Pharmacological Treatment of Alcohol Withdrawal

Tratamento Farmacológico da Síndrome de Abstinência Alcoólica

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ABSTRACT

Introduction: Excessive chronic alcohol users, and particularly patients with alcohol use disorder, may present an alcohol withdrawal syndrome if they abruptly stop drinking. Alcohol withdrawal syndrome requires pharmacological treatment for the treatment of withdrawal symptoms and to prevent withdrawal complications. Medically assisted withdrawal treatment is used in alcohol treatment units, but it is also frequently required in patients admitted to hospital for other conditions.

Methods: Review of major guidelines covering treatment of withdrawal syndrome with the aim to describe recent evidence and recommendations about the pharmacological treatment for alcohol withdrawal syndrome.

Results: Four major guidelines concerning treatment of withdrawal syndrome were selected (National Institute for Health and Care Excellence, American Society of Addiction Medicine, World Federation of Societies of Biological Psychiatry and American Psychiatric Association) and screened for the recommendations and level of evidence on drug prescribing for alcohol withdrawal syndrome. The Maudsley guidelines were also considered in this review.

Conclusion: Maintaining a high level of suspicion for alcohol withdrawal syndrome is important across all clinical settings, and it should be promptly treated.

Keywords: Alcohol Abstinence; Alcoholism/drug therapy; Substance Withdrawal Syndrome

RESUMO

Introdução: Quando os consumidores excessivos crónicos de álcool, particularmente os indivíduos com o diagnóstico de perturbação de uso de álcool, suspendem abruptamente o consumo de bebidas alcoólicas, pode surgir um quadro clínico denominado síndrome de abstinência alcoólica. Nestes casos, é necessário muitas vezes instituir tratamento farmacológico para aliviar os sintomas e prevenir as complicações da abstinência. O tratamento farmacológico da síndrome de abstinência alcoólica é utilizado em unidades especializadas no tratamento de perturbação de uso de álcool, mas também pode ser necessário em serviços médico-cirúrgicos, quando esta síndrome se manifesta em doentes com perturbação de uso de álcool internados por patologias orgânicas.

Métodos: Revisão de *guidelines* disponíveis na literatura sobre tratamento da síndrome de abstinência alcoólica com o objetivo de determinar qual o tratamento farmacológico recomendado.

Resultados: Foram analisadas as quatro *guidelines* sobre tratamento farmacológico da síndrome de abstinência alcoólica (National Institute for Health and Care Excellence, American Society of Addiction Medicine, World Federation of Societies of Biological Psychiatry e American Psychiatric Association), em relação às suas recomendações e evidência da eficácia dos fármacos para tratamento da síndrome de abstinência alcoólica. Esta análise foi ainda complementada pela consulta das *guidelines* de Maudsley.

Conclusão: É fundamental manter um nível elevado de suspeita para o eventual aparecimento da síndrome de abstinência alcoólica em todos os contextos clínicos. Nesses casos, importa saber intervir precocemente.

Palavras-chave: Abstinência de Álcool; Alcoolismo/tratamento farmacológico; Síndrome de Abstinência

INTRODUCTION

Portugal is among the countries with the highest consumption of alcoholic beverages.[1] Data from the Health Portrait published by the Ministry of Health in 2018 shows that 38.3% of Portuguese men consumed alcohol daily, the highest rate in Europe, and that Portuguese women registered the highest daily alcohol consumption in the European Union (11.8%).[2] The WHO 2018 Report shows that the prevalence of alcohol use disorders (AUD) in Portugal is 6.8% and that of alcohol dependence is 3%.[3,4]

The risks associated with the consumption of alcoholic beverages increase progressively and in continuity with the frequency and intensity of alcohol ingestion, and it is known that chronic excessive alcohol consumption causes neurochemical changes in the central nervous system.

Despite being a simple molecule, ethanol affects several brain neurotransmitter systems. The mechanism of action of alcohol includes effects on the gabaergic system, in which the recurrent activation of GABA receptors, resulting from the continued consumption of alcohol, alters the normal GABA / glutamate balance. This imbalance, in the long run, leads to an adjustment whereby the levels of glutamate increase in order to achieve a new GABA / glutamate balance.[5,6]

When chronic excessive alcohol users, particularly individuals diagnosed with AUD, abruptly stop drinking alcohol, a situation of withdrawal from alcohol use, called alcohol withdrawal syndrome, may appear.

The alcohol withdrawal syndrome, whose diagnostic criteria are described in the DSM-5 and ICD-10, includes a wide spectrum of symptoms, varying from individual to

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individual, and typically appear in the first three to 12 hours after suspension, or after a marked reduction in alcohol consumption, which may persist for four or five days.[7,8]

Symptoms of alcohol withdrawal, resulting from autonomic hyperactivity, include tremors, nausea and vomiting, sweating, anxiety, insomnia, tachycardia, elevated blood pressure and mood swings.

In mild cases of AUD, the alcohol withdrawal syndrome can resolve without complications and often without the need for pharmacological treatment. However, in moderate to severe cases of AUD, the withdrawal syndrome may evolve and become complicated if the patient does not receive adequate pharmacological treatment. The most frequent complications of alcohol withdrawal syndrome are seizures and *delirium tremens*.

Delirium tremens is the most serious and most dangerous complication of alcohol withdrawal syndrome and is considered a medical emergency.[9] It has a prevalence of about 5% (3% - 15%) in patients who experience symptoms of alcohol withdrawal.[10] It usually lasts between 48 and 72 hours but can persist for a longer period. It is more frequent in critically ill patients, in whom pharmacological treatment in high doses is recommended to prevent alcohol withdrawal syndrome.[11] The most frequent features of *delirium tremens* are autonomic instability, fever, dehydration, electrolyte imbalances, hypoglycemia, liver failure, pancreatitis, sepsis, meningitis, intracranial hemorrhage and Wernicke-Korsakoff encephalopathy. Control of agitation is essential in patients with *delirium tremens*, and in these situations the levels of agitation should be reduced for the duration of the *delirium tremens* period.[8]

The pharmacological treatment of alcohol withdrawal syndrome aims to improve withdrawal symptoms, prevent the complications of alcohol withdrawal and, when inserted in a treatment program for an AUD, start the rehabilitation process of the individual.

However, if the need to prescribe pharmacological treatment for the prevention of withdrawal syndrome in patients with moderate or severe AUD who undergo inpatient alcohol detoxification in specialized units is expected, there are other settings in which this need would not have been foreseeable in the first place.

It is known that the prevalence of substance use in patients who present to emergency departments is high, with several medical specialties being confronted with the physical and psychiatric complications of substance dependence.[12,13] Additionally, the symptoms or complications of alcohol withdrawal may themselves be the reason for resorting to the Emergency Department. Screening for substance use disorders is not yet a routine procedure in the hospital emergency department and the priority for intervention in the emergency department does not often include screening for substance use.[14,15] However, since patients with AUD are frequent users of emergency departments, it may be necessary to admit these patients to medical or surgical departments, due to decompensation of associated organic conditions or acute traumatic injuries, which are very common in this population.[16]

In addition, if it is necessary to admit a patient with AUD to undergo elective medical-surgical treatment, and given the absence of alcohol consumption during hospitalization, alcohol withdrawal syndrome may develop, with the need for pharmacological intervention to relieve symptoms and prevent the onset of complications of alcohol withdrawal.

Therefore, whenever non-voluntary cessation of alcohol consumption in patients with AUD occurs, and when AUD is not the reason why the patient is receiving hospital treatment, it is particularly important for doctors to have a high level of suspicion for the clinical manifestation of an alcohol withdrawal syndrome and for the subsequent need for early intervention, with rapid institution of therapy indicated in these cases in order to improve symptoms and prevent complications of alcohol withdrawal syndrome.

When choosing drug therapy for treatment of inpatient alcohol detoxification, whether voluntary during AUD treatment or involuntary due to the need to be admitted to a medical or surgical department for the treatment of an organic condition, there are several aspects to consider.

The aim of this paper is to review the recommended pharmacological treatments for the treatment of alcohol withdrawal syndrome.

METHODS

Review of clinical guidelines available in the literature on the pharmacological treatment of alcohol withdrawal syndrome: guidelines from the National Institute for Health and Care Excellence (NICE), the American Society of Addiction Medicine (ASAM), the World Federation of Societies of Biological Psychiatry (WFSBP), and the American Psychiatric Association (APA).[9,17-21] It should be noted that in the preparation of the WFSBP guidelines, the evidence from the German Association of Psychiatry, Psychotherapy and Psychosomatics (DGPPN), the English Association of Psychopharmacology, the French Society of Alcohology and the European Federation of Addiction Societies was incorporated.[9] The review was complemented by consulting the Maudsley's Prescribing Guidelines in Psychiatry.[5]

RESULTS

According to the NICE guidelines for the treatment of alcohol use disorders (October 2020), the first-line pharmacological treatment recommended for the treatment of alcohol withdrawal syndrome is benzodiazepines.[17-19] As a second line, as an alternative to benzodiazepines,

carbamazepine and clomethiazole are recommended, although the latter should only be used with caution and in a hospital setting.[17-19]

In the event of complications arising from alcohol withdrawal, such as *delirium tremens* and seizures, the NICE guidelines also make some recommendations. In *delirium tremens,* the first line treatment indicated is oral lorazepam. If symptoms persist or the patient refuses to take oral therapy, parenteral lorazepam or haloperidol should be used. It is also recommended that in situations of *delirium tremens* in patients who are undergoing treatment for alcohol withdrawal syndrome, a review of the prescribed pharmacological therapy is carried out. In the event of alcohol-deprivation induced seizures, the use of short half-life benzodiazepines, such as lorazepam, is recommended. The use of phenytoin is contraindicated in the treatment of seizures due to alcohol deprivation. It is also recommended that when seizures occur, in the context of alcohol deprivation in patients who are undergoing treatment for alcohol withdrawal syndrome, a review of the prescribed pharmacological therapy should be carried out.[17-19]

The NICE guidelines also recommend prescribing thiamine in patients at high risk for developing Wernicke's encephalopathy, or in suspected cases. The use of prophylactic oral thiamine is recommended in patients with AUD who are malnourished or at risk of malnutrition, in the presence of decompensated liver disease, or during the treatment of medically assisted alcohol withdrawal. The administration of prophylactic thiamine should initially be performed parenterally and later replaced by oral thiamine in patients with AUD who are either malnourished, at risk of malnutrition, have decompensated liver disease are also in an emergency department, or when they are admitted to the hospital due to an acute condition. In suspected cases of Wernicke's Encephalopathy, parenteral thiamine should be administered. Maintaining a high level of suspicion of the occurrence of Wernicke's encephalopathy, particularly in patients with acute alcohol intoxication, is recommended. Parenterally administered thiamine should be maintained for a minimum of five days unless the diagnosis of Wernicke's Encephalopathy is excluded. At the end of this period, thiamine should be administered orally.[17-19]

According to the 2020 guideline from the American Society of Addiction Medicine (ASAM), treatment for alcohol withdrawal syndrome differs depending on whether it is performed on an outpatient or inpatient setting.[20] In the inpatient setting the ASAM guidelines recommend benzodiazepines as first line treatment, due to the well-documented evidence of their effect in reducing the symptoms of alcohol withdrawal , including in reducing the incidence of seizures and *delirium*. According to the ASAM recommendations, carbamazepine and gabapentin can also be used as an alternative to benzodiazepines in patients with mild to moderate withdrawal syndrome (a score below 19 obtained on the CIWA-AR withdrawal rating scale[21]). In patients with contraindications to the use of benzodiazepines, the use of phenobarbital is recommended, but the latter should only be prescribed by physicians experienced in its use.[20]

Considering the choice of benzodiazepines, the ASAM guidelines recommend choosing one with a longer half-life, despite stressingthat no benzodiazepine has documented superior efficacy compared to the others. Pending the results of the blood screening tests for assessing liver function, or in situations of lack of availability of this assessment, as well as in cases of significant liver disease, benzodiazepines that do not undergo hepatic metabolism, such as lorazepam and oxazepam, should be prescribed. «ASAM also recommends using lower doses of benzodiazepines in patients with hepatic impairment and in the elderly. In order to use lower doses of benzodiazepines; an antipsychotic may be prescribed in association with benzodiazepines.[20]

The ASAM guidelines recommend, in cases where there is a contraindication to the use of benzodiazepines, prescribing carbamazepine or gabapentin as an alternative, but only for mild to moderate deprivation syndromes. However, the guidelines emphasize that there is no evidence of superior efficacy of these over benzodiazepines in the treatment of alcohol withdrawal syndrome. The ASAM guidelines also state that, as an association with benzodiazepines, carbamazepine, gabapentin or valproic acid may be used to treat alcohol withdrawal syndrome. However, ASAM warns that valproic acid should not be prescribed in patients with liver disease or in women of childbearing age.[20]

Another alternative presented by ASAM, for situations in which the prescribing of benzodiazepines is contraindicated, is the use of phenobarbital. However, ASAM warns that phenobarbital should only be prescribed in a hospital environment and by physicians experienced in its use, due to its narrow therapeutic window and side effects.[20]

The ASAM guidelines recommend that beta-blockers and alpha-2 adrenergic agonists, such as propranolol and clonidine, be strictly used in combination with the prescribing of benzodiazepines to control signs of autonomic hyperactivity and anxiety when these are not controlled by benzodiazepines alone, and not as monotherapy to prevent or treat alcohol withdrawal syndrome. The use of magnesium, for prophylaxis or treatment of alcohol withdrawal syndrome, is not recommended by the most recent ASAM guidelines, contrary to what happened in the 2004 guidelines, given the lack of proven benefit of magnesium for this purpose, according to a recent Cochrane review.[22] Presently, magnesium prescribing is only recommended in patients with hypomagnesaemia, cardiac arrhythmias, hydroelectrolytic imbalances, or in patients with a previous history of

seizures in the context of alcohol deprivation.[20]

The ASAM guidelines also recommend, in situations of dehydration or hydroelectrolytic imbalances due to deficits in folic acid, magnesium, phosphorus or potassium, that these deficits should be corrected.[20,23]

Regarding the treatment of the complications of the withdrawal syndrome, the ASAM guidelines recommend, both in the treatment of seizures and in the treatment of *delirium*, the use of benzodiazepines as first-line drugs, preferably administered parenterally. In cases where the clinical picture of *delirium* includes the presence of hallucinations and patients are not adequately stabilized with benzodiazepines alone, prescribing antipsychotics is recommended.[20]

According to the WFSBP guidelines, benzodiazepines are the first-line drugs for the treatment of alcohol withdrawal syndrome. The most frequently used benzodiazepines are diazepam, chlordiazepoxide, oxazepam, lorazepam and alprazolam. The indicated dose of benzodiazepine to be prescribed depends on the severity of the AUD, the intensity of the alcohol withdrawal syndrome and the characteristics of the patient.[9]

The WFSBP guidelines refer to the existence of preliminary evidence on the usefulness of lamotrigine, memantine and topiramate in the treatment of alcohol withdrawal syndrome (level C recommendation for topiramate and level D recommendation for lamotrigine and memantine). It is also reported that carbamazepine and oxcarbamazepine proved effective in the treatment of moderate to severe alcohol withdrawal syndrome, and that valproic acid was effective only in the treatment of moderate alcohol withdrawal syndrome. Both carbamazepine and valproic acid are contraindicated in patients with hepatic and hematological disease.[9]

Regarding the use of alpha-2 adrenergic receptor agonists, such as clonidine, the WFSBP guidelines recommend its use only in situations where the signs of adrenergic hyperactivity are severe.[9]

The WFSBP guidelines recommend the prophylactic administration of thiamine parenterally to patients with a history of alcohol dependence or with signs or symptoms suggestive of Wernicke-Korsakoff syndrome.[9] In *delirium* due to alcohol deprivation the guidelines recommend the use of benzodiazepines.[9]

The most recent guidelines of the American Psychiatric Association (APA), of 2018 regarding the treatment of AUDs do not address the pharmacological component for alcohol detoxification, but only report which psychotropic drugs are recommended for the treatment of the abstinence maintenance.[24] However, there is a reference to the subject in these guidelines, in the benzodiazepines section, where it is mentioned that these are the first-line drugs in the treatment of alcohol withdrawal syndrome. However, the 2006 APA guidelines, which address the pharmacological treatment of alcohol withdrawal syndrome, recommend the use of benzodiazepines for the treatment of this syndrome, with diazepam, oxazepam and lorazepam being the most frequently prescribed. Beta-blockers, clonidine, anticonvulsants and antipsychotics are recommended to be used in combination with benzodiazepines, if necessary, but are not recommended for use as monotherapy, as they have not shown to be effective in preventing either seizures or *delirium* by alcohol withdrawal.[25]

Regarding the use of anticonvulsants, the APA guidelines state that carbamazepine has shown similar efficacy to benzodiazepines for preventing seizures due to alcohol deprivation, but they do not recommend the use of phenytoin for this purpose, unless it is already used in outpatients diagnosed with epilepsy who have stopped treatment. The use of carbamazepine is recommended especially for mild to moderate alcohol withdrawal syndromes.[25]

In patients with delirium, delusions, or hallucinations, the 2006 APA guidelines recommend the use of antipsychotic drugs, in particular haloperidol. However, the guidelines recommend that antipsychotics should be used in combination with the benzodiazepines since antipsychotic drugs are not responsible for the treatment and remission of the referred symptoms.[25]

The main recommendations of the NICE, ASAM, WFSBP and APA guidelines are summarized in Table 1.

DISCUSSION

From the set of the four main guidelines related with the recommended pharmacological treatments for the prevention and treatment of alcohol withdrawal syndrome, we can conclude that:

- Benzodiazepines are the first-line treatment recommended in all guidelines for the prevention and treatment of alcohol withdrawal syndrome.
- The main benzodiazepines described in the literature as being used for these situations are diazepam, oxazepam, lorazepam, alprazolam and chlordiazepoxide, although no benzodiazepine has been shown to outperform others in preventing and treating alcohol withdrawal syndrome.
- The dosage of benzodiazepines to be prescribed should be calculated according to the severity of the AUD, the severity of the withdrawal syndrome and the individual characteristics of the patient and should be adjusted in elderly patients or patients with liver disease.
- The use of carbamazepine is recommended in the four guidelines as an alternative to the use of benzodiazepines when these are contraindicated; however, most of these guidelines refer to carbamazepine as a possible alternative to benzodiazepines,

Table 1 – Main recommendations of the NICE, ASAM, WFSBP and APA guidelines

NICE (UK, 2020)	- First-line treatment: benzodiazepines - Second-line treatment: carbamazepine - Third line treatment: clomethiazole - Thiamine: to prevent Wernicke Korsakoff encephalopathy - Antipsychotics: in association with benzodiazepines for the treatment of delirium tremens
ASAM (USA, 2020)	- First-line treatment: benzodiazepines - Second-line treatment: carbamazepine, gabapentine or valproate (do not prescribe valproate if hepatic disease or childbearing women) - Third-line treatment: phenobarbital (to be used only by doctors used to prescribe it) - Thiamine: to prevent Wernicke Korsakoff encephalopathy - alpha-2 adrenergic agonists and beta-blockers: in association with benzodiazepines if severe adrenergic hyperactivity - Antipsychotics: in association with benzodiazepines to prevent using high doses of benzodiazepines - Magnesium: prescribe only in presence of magnesium deficit
WFSBP (2017)	- First-line treatment: benzodiazepines - Second-line treatment: lamotrigine, topiramate, carbamazepine, oxcarbamazepine, valproate (do not prescribe valproic acid if hepatic disease or childbearing women) - Thiamine: to prevent Wernicke Korsakoff encephalopathy - alpha-2 adrenergic agonists and beta-blockers: in association with benzodiazepines if severe adrenergic hyperactivity
APA (USA, 2006)	- First-line treatment: benzodiazepines - Second-line treatment: carbamazepine - alpha-2 adrenergic agonists and beta-blockers: in association with benzodiazepines if necessary - Antipsychotics: in association with benzodiazepines, if necessary

NICE: National Institute for Health and Care Excellence; ASAM: American Society of Addiction Medicine; WFSBP: World Federation of Societies of Biological Psychiatry; APA: American Psychiatric Association; UK.: United Kingdom; USA: United States of America

but only for mild to moderate alcohol withdrawal syndrome.

- The use of anticonvulsants is consensual in all the guidelines, namely carbamazepine and valproate, namely in combination with benzodiazepines with the purpose of reducing the dosage used. However, the use of phenytoin is contraindicated, and carbamazepine and valproate should be prescribed with caution in patients with hepatic and hematological disease, or in women of childbearing age.
- Most guidelines recommend the prophylactic use of thiamine to all patients to prevent the development of Wernicke-Korsakoff encephalopathy.
- The recommended route of administration of thiamine is, in an initial phase, the parenteral route, and the oral route can be used later.
- The use of magnesium is recommended only in patients with hypomagnesaemia, cardiac arrhythmias, hydro-electrolytic imbalances or in patients with a history of seizures in the context of alcohol withdrawal.
- In situations of hydro-electrolytic imbalance, namely deficits in folic acid, magnesium, phosphorus and potassium, these deficits should be corrected.
- Alpha-2 adrenergic agonists and beta-blockers should be only be used in combination with benzodiazepines and in patients with signs of autonomic hyperactivity that are of significant intensity.

- In case of seizures due to alcohol deprivation, the recommended first-line treatment is benzodiazepines.
- In case of *delirium tremens*, the recommended first-line treatment is benzodiazepines, which may or may not be associated with the use of antipsychotics.

According to The Maudsley prescribing guidelines in Psychiatry,[5] the recommended duration for the pharmacological treatment ofalcohol withdrawal syndrome is seven to 10 days. During this period, the dosage of benzodiazepines should be progressively reduced, by about 20% to 25% per day, in order to, ideally, finish the treatment of physical withdrawal without prescribing benzodiazepines

In the presence of psychomotor agitation, the diagnosis of *delirium tremens* should be considered. In its

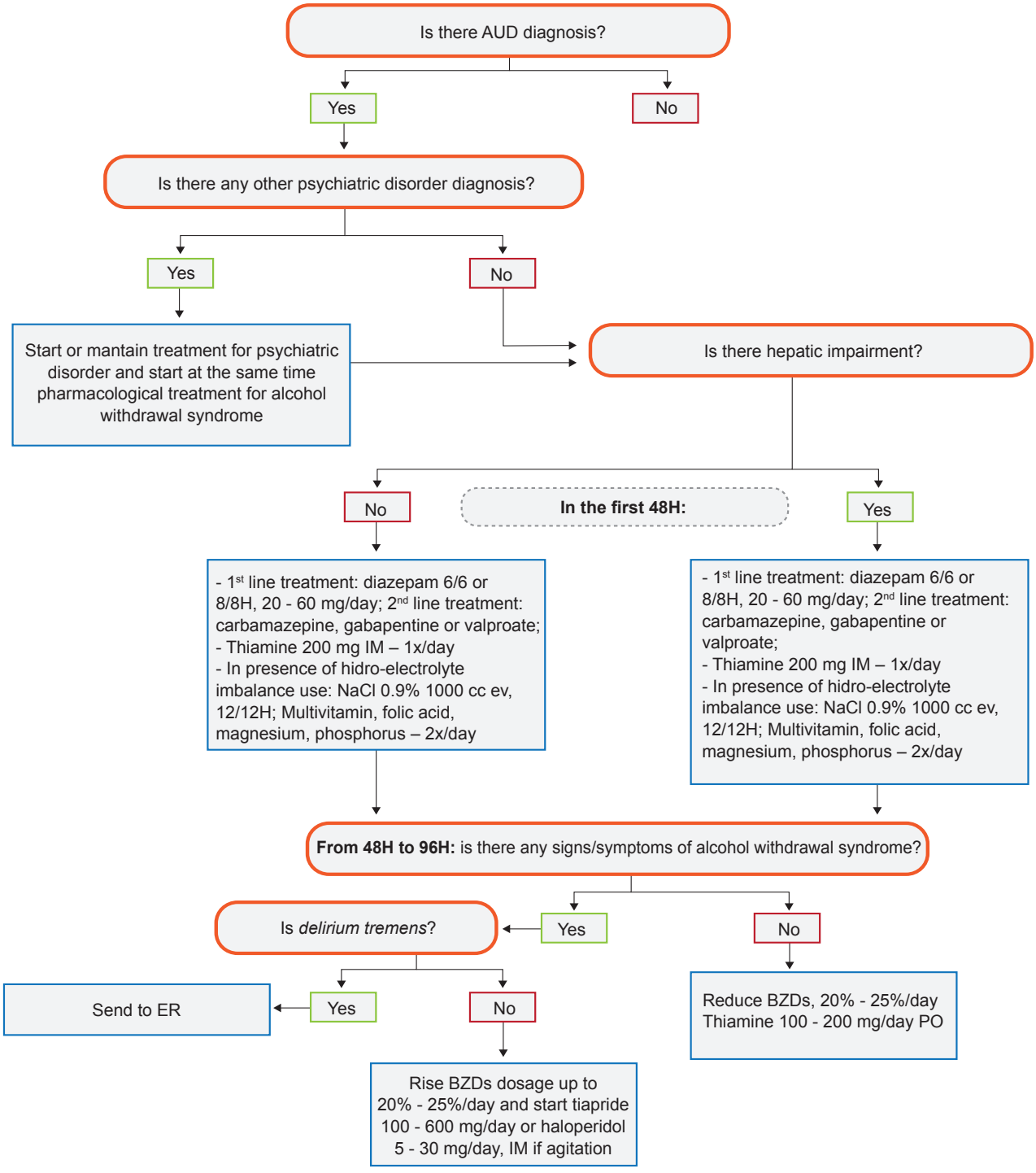

Figure 1 – Pharmacological treatment of alcohol withdrawal syndrome

ER: emergency room; BZDs: benzodiazepines; PO: per os; IM: intramuscular

exclusion, the dosage of benzodiazepines prescribed should be revised and, if this measure is not sufficient, the use of intramuscular therapy to control psychomotor agitation (haloperidol or tiapride) should be considered as recommended in the guidelines.[5,26]

It is also important, in patients who need treatment for alcohol withdrawal syndrome, to assess the presence of psychiatric comorbidities. A high rate of comorbidities between AUD and psychiatric disease has been demonstrated. Therefore, of the treatment of any acute psychiatric disorder must also cover the treatment for the alcohol withdrawal syndrome.[27,28]

When analyzing the set of these recommendations, and considering their generalizability to the Portuguese reality, a flow chart is presented below that summarizes the recommended pharmacological treatment of alcohol withdrawal syndrome (Fig. 1).

CONCLUSION

The high prevalence of AUD in Portugal, associated with the very frequent admission of patients with AUD to the Emergency Departments for causes directly or indirectly related with it, makes it very likely that doctors from the various medical and surgical specialties have frequent contact with alcohol withdrawal syndrome.

It is essential to maintain a high level of suspicion for the diagnosis of alcohol withdrawal syndrome, in order to detect these cases prematurely and immediately start the most appropriate pharmacological treatment.

This review contributes to make up for the lack of clinical guidelines in Portugal regarding the pharmacological treatment of alcohol withdrawal syndrome. The international guidelines available on this topic gather consensus on the general basic principles of treatment, and all present information that is relevant in certain aspects but not in others.

COMPETING INTERESTS

The author declared no competing interests.

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