of the tongue, eyelids or outstretched hands
b) sweating, nausea or vomiting
c) tachycardia and/or hypertension
d) psychomotor agitation
e) headache
f) insomnia
g) malaise or weakness
h) transient visual, tactile or auditory hallucinations or illusions
i) grand mal convulsions
3) The symptoms are not accounted for by a medical disorder unrelated to the use of alcohol or other psychoactive substances, other mental or behavioural disorders
4) If delirium is present, the diagnosis of AWS with delirium (F10.4) should be made

Symptoms of alcohol withdrawal syndrome typically develop within 6–12 hours of the last alcohol intake and typically last for 5–10 days. Most individuals experience mild to moderate symptoms (uncomplicated AWS); approximately 5% of AWS cases progress with neuropsychiatric complications, in particular seizures and/or alcoholic delirium (*delirium tremens*) [16-18]. These complications usually occur on day 2–3 after the last alcohol intake; however, in profoundly dependent individuals with high alcohol tolerance, symptoms of severe or complicated forms of AWS may appear even when still drinking, while alcohol is present in their serum [19-21]. Alcoholic delirium is diagnosed when severe symptoms of AWS are accompanied by delirium-like confusion, in particular impaired orientation, attention

deficit, perceptual (visual, sensory, auditory hallucinations) and thinking disorders (delusional interpretation of sensations and hallucinatory experiences), anxiety, severe restlessness, circadian fluctuations with typical exacerbation of symptoms in the evening and at night [16, 17, 22].

The risk of developing AWS is difficult to predict, it is undoubtedly higher in heavy drinkers, and increases with increasing alcohol intake and frequency of drinking. It is especially high in people who consume more than 8 standard drinks per day for at least a few consecutive days. Repeated episodes of alcohol withdrawal and increased CNS activity in addicts may promote the development of *kindling*, which may be responsible for lowering the seizure threshold and predisposing the patient to seizures and alcoholic delirium [17, 22-24].

To diagnose AWS and its complicated forms, the diagnostic criteria of the International Classification (ICD-10; Table 1) or the American classification of mental disorders (DSM-5) should be used. In individuals with symptoms suggestive of AWS, the first thing to do is to confirm the pattern of recent alcohol drinking (amount and frequency) and the time since last consumption to ensure that the observed symptoms are related to elimination or reduction of alcohol intake in the addicted individual. Information can be obtained from the subject, his/her family or friends; heavy drinking can also be confirmed by determination of biological markers of alcohol use [mean corpuscular volume (MCV), desialylated transferrin (CDT), beta-hexosaminidase (β-HEX), ethyl glucuronate (EtG), and phosphatidylethanol (PETH)] [11, 25].

The severity of AWS symptoms can be determined using the CIWA-Ar (*Clinical Instrument Withdrawal Assessment for Alcohol, Revised*) scale [26], which is a key clinical tool recommended by most standards and treatment guidelines. It is not a diagnostic tool, just a descriptive tool. Its result should be supplemented with basic vegetative parameters, including the examination of heart function and blood pressure. The assessment of the severity of AWS symptoms and CIWA-Ar score in an individual patient can provide the rationale for drug treatment and the basis for drug dosing (Table 2). During the course of AWS treatment, symptom severity assessment using the CIWA-Ar scale should be repeated many times to monitor the course of AWS and to evaluate the effects of its treatment. Physical examination should also be repeated during therapy, as some neurological symptoms or somatic complications may develop later in the course of AWS [11, 25, 27]. It is also important to assess the risk of developing severe/complicated forms of AWS by identifying predictors of alcoholic delirium and seizures (Table 3) [28, 29].

Table 2. **Severity assessment of AWS symptoms**

Severity of AWS symptoms	CIWA-Ar score range	Symptom description
Mild	CIWA-Ar <10	Mild to moderate anxiety, sweating, insomnia, no tremor
Moderate	CIWA-Ar 10–18	Moderate anxiety, sweating, insomnia, muscle tremor
Severe	CIWA-Ar ≥19	Severe anxiety, moderate to severe tremor, no confusion, hallucinations or seizures
Complicated	CIWA-Ar ≥19	Seizures or symptoms indicating disturbance of consciousness (delirium) – impaired understanding of commands, blurred consciousness, hallucinations

Table 3. **Predictors of development of severe AWS (seizures and alcoholic delirium)**

Age ≥45 years
Severe comorbid medical disease
Alcoholic delirium or seizures in the course of previous AWS episodes
Severe course/very severe symptoms since the beginning of the current AWS episode
Severe AWS symptoms with the presence of alcohol in the blood
Dehydration
Seizure(s) during the current AWS episode
Hyponatraemia or hypokalaemia
Elevated serum AST or GGT levels
Low platelet count
Structural brain damage
The duration of drinking episode and daily alcohol intake are not consistent predictors of severe forms of AWS

Drugs used in therapy of alcohol withdrawal syndromes

Benzodiazepines (BDZs) are first-line medications in the treatment of alcohol withdrawal syndromes and are considered the "gold standard" in this condition. It is the only form of treatment that is causal, as it targets directly the normalisation of GABAergic activity (see neurobiological mechanisms leading to AWS). BDZs act as agonists of the GABA-A receptor, thus inhibiting the activity of the central nervous system, leading to a reduction of all AWS symptoms, both somatic (associated with sympathetic nervous system excitation), neurological (hyperalgesia, tremor, attention deficit disorder), and psychological (anxiety, insomnia, restlessness, hallucinations). Benzodiazepines are the only substances for which a reduction in AWS mortality and efficacy in preventing the complications of AWS, seizures and alcoholic delirium, have

been proven [30]. At the same time, benzodiazepines are also first-line treatment for the aforementioned complications of AWS.

The basic features of BDZs and recommendations for their use are itemised below:

- Because of the GABA-A receptor adaptation (down-regulation) that occurs in alcohol-dependent individuals, higher doses are needed in AWS treatment than those used in non-addicted individuals for sedation, myorelaxation, or sleep induction. The dose must be individually adjusted to the patient and his/her tolerance to the effects of benzodiazepines (developed over years of alcohol use). Therefore, it is believed that a maximum dose cannot be defined in AWS treatment [31]. If the doses required by the patient's condition exceed the values approved for specific BDZ products, inpatient treatment is required.
- The combination of BDZ drugs with ethanol produces a synergistic effect. Therefore, it is generally contraindicated to administer BDZ to patients in a state of alcohol intoxication because of the risk of muscle relaxation, respiratory centre depression, and potential subsequent respiratory failure.
- Most studies have not demonstrated a specific pharmacodynamic advantage of any of the BDZs in the treatment of AWS. The decision to choose a formulation is based on its pharmacokinetic properties, comorbidities, and the patient's condition [20].
- Long-acting benzodiazepines (e.g. diazepam) are preferred for first-line treatment of AWS. This pharmacokinetic profile provides a lower total dose of drug administered, smoother reduction of AWS symptoms, more reliable protection against seizures, and a lower risk of the so-called rebound effect [28, 30, 32].
- For elderly patients (over 60 years of age) and those with signs of hepatic failure, benzodiazepines with intermediate half-lives that have no active metabolites and are metabolised via glucuronidation, a mechanism that is usually unaffected even in the failing liver (lorazepam, oxazepam), are preferred because of the risk of drug accumulation and excessive sedation [32].
- If the patient is uncooperative (refuses to take medication orally), the drug of choice is injectable lorazepam (best pharmacokinetic properties after IM administration), or alternatively clorazepate, which is also well absorbed after intramuscular administration.
- In the case of insufficient symptom control and the need for additional treatment (haloperidol, a β-blocker), the additional treatment should always be given in combination with a BDZ drug.

Diazepam

Because of its general availability, pharmacokinetic properties, and the large number of studies, diazepam is the primary drug used to treat AWS. Diazepam has a half-life of $T_{1/2}$ = 20–40 h, but is metabolised in the liver to active metabolites: nordiazepam (desmethyldiazepam, $T_{1/2}$ = 36–200 h), 3-hydroxydiazepam ($T_{1/2}$ = 5–20 h) and oxazepam ($T_{1/2}$ = 4–15 h). It is very well absorbed after oral and intravenous administration; after such administration, diazepam acts faster than other BDZs used to treat AWS (lorazepam, oxazepam, or clorazepate). This is due to the lipophilicity of diazepam, which allows the drug to cross the blood-brain barrier very well. Diazepam is poorly and unpredictably absorbed after intramuscular administration. For this reason, it is not advisable to administer diazepam by the intramuscular route. The maximum approved dose of diazepam for adults is 40 mg/d. In the rapid loading method, significantly higher doses may be used depending on the patient's condition, which should always be justified by an appropriate entry in the medical record.

Dosage:

(5) Fixed-dose method: diazepam 10 mg every 6 hours for the first 24 hours (3–4 doses); on subsequent days, diazepam doses should be gradually reduced by 5 mg/day (day 2: 25 mg/d, day 3: 20 mg/d, etc.). Due to insomnia typical in the course of the initial period of AWS, it seems rational to discontinue the evening doses at the end of the detoxification period.

(6) Rapid loading method: 10–20 mg of diazepam every hour until drowsiness is achieved or CIWA-Ar score decreases to less than 10 points.

Lorazepam

A benzodiazepine with an intermediate half-life ($T_{1/2}$ = 9–19 h), which has no active metabolites and is metabolised in the liver only by glucuronidation (no oxidation); it is absorbed well and predictably after intramuscular administration. It is available in both oral and injection forms. Due to the above characteristics, it is considered a first-line drug in uncooperative patients (who require IM administration) and in the elderly or those with known hepatic insufficiency. Lorazepam and diazepam in IV form find their use for the interruption of seizures occurring as a complication of AWS.

Dosage:

(1) Fixed-dose method: lorazepam 2 mg every 6 hours for the first 24 hours (3–4 doses); on subsequent days, lorazepam doses should be gradually reduced by 1 mg/day (day 2: 5 mg/d, day 3: 4 mg/d, etc.).

(2) Rapid loading method: 2–4 mg of lorazepam every hour until drowsiness is achieved or CIWA-Ar score decreases to less than 10 points.

Oxazepam

Like lorazepam, it is a benzodiazepine with an intermediate half-life ($T_{1/2}$ = 4–15 h), which has no active metabolites and is metabolised in the liver only by glucuronidation (no oxidation). The drug has no injection form. As an alternative to lorazepam, it is a first-line drug in the elderly or those with known hepatic insufficiency. Dosage is analogous to diazepam and lorazepam in equivalent doses (see Table 4).

Clorazepate

A benzodiazepine with a long half-life, well absorbed after intramuscular administration. Together with lorazepam (as indicated based on other pharmacokinetic properties), it should be considered as a first-line drug in uncooperative patients (requiring IM administration). It is available in both oral and injection forms. Dosage is analogous to diazepam and lorazepam in equivalent doses (see Table 4).

Table 4. **Pharmacokinetic properties of benzodiazepines used in the treatment of alcohol withdrawal syndromes**

Substance	Recommended route of administration	Doses equivalent up to 10 mg of diazepam [mg]	Half-life [h]	Active long-acting metabolites
Diazepam	PO; IV	10	20–40 (36–200)*	Yes
Lorazepam	PO; IM; IV	2	9–19	No
Oxazepam	PO	30	4–15	No
Clorazepate	PO; IM	20	48	Yes

PO – per os, IV – intravenously, IM – intramuscularly

*nordiazepam – active metabolite of diazepam, half-life shows high inter-individual variation.

Antipsychotics

The addition of an antipsychotic drug (APD) is indicated only if positive symptoms occur in the course of AWS. Neuroleptics are not recommended for the treatment of uncomplicated withdrawal syndromes. APDs do not relieve most of the symptoms of AWS and do not prevent seizures; and they even lower the seizure threshold. APDs with a sedative effect, without anticholinergic activity, and with the least possible effect of lowering the seizure threshold are recommended. Each dose of an antipsychotic should be given together with a benzodiazepine. There is no need for further antipsychotic medication after a history of alcoholic delirium. Because of its strong antipsychotic and sedative effects and the lack of anticholinergic effect, the neuroleptic of choice for the treatment of alcoholic delirium is haloperidol. Haloperidol is available as tablets and

liquid for oral administration, and it is also well absorbed when given intramuscularly. The maximum daily dose for the treatment of alcoholic delirium should not exceed 10 mg. Haloperidol should always be used in combination with benzodiazepines (continue benzodiazepines with each dose of a neuroleptic) to minimise the risk of adverse drug reactions (such as increased muscle tone, hyperthermia, and decreased seizure threshold). Alternatives to haloperidol may include other neuroleptics with similar pharmacodynamic characteristics, e.g. risperidone or tiapride.

Antiepileptic drugs

Meta-analyses on the use of antiepileptic drugs in the treatment of AWS clearly indicate that in patients with moderate to severe AWS symptoms (treated in an inpatient setting), the use of an antiepileptic drug is of no benefit [35]. Carbamazepine and gabapentin in monotherapy may find use in the outpatient treatment of mild AWS [27]. For moderate to severe AWS, antiepileptic drugs are used only if there is a concurrent other indication for their use (e.g. previously diagnosed epilepsy). A withdrawal seizure is not an epileptic seizure in the strict sense and therefore does not require the routine inclusion of antiepileptic treatment, either during detoxification or when the patient is discharged home. It is important to remember that a patient's abrupt withdrawal of an antiepileptic drug is itself a risk factor for a seizure.

Management of uncomplicated and complicated alcohol withdrawal syndromes

A simple, clinical (with regard to therapeutic management) classification of AWS has two main types: (1) uncomplicated withdrawal syndrome (uAWS), which is mild in most cases (nearly 75%), often requires no treatment or is managed on an outpatient basis and generally does not require hospitalisation, and (2) complicated alcohol withdrawal syndrome (cAWS), in which the complications are withdrawal seizures and/or alcoholic delirium.

When AWS is suspected, secure peripheral venous access, and assess symptom severity using the CIWA-Ar scale, recording the time of measurement and the score. A breathalyser test is imperative, as symptoms of AWS (as well as its complications) can occur even before the patient becomes fully sober. The result of the breath alcohol measurement determines the further therapeutic procedure. It should be assumed that in the absence of anaesthetic services, any ethanol content in the serum/exhaled air is an absolute contraindication to the administration of BDZ drugs. In specific situations where symptoms of alcoholic delirium or withdrawal seizures occur in a state of alcohol intoxication, the risks associated with possible BDZ administration should be assessed before the patient is sober. If, in the physician's opinion, the risks associated with failure to administer BDZ treatment (severe psychomotor agitation, symptoms of

severe hyperactivity of the sympathetic nervous system, status epilepticus) are higher than the risks associated with the administration of BDZ to an intoxicated person, it is permissible to administer benzodiazepines (only when anaesthetic services are available). It should be emphasised that such a procedure is allowed only in exceptional circumstances and cannot be routine. Moreover, it requires a detailed justification through appropriate entries in the medical records. The standard procedure is to administer IV or PO fluids, then initiate BDZ treatment once the patient is completely sober.

Collect a thorough history from the subject, and if possible from people around them, and obtain samples for preliminary tests (including CBC, electrolytes, AST, ALT, GGTP, bilirubin, urea, creatinine, d-dimers, serum amylase, CRP, glucose, and urinalysis). Differential diagnosis is necessary. Once AWS is confirmed, re-assess symptom severity using the CIWA-Ar, record the time of the measurement, and compare the result to the previous measurement. The test is performed at least every hour until the symptoms resolve. The physical condition should also be evaluated. Additional tests or consultations are ordered as needed. Each patient, in the absence of contraindications (e.g. allergy), should receive vitamin B1. In the correct management of cAWS, it is important to pay particular attention to the possible medical issues. In short, it should be assumed that each patient requires an in-depth diagnosis of his/her medical condition, as it can significantly affect the course of treatment. The most common medical abnormalities include water and electrolyte disturbances, including hypokalaemia, vitamin B deficiencies, and other nutritional deficits (e.g. protein deficit). Patients may have infections, often of the upper respiratory tract or urinary tract, and acute pancreatitis, hepatitis, or exacerbation of these conditions. Patients with AWS often have multiple past or fresh injuries [33, 35-39].

In the diagnostic management of uAWS, taking a proper history generally does not pose difficulties. However, it is absolutely advisable to order and analyse investigations, and, in the individual assessment of the patient, to decide on the introduction of therapeutic management, including treatment with benzodiazepines, when necessary. Whenever possible, oral administration is the preferred form of BDZ treatment.

Depending on the severity of symptoms and presence of AWS complications, the patient should be assigned to one of 3 therapeutic pathways (see Figure 1):

(1) Subjects with mild AWS (CIWA-Ar <10 points) do not require drug treatment and do not require hospitalisation. Given the possible worsening of AWS symptoms over time, it is recommended to obtain at least 3 CIWA-Ar scores at 30-minute intervals before deciding to forgo hospitalisation.
(2) Subjects with moderate AWS symptoms (CIWA-Ar = 10–18) should be treated in an inpatient setting with the fixed-dose method whenever possible. Assessment of the patient's medical condition is absolutely recommended. When outpatient treatment is necessary, a prescription for a rationed number of BDZ

tablets should be issued with strict instructions to take them and a warning about the risk of becoming dependent on the drug and the toxic interaction with alcohol.

(3) Individuals with severe AWS symptoms (CIWA-Ar ≥19) or with complicated AWS absolutely require hospitalisation and BDZ treatment using the rapid loading method (treatment with a symptom-based approach). It is absolutely necessary to evaluate the patient's medical condition in order to exclude other non-psychiatric life-threatening conditions.

Fixed-dose method

It assumes "fixed" BDZ dosing based on baseline assessment of AWS severity. Dosage: diazepam (or equivalent doses of other BDZs as indicated): 10 mg every 6 hours for the first 24 hours (3–4 doses); monitor clinical status with the CIWA-Ar scale every 4–6 hours and add BDZ as needed if AWS symptoms persist despite the treatment (CIWA-Ar >10).

On subsequent days, diazepam doses are gradually reduced by 5 mg/day (day 2 – 25 mg/d, day 3 – 20 mg/d, etc.). Due to insomnia typical in the course of the initial period of AWS, it seems rational to discontinue the evening doses at the end of the detoxification period.

Alternatively: starting on day 2, diazepam for 48 hours, 5 mg every 6 hours (8 doses), then discontinue BDZ.

If over-sedation is observed faster reduction of the diazepam dose in subsequent days should be considered to avoid excessive accumulation. Flexible dose adjustment of BDZs according to the patient's mental and physical state may reduce the risk of recurrence of drinking due to a decreased BDZ serum level a few weeks after discharge from the detoxification centre.

Rapid loading method

This method is based on a dosage formula based on symptom severity. It is considered to be a safe and effective treatment, allowing the optimal dose to be delivered at the right (early) time, reducing the total dose of drugs administered, shortening the duration of therapy and avoiding toxic complications. The loading method has been shown to be more effective than the fixed-dose method in severe and complicated AWS, reducing the number of withdrawal seizures and the total duration of alcoholic delirium symptoms [40].

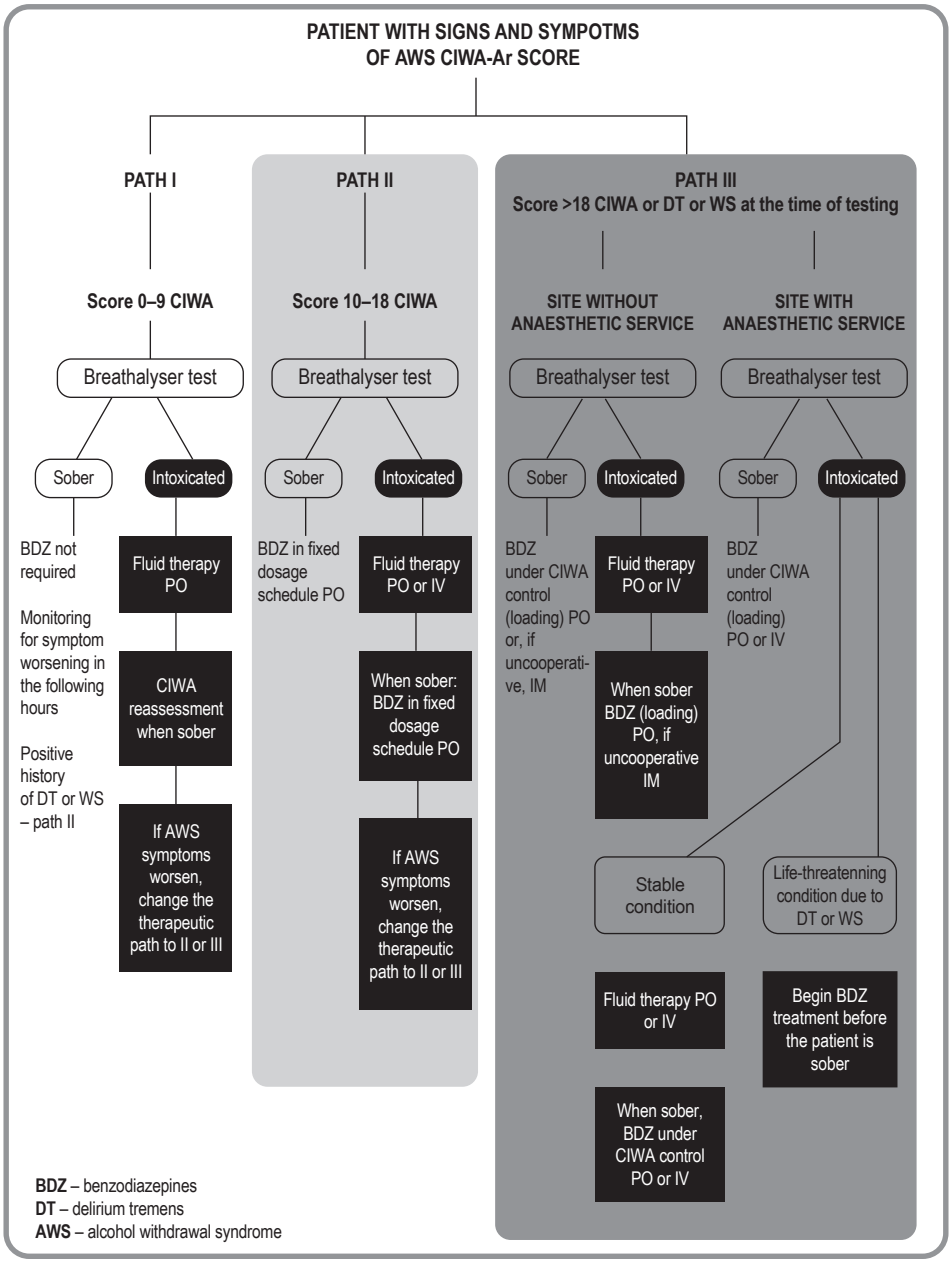

Figure 1. **AWS treatment – flow chart**

Loading procedure:

(1) Monitor clinical status: CIWA-Ar score on an hourly basis, before each dose.
(2) Dosage: 10–20 mg of diazepam PO (or equivalent doses of other BDZs as indicated) every hour until drowsiness is achieved or CIWA-Ar score decreases to less than 10 points. No BDZ is administered in the following days after achieving loading, despite the persistence of some symptoms, such as sleep disturbances.
(3) If patient is uncooperative and does not take medications orally: clorazepate 20–40 mg IM every 2–3 h or lorazepam 2–4 mg IM every 2–3 h until drowsiness is achieved or improvement allows the patient to be given BDZ PO.
(4) IV administration of BDZ (diazepam or lorazepam) according to the above schedule is recommended only at centres with anaesthetic services and personnel trained in the management of sudden respiratory failure.
(5) With failure of 100 mg diazepam daily or equivalent doses of other BDZs, or if the patient has significant restlessness that does not resolve with a benzodiazepine, it is advisable to include haloperidol and continue loading.
(6) If after completion of loading (CIWA-Ar score less than 10) there is a recurrence of alcoholic delirium symptoms (re-increase in CIWA-Ar score), the cause of the delirium syndrome should be verified, and if no cause other than alcohol withdrawal syndrome is found, then:
   – if the patient on the loading regimen received less than 100 mg, continue loading until drowsiness is achieved or CIWA-Ar <10;
   – if the patient already received 100 mg or more of diazepam according to the loading regimen, treatment with a neuroleptic should be started by giving each dose together with a BDZ (1–5 mg haloperidol PO or IM every 4 to 6 hours, the dose may be increased or decreased depending on response).

Contraindications for BDZ administration according to the loading regimen:

– recent head injury;
– respiratory disorders and comorbid respiratory diseases that can lead to respiratory failure;
– presence of alcohol in the blood;
– intoxication with other drugs or psychoactive substances;
– no data on the amount of BDZ drugs previously administered.

Inpatient treatment of AWS patients requiring hospitalisation is safest in a unit with monitored beds. As a rule, patients are referred for treatment in a detoxification

unit – withdrawal syndrome treatment unit (*Polish: OLZA, OLAZA*). The aim of AWS treatment is always to control the patient's somatic and psychological state as quickly and safely as possible. It is crucial to administer pharmacotherapy in such a way as to slow down and then inhibit the threatening progression of AWS to its complicated forms (alcoholic delirium, withdrawal seizures). One important prognostic factor is the time from the onset of AWS symptoms to the patient's hospital admission [27]. Some patients with newly diagnosed AWS still develop alcoholic delirium despite intensive treatment, so it seems important to treat each case of AWS as involving a risk of developing a life-threatening complication.

Special populations

Medically ill patients

For patients with comorbidities, the pharmacotherapy and/or management protocol used to treat the withdrawal syndrome should be modified accordingly in consultation with other specialists. Patients with conditions that preclude oral medication should receive the drugs intravenously or intramuscularly. Because of the risk of complications associated with sympathetic overactivity, intensive treatment of withdrawal symptoms is indicated in patients with cardiovascular disorders. In patients with hepatic impairment, drug dosage must be adjusted accordingly or drugs that are less dependent on hepatic metabolism should be used.

Heart diseases require early diagnosis, and their presence warrants intensive treatment. In such cases, at least one dose of benzodiazepines may be given to prevent even mild withdrawal symptoms. Other treatment modifications may be necessary due to hepatic impairment, drug interactions, or diseases whose presence prevents oral drug administration [27, 31].

Pregnant women

Inpatient treatment should be considered in all pregnant patients with alcohol dependence and AWS symptoms. Pregnant patients with withdrawal symptoms of at least moderate severity (i.e. CIWA-Ar score >10) should be hospitalised. It should be considered whether the presence of nausea, headache, anxiety, and insomnia is related to alcohol withdrawal or pregnancy, assuming that withdrawal symptoms should resolve in response to effective pharmacological management. Treatment of withdrawal symptoms in pregnant women requires gynaecological consultation. Referral for alcohol addiction therapy is especially important in pregnant patients who present symptoms of AWS, given the high risk of foetal alcohol syndrome (FAS) in the child [41, 42].

Before giving any medication to pregnant patients, make sure they understand the risks and benefits of pharmacotherapy, both for themselves and for the developing foetus. Benzodiazepines are the drugs of choice for the treatment of AWS symptoms in pregnant women. Although their use carries a risk of teratogenic effects in the first trimester of pregnancy, this risk appears to be low, especially when compared to the risk of foetal alcohol syndrome in the child, and considering the consequences for the mother and foetus if the mother develops a severe form of withdrawal syndrome. Due to the high risk of teratogenic effects, administration of valproic acid to pregnant patients is not recommended. Short-acting benzodiazepines are recommended for patients in the late third trimester of pregnancy or at risk for preterm delivery. Because of their faster onset of action and shorter half-life, their use minimises the risk of benzodiazepine intoxication in newborns. The circumstances and rationale for the decisions made should be described in detail in the medical record.

Suspected head injury

Treatment of these patients should take place in facilities that have the ability to intensively monitor the patient's condition for possible complications.

Indications for hospitalisation of a patient with AWS in a multispecialty centre with anaesthesiology/internal medicine/neurology services:

- AWS patient after recent (within the last 3 months) head injury.
- AWS patient with comorbid severe, uncontrolled medical diseases (hepatic failure, renal failure, severe hypothermia, unstable diabetes, pneumonia, acute pancreatitis, cardiac arrhythmias, unstable ischaemic heart disease, etc.).
- AWS patient in a state of alcohol intoxication who presents with withdrawal seizures/confusion/psychotic symptoms even before sobriety is achieved. BDZ treatment may be required before the patient is sober.
- Patient with respiratory disease at increased risk of adverse reactions following high doses of BDZ.
- Patient with a history of poor tolerance, complications after medication use in routine alcohol detoxification.

Summary

Alcohol addiction is one of the most common health problems. Long-term consumption of high doses of ethanol leads to numerous adaptive changes in the central and peripheral nervous systems, most notably a decrease in the activity of inhibitory GABAergic pathways and an increase in the activity of excitatory glutamatergic pathways. Up to half of patients may develop alcohol withdrawal syndrome (AWS) when

they stop drinking alcohol. Diagnostic criteria for AWS contained in the classifications of diseases (ICD-10, ICD-11, and DSM-5) include sweating, nausea, vomiting, tremor of the tongue, eyelids and/or hands, tachycardia, elevated blood pressure, restlessness, headache, insomnia, and transient visual, tactile, auditory hallucinations or illusions. More severe forms may be accompanied by seizures (grand mal) and delirium. Symptoms of alcohol withdrawal syndrome typically develop within 6–12 hours of the last alcohol intake and typically last for 5–10 days. Most individuals experience mild to moderate symptoms (uncomplicated AWS); approximately 5% of AWS cases progress with neuropsychiatric complications, in particular withdrawal seizures and/or delirium (complicated AWS). The severity of AWS symptoms can be assessed using the CIWA-Ar scale. Uncomplicated AWS usually does not require treatment or is treated on an outpatient basis; complicated AWS is always an indication for hospitalisation.

Benzodiazepines are the drugs of choice in the treatment of AWS. These medications are the only form of treatment that is causal, as it targets directly the normalisation of GABAergic activity. All BDZs show similar efficacy in the treatment of AWS. The decision to choose a specific formulation should be based on its pharmacokinetic properties, comorbidities, and the patient's condition. Long-acting benzodiazepines (e.g. diazepam) are preferred for first-line treatment of AWS. For elderly patients (over 60 years of age) and those with signs of hepatic failure, benzodiazepines with intermediate half-lives that have no active metabolites and are metabolised via glucuronidation (e.g. lorazepam) are preferred because of the risk of drug accumulation and excessive sedation. If the patient is uncooperative (refuses to take medication orally), the drugs of choice are injectable lorazepam or clorazepate due to the best pharmacokinetic properties after intramuscular administration. In patients with hepatic impairment, drug dosage must be adjusted accordingly or drugs that are less dependent on hepatic metabolism should be used. Heart diseases require early diagnosis, and their presence warrants aggressive treatment. In such cases, at least one dose of benzodiazepines may be given to prevent even mild withdrawal symptoms. Inpatient treatment should be considered in all pregnant patients with alcohol dependence and AWS symptoms.

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