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Management of alcohol withdrawal syndrome (AWS)

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Abstract:

Alcohol withdrawal syndrome (AWS) is a complex set of symptoms that occur in alcohol-dependent individuals after sudden withdrawal or a significant reduction in alcohol consumption. AWS symptoms occur in about 50% of alcohol abusers. These symptoms may include restlessness, tremor, nausea, nervousness, tachycardia, elevated blood pressure, hyperhidrosis, insomnia, hyperactivity, and hallucinations. In some cases, seizures may occur and delirium tremens may develop, which is life-threatening and an absolute indication for hospitalization of the patient. Effective treatment of AWS is the key to prevent complications and to reduce the risk of death. Treatment of alcohol withdrawal syndrome requires a complex approach that combines properly performed diagnosis, careful monitoring of the patient's condition, pharmacotherapy, equalization of electrolyte disorders, adequate hydration of the patient, supplementation of thiamine deficiencies and, in the case of symptoms of alcoholic delirium, intensive medical care. Pharmacological treatment plays a key role, with the first line of treatment being benzodiazepines, which reduce the risk of epileptic seizures and delirium tremens, and reduce mortality in the course of AWS. Individualized therapy adjustment and patient monitoring are crucial to ensure effective and safe treatment.

Keywords: alcohol withdrawal syndrome, AWS, AWS management, AWS treatment

Introduction

Alcohol withdrawal syndrome (AWS) is a condition occurring in alcohol-dependent individuals that results from the sudden cessation of alcohol consumption or a significant reduction in the amount of alcohol consumed. [1] About 50% of alcohol abusers experience symptoms of AWS. [2] Ethyl alcohol has an inhibitory effect on the central nervous system. Among other things, ethanol affects NMDA and GABA receptors (especially $GABA_A$ receptors). [3] Long-term alcohol abuse can lead to neuroadaptation by altering the expression of GABA receptors [4, 5] and consequently contribute to seizures when alcohol consumption is abruptly discontinued by addicts. [6, 7]. Ethyl alcohol has an inhibitory effect on NMDA receptors, leading to a compensatory increase in the number of NMDA receptors in a long-term abuse. Changes in the regulation of NMDA receptors lead to symptoms of abstinence syndrome when alcohol consumption is discontinued. [8, 9]. Symptoms of AWS can occur 6 - 12 hours after cessation of alcohol consumption and usually persist for 5-10 days. The duration of AWS is proportional to the severity of symptoms. [10, 14]. The clinical manifestations of AWS can vary in severity. The literature lists 4 stages of AWS, which may follow one another, but this is not the case for all patients, and symptoms occurring in each stage may overlap. Grade one are minor, non-severe symptoms that may appear 6-8 hours after stopping alcohol consumption even when elevated blood alcohol levels persist. These symptoms include restlessness, non-increased tremor, nausea, nervousness, tachycardia, and elevated blood pressure. Stage two of AWS can begin about 24 hours after stopping alcohol consumption. Its symptoms include hyperhidrosis, increased tremor, insomnia, and hyperactivity. Hallucinations - visual, tactile or auditory - may occur. Grade three are symptoms that can occur about 12-48 hours after stopping alcohol consumption. Symptoms are similar to grade two, while the presence of tonic-clonic seizures is also characteristic. The last stage is alcoholic delirium (delirium tremens), which can occur 3-5 days after alcohol withdrawal. [10, 11, 14] Most patients experience mild to moderate AWS symptoms (grades 1 and 2), while 3-5% of patients hospitalized for AWS have a complication of tonic-clonic seizures (grade 3) or alcoholic delirium (grade 4). [11, 12] Alcoholic delirium is characterized by a sudden, intense course with disturbances in consciousness (disorientation), attention, perception (visual, auditory, sensory hallucinations) and thinking (delusions), anxiety, excessive psychomotor activity, increased tremor. Symptoms of alcoholic delirium usually

worsen in the evening and night. [15, 16]. Alcoholic delirium is an absolute indication for hospitalization of the patient. [11, 13, 14] The mortality rate for inadequate treatment of delirium tremens is 5-15%, and the most common causes of death are cardiac arrhythmias and respiratory failure. [17] Conditions that may accompany AWS symptoms include trauma, gastrointestinal bleeding, pancreatitis, diabetic ketoacidosis, pneumonia, respiratory failure, cardiovascular disorders, and electrolyte disorders (hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, hyponatremia) [11, 18, 19] Patients who end up in the ICU due to AWS often need mechanical ventilation. [20] The CIWA-Ar scale is used to clinically assess the severity of AWS symptoms. [21]

People experiencing symptoms of alcohol withdrawal syndrome require medical attention. [1, 11, 13] Ways to deal with the occurrence of AWS and known methods of treatment and symptom relief will be discussed in this article.

In purpose to create this Article, the scientific papers published to date in the PubMed database were reviewed and analyzed. Keywords used: "alcohol withdrawal syndrome", "alcohol withdrawal delirium", "delirium tremens", "alcohol withdrawal treatment".

Discussion

Procedure in case of a patient with AWS symptoms includes examining and monitoring the patient, performing diagnostics including laboratory tests as well as non-pharmacological and pharmacological treatment. [11] Recommended laboratory tests include blood count, blood glucose, sodium, potassium, magnesium, phosphorus, calcium and chlorine levels, arterial blood gas, ALT and AST, GGT, bilirubin, lipase, urea, creatine kinase, CRP, lipidogram, coagulogram and alcohol level in serum determination. A urine toxicology test, EKG, and, of the imaging tests, a chest X-ray are also recommended. Depending on the patient's condition, the history taken and the possibility of trauma, additional laboratory and imaging studies should be considered. [1, 11, 18] The basic procedure includes venipuncture, hydrating the patient, supplementing glucose deficiency, equalizing electrolyte balance and supplementing thiamine deficiency. [2] Hypoglycemia is common in patients with AWS. [22] When supplementing glucose deficiencies, far-reaching caution should be exercised to avoid the development of Wernicke's encephalopathy in the case of existing thiamine deficiency. For this purpose, glucose should be administered only after the patient has received thiamine supplementation. [23, 24] The effectiveness of magnesium supplementation in patients with

AWS remains a subject of research. Currently, there is insufficient evidence to show a clear benefit of magnesium supplementation in AWS. [25] The study found an effect of magnesium supplementation on accelerating the decline in AST levels, which the study authors linked to a likely lower risk of developing alcoholic liver failure. [26] Similar observations arise from the study by V. Vatsalya et al. - low serum magnesium levels appear to be associated with the onset of liver failure symptoms. [27] Impaired absorption of supplemented thiamine can occur in hypomagnesemia. [28] In a study by D. Maguire et al. it was observed that simultaneous administration of thiamine and magnesium to patients with AWS resulted in faster resolution of AWS symptoms. [29] In alcohol-dependent individuals, thiamine deficiency is a common syndrome and it contributes to the development of Wernicke's encephalopathy (WE). [30] It is recommended to administer thiamine parenterally at a dose of 200 mg per day for 3-5 days, and to increase the dose of parenterally supplemented thiamine to 500 mg i.m. or i.v. every 8 hours for at least 3 days if WE symptoms occur. [31] It has been observed that faster incorporation of thiamine supplementation is associated with faster treatment results. Studies suggest administering thiamine within the first 2 hours of treating patients with AWS symptoms. [32] The first-choice drugs for treating the symptoms of AWS and preventing its complications are benzodiazepines. [33] Benzodiazepines are used to prevent the occurrence of epileptic seizures - studies have shown them to be more effective in this regard than placebo and antipsychotics. Benzodiazepines also reduce the risk of developing symptoms of delirium tremens and reduce mortality in the course of AWS. Studies have shown that diazepam has a rapid effect in reducing the severity of symptoms, reduces the risk of seizures and shortens the duration of delirium tremens. [34-37] Studies have not shown increased efficacy of any of the drugs in this group in the treatment of AWS, but long-acting benzodiazepines are usually recommended in clinical recommendations. The most commonly used drugs in this group are diazepam and chlordiazepoxide. Short-acting benzodiazepines should not be used due to the possibility of fluctuating concentrations. Patients with liver damage and those over 60 years of age are recommended to use benzodiazepines with an intermediate duration of action: oxazepam or lorazepam. Benzodiazepines act as agonists on the $GABA_A$ receptor, having an inhibitory effect on the central nervous system. These drugs are recommended to be taken orally, and they can also be administered intravenously. [31, 38, 39] Benzodiazepines are administered through various dosage methods. The first is a fixed-schedule protocol, in which the drug is administered at regular intervals. The dose of the administered benzodiazepine is gradually reduced, and treatment lasts for 7 days. If symptoms

are not adequately controlled, additional doses of the drug can be included. The second method is a symptom-triggered protocol, in which a patient's AWS symptom severity is assessed hourly, with a symptom-adjusted dose of benzodiazepines administered hourly until the patient scores <8 on the CIWA-Ar scale. [1, 31, 38] In studies, the use of symptom-triggered protocol dosing has been proven to reduce the duration of pharmacotherapy and the total applied dose of benzodiazepines given to the patient. [39-42] An additional dosing regimen for benzodiazepines (usually diazepam) that can be used for patients in hospitals, where intensive care is possible, is the loading-dose treatment strategy, which involves administering a satiating dose until the patient is sedated. This method allows for a rapid effect in terms of resolving the symptoms of AWS and achieving a calming effect. This method shortens the duration of alcoholic delirium. It is necessary to carefully monitor the patient's condition due to the possible toxicity of the used doses of the drug . [1, 31, 37] It is important to keep in mind the possible adverse effects of drugs from the benzodiazepine group, especially in patients under the influence of alcohol. [43] In cases of inadequate symptom control despite the use of benzodiazepines in optimal doses, drugs from the neuroleptic, ß-blocker and α-2-agonist groups can be used in addition. If excessive agitation, thinking or perceptual disturbances persist, haloperidol is recommended at a dose of 0.5-5 mg every 30-60 min intravenously or intramuscularly, or 0.5-5 mg every 4 hours orally. If hypertension persists, clonidine at a dose of 0.150-0.300 mg/day administered intramuscularly or orally should be used, and if tachycardia persists, atenolol at a dose of 100 mg/day should be administered orally. [31] The efficacy of anticonvulsants in patients with AWS symptoms remains a subject of research. At present, there is insufficient evidence to conclusively demonstrate the effectiveness and benefit of use of drugs from this group. There are reports of good efficacy of carbamazepine in treating the symptoms of AWS, but further studies are needed. [44] The use of drugs from other groups to alleviate the symptoms of AWS is also currently under research. One of the substances tested is gamma-hydroxybutyric acid (GHB) in the form of sodium oxybate. A Cochrane meta-analysis showed that GHB at a dose of 50 mg was more effective than placebo in treating the symptoms of AWS. GHB is more effective as an abstinence maintenance aid compared to placebo and disulfiram, and its side effects are no more severe than those of benzodiazepines and disulfiram. However, the substance's addictive potential remains a controversial issue. [45] A study by G. Addolorato et al. found that GHB was as effective as diazepam in treating the symptoms of AWS and had a faster effect compared to diazepam in reducing the severity of anxiety, agitation and depressive

symptoms in patients undergoing the study. [46] A 2014 phase IV, multicenter, randomized, controlled, double-blind study with parallel groups (GATE 1) showed that sodium oxybate was as effective in treating AWS symptoms as oxazepam, and that it showed good tolerability and no serious side effects. [47] The possibility of using baclofen to alleviate the symptoms of AWS remains of interest to researchers [48, 49], but a Cochrane review published in 2017 found no evidence for the efficacy and safety of use of baclofen in AWS treatment, and the studies conducted to date have been insufficient and of low quality. [50] Studies are also currently underway on the potential use of clomethiazole [51], pregabalin, and tiapride [52] in the treatment of AWS.

Treatment of alcoholic delirium is the best when it is carried out in an intensive care unit (ICU), where the patient's condition should be carefully monitored. The goal of treatment is to control agitation, reduce the risk of seizures and the risk of death. Drugs used to treat delirium tremens include diazepam or lorazepam in high doses; intravenous administration is preferred, and the duration of administration is about 3 days. Benzodiazepines are the first line of treatment. Patients with DT are also given thiamine that is administered intravenously, and the antipsychotic haloperidol if psychotic symptoms or excessive agitation are present. [13]

Conclusions

Alcohol withdrawal syndrome is a serious condition that can be complicated by life-threatening delirium tremens. Treatment of alcohol withdrawal syndrome is a complex process that requires a multifaceted approach and careful monitoring of the patient's condition. It is important to carry out a full diagnosis and introduce treatment as soon as possible to prevent the development of serious complications. Pharmacological treatment plays a key role, with benzodiazepines being the first line of treatment. The literature describes different dosing regimens for drugs in this group: fixed-schedule protocol, symptom-triggered protocol and loading-dose treatment strategy. If symptoms are insufficiently controlled with drugs from the benzodiazepine group, drugs from other groups such as neuroleptics, ß-blockers and α-2-agonists may be introduced. The main goal of pharmacotherapy is to alleviate symptoms and prevent the occurrence of dangerous complications. In case of delirium tremens symptoms, hospitalization and intensification of treatment is indicated. Individualized therapy adjustment and patient monitoring are crucial to ensure effective and safe treatment. Research is currently underway on the potential use of new drug groups to treat the symptoms seen in AWS. Given

the possible side effects of benzodiazepines, especially when used in patients under the influence of alcohol, and the desire to optimize and potentially reduce treatment time, the development of new treatments that take into account individual patient needs and conditions remains a subject of interest to researchers. More research is needed to develop new treatment regimens and test the effectiveness of new drug groups in treating patients with AWS symptoms.

Disclosure

Author's contribution

Conceptualization: Piotr Ćwikła, Ewelina Machała-Ćwikła; methodology: Kacper Szeląg; software: Piotr Zdziebło; check: Dominika Machała, Urszula Łapińska; formal analysis: Antoni Kujawski, Kamila Machała; investigation: Ewelina Machała-Ćwikła, Piotr Zdziebło; resources: Kacper Szeląg; data curation: Piotr Ćwikła; writing - rough preparation: Dominika Machała, Antoni Kujawski; writing - review and editing: Kamila Machała, Ewelina Machała-Ćwikła; visualization: Urszula Łapińska; supervision: Piotr Ćwikła; project administration: Ewelina Machała-Ćwikła, Dominika Machała; receiving funding- not applicable
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