REVIEW ARTICLE

ALCOHOL USE DISORDER. THE OTHER DISEASE.

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Abstract

Alcohol consumption throughout history has been conditioned by cultural and social elements, and its widespread use has led to a sometimes dangerous normalization in certain countries. Globally, it is known that alcohol-related disease causes around three million deaths per year[1].

Our aim as health promoters should be to intervene early in order to detect mild and moderate cases of Alcohol Use Disorder (AUD) in order to prevent them from being treated in specialized hepatology units.

Addiction treatment centers are the first specialized step in the approach to this pathology, so knowledge of specific pharmacotherapy for moderate and severe AUD is required, as well as the necessary psychotherapeutic tools for this purpose.

Coordination between the different hospital services involved in the treatment of organic pathology and addiction treatment centers should be considered as a necessary strategy in the approach to patients with severe alcohol use disorder, as well as a relapse prevention tool in transplant patients.

Keywords: alcoholism, pharmacotherapy, dual pathology, liver disease.

Definition and diagnosis

"*Alcohol use disorder*", as it is now called according to DSM-5, was listed as "alcohol addiction" in DSM-1 in 1952, although it was not recognised by the WHO as a nosological entity per se until the 1960s[2].

Alcohol use disorder is defined according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) as[3]:

1. A problematic pattern of alcohol consumption that results in clinically significant impairment or distress and is manifested by at least two of the following events within 12 months

- Alcohol is often consumed in greater quantities or for a longer period than intended.

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Lobo Lara MJ, Vallejo Gea A, Bibiloni Martínez M. Alcohol use disorder. The other disease. RAPD 2024;47(1):30-36. DOI: 10.37352/2024471.3

- Persistent craving or unsuccessful efforts to reduce or control alcohol consumption.

- A lot of time is spent on the activities necessary to obtain alcohol, consume alcohol or recover from the effects of alcohol.

- Craving or strong desire or urge to consume alcohol.

- Recurrent alcohol use resulting in a failure to perform essential duties at work, school or home.

- Continued use of alcohol despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.

- Significant withdrawal from social, occupational or recreational activities due to alcohol use.

- Recurrent alcohol use in situations where it causes physical risk.

- Continued use of alcohol despite knowledge of a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by alcohol.

- Tolerance, defined by any of the following:

* A need to consume increasing amounts of alcohol to achieve the desired intoxication or effect.

* A markedly diminished effect with continued use of the same amount of alcohol.

- Abstinence, as manifested by any of the following:

* Presence of the withdrawal syndrome that is characteristic of alcohol.

* Alcohol (or a very similar substance, such as a benzodiazepine) is used to relieve or avoid withdrawal symptoms.

2. Symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

3. The symptoms are not better explained by an unrelated mental or medical disorder, and are not due to another medical condition.

4. If criteria for more than one severity level are met, the alcohol use disorder should be diagnosed with the highest severity that is fulfilled.

The previous classification, DSM-IV[4], established the terms "abuse" and "addiction", however, the current classification determines the categories of mild, moderate and severe depending on the number of symptoms met, with 2-3 for mild, 4-5 for moderate and 6 or more for severe.

Historical framework of the treatment centers

The Outpatient Addiction Treatment Centres (CTA for its Spanish abbreviation) arose at the end of the 1980s in response to the need to cover the demand caused by the appearance of the first heroin addicts in Spain, which would later become the great epidemic of the time.

With the passing of the years and the stabilization of patients dependent on opiates thanks to the introduction of substitution programmes and other programmes of dishabituation, these centers have been modifying their population and expanding their therapeutic offer, and are now able to attend to all types of addictions and associated pathologies.

The treatment of alcoholism, dependence on cannabis, cocaine and other stimulants, as well as attention to pathological gambling and non-substance addictions, has given way in recent years to the appearance of a new patient profile.

These centers are the first step in the treatment of AUD, and there are also inpatient centers known as Therapeutic Communities scattered throughout Andalusia; these are accessed from the CTA where the assessment by the three professional figures, psychologists, doctors and social workers, is essential for referral to these resources. The approach is therefore multidisciplinary, both on an outpatient and inpatient basis, due to the biopsychosocial component of the addictive disease.

DOI: 10.37352/2024471.3

On the other hand, the Hospital Detoxification Units (UDH) are another alternative for those patients who find it difficult to undergo outpatient treatment, and there are currently three hospitals in Andalusia where they are carried out: Hospital Universitario Punta Europa in Algeciras, San Cecilio in Granada and Cruz Roja in Seville.

Approach and outpatient treatment

What we could call the "therapeutic itinerary" begins with the first "Welcome" appointment, where the motivational interview plays an important role, since our objective is to achieve adherence and "therapeutic alliance" with the patient. Empathy and reflexive listening, avoiding direct confrontation, are fundamental pillars in this first interview, encouraging the patient's self-efficacy and decision-making, thus avoiding an authoritarian or imposing attitude on the part of the interviewer[5].

Many patients come after a period of abstinence, which implies motivation to change and therefore does not require an outpatient detoxification programme, but if it is carried out, the collaboration of the family is important, if possible, both to control the drugs and to assess the patient's condition. In this sense, benzodiazepines have historically been the treatment of first choice, with those with a long half-life, such as diazepam, being the most recommended, and in cases of advanced liver disease, lorazepam, as it is not metabolized in the liver. Clomethiazole has also been widely used for years; more widely used in Europe than in the USA, this drug can be considered a good ally in the treatment of "delirium tremens", but its high addictive power, as well as cross-tolerance with alcohol and a greater number of adverse effects, means that its use should be restricted, especially in the home and outpatient setting[6]. Despite having been the first-line treatment for Alcohol Withdrawal Syndrome (AAS) for decades, its capacity to generate addiction, as well as its adverse effects, have led to the search for safer alternatives.

The emergence of new generation anticonvulsants has brought a new paradigm in detoxification treatments for both alcohol and other substances. In clinical practice, oxcarbazepine, gabapentin or pregabalin are frequently used in the treatment of AUD, both in the detoxification process and in the control of anxious symptoms related to the disease. These drugs decrease the likelihood of seizures in AAS, reduce craving and are useful in patients with mood disorders. According to the evidence, almost all of them will help in the detoxification process, favoring a slight or moderate improvement with respect to benzodiazepines, although gabapentin has the best safety profile and can be used up to 1600 mg daily[7].

In the search for drugs that can contribute to clinical improvement during the dishabituation process, research has focused on those that could have an "anticraving" and "antipriming" effect. Craving, in the context of addiction, is the desire or need to consume impulsively or to carry out the addictive behaviour; priming is a sign that could be said to be almost pathognomonic of AUD, manifesting itself as the inability to stop consumption once the subject has been exposed to a minimum amount of alcohol.

In the literature there is a large sample of studies on the main drugs developed to combat craving, with naltrexone, acamprosate and nalmefene providing the most evidence (Table 1). In 2022, an interesting review was published on the subject, with a large sample obtained from 156 publications[8].

DRUG	LEVEL OF EVIDENCE	NUMBER OF PUBLICATIONS
Naltrexone	High	54
Acamprosate	High	35
Nalmefene	High	9
Topiramate	Medium/Low	12
Gabapentin	Low	6
Baclofen	?	14
Disulfiram	High	13
Others	-	13

Table 1. ***Level of evidence for drugs used in withdrawal.***

In addition to the drugs that have already been proven to be effective, others such as topiramate, baclofen or even atypical antipsychotics and antidepressants were included; although disulfiram was also included, it is a deterrent or interdictor drug, as we will see later on and which will be dealt with in a separate section.

Naltrexone and nalmefene are two opioid receptor antagonists, the difference being that naltrexone is also a partial agonist, so that blocking these receptors in the central nervous system reduces the reward sensation associated with alcohol consumption. On the other hand, nalmefene has shown some ability to control priming, but there is currently no drug specifically designed for this purpose. Although both have

DOI: 10.37352/2024471.3

demonstrated their efficacy, there are many publications on the use of naltrexone, but not on nalmefene, which has a higher dropout rate in the publications reviewed, mainly due to the appearance of adverse effects. On the other hand, the studies carried out compare nalmefene with placebo, which in practice is of little value to clinicians, as it would have supported more evidence if it had been done with naltrexone[8].

Acamprosate acts by restoring normal GABAergic activity, diminished by chronic alcohol consumption, while reducing the state of hyperfunction of glutamatergic excitatory neurotransmission, thus alleviating the state of residual hyperexcitability of the central nervous system that would persist after cessation of alcohol consumption in people who have developed alcohol dependence[9].

The dosage of naltrexone and nalmefene, 50 mg and 18 mg a day respectively, facilitates therapeutic compliance, but this is not the case with acamprosate, which requires two 333 mg tablets every 8 hours, which in clinical practice leads to a high dropout rate in patients with certain difficulties in complying with treatment.

It is worth mentioning another drug that has sometimes shown favourable results, baclofen, but which has nevertheless been found to have mixed results attributable to methodological differences, so that more studies are needed to give it more importance in the treatment of alcohol dishabituation[8].

Austria and Italy have pioneered the use of **Gamma hydroxybutyrate (GHB)** in the treatment of alcohol dishabituation, but since it is a recreational drug known as "liquid ecstasy", it is used in very restricted contexts and for hospital use, and is the only country in Europe where it is approved[10].

The conclusion, therefore, with regard to drugs that favour the reduction of craving, is that the evidence supports the use of naltrexone, acamprosate and nalmefene as highly effective drugs in the treatment of alcohol withdrawal, although in clinical practice we may encounter difficulties in compliance due to both adverse effects and difficulties in dosage.

Disulfiram is a so-called 'deterrent' or 'interdictor' drug, whose mechanism of action is based on blocking the action of the enzyme aldehyde dehydrogenase, thereby causing the accumulation of acetic acid and generating the full range of symptoms when alcohol is consumed.

It is striking that disulfiram has attracted little interest in research over the decades despite being a widely used drug with a high degree of evidence. In 2014, Sebastián Girón[11] published an interesting review including all the studies existing up to that time, establishing three groups of authors among all the publications, whether in observational studies, trials or meta-analyses (Table 2).

The authors conclude that it is a drug with a high degree of evidence as long as it is taken under supervision. In this regard, there are several publications on the subject, with studies showing that abstinence rates after six months of treatment were 78% in patients who took the drug under supervision, compared to 58% who took it unsupervised[12]. On the other hand, other studies conclude that the results are even better if the patients have good family and social support, a non-alcoholic partner and the treatment providers are trained to improve the quality of supervision[13].

De Sousa et al. published several studies comparing the days of abstinence in patients treated with disulfiram versus others treated with naltrexone and acamprosate, with the days of abstinence being significantly longer in those treated with disulfiram[14].

	TYPES OF STUDIES			TOTAL
Opinion groups of authors	Clinical trials	Naturalistic, observational and series of cases	Reviews and meta-analyses	
Support efficacy	5	12	10	27
Determine moderate efficacy	4	1	6	11
Do not support efficacy or consider it a second-choice treatment	2	0	7	9
Total	11	13	23	47

Table 2. ***Opinion groups regarding the efficacy of disulfiram.***

DOI: 10.37352/2024471.3

And although in view of these results it might seem that the approach to addictive pathology is fundamentally based on pharmacotherapy, we must not forget that there are certain contraindications or adverse effects of the drugs we have just analysed that prevent their use. This is why psychotherapy plays an essential role, as well as the treatment of the underlying psychiatric pathology.

Alcohol use disorder often coexists with other pathologies, especially depressive or anxiety disorders, which are frequently aggravated or induced by alcohol consumption itself and which tend to improve with abstinence; however, sometimes they are independent entities, and it is this comorbidity that we call dual pathology, with the evolution of the process being favoured by the joint approach of both, which would merit a separate space for detailed analysis.

Alcohol use disorder, liver disease and transplant patients

Alcoholic liver disease (ALD) encompasses various liver conditions caused by alcohol consumption, ranging from hepatic steatosis to steatohepatitis and ultimately cirrhosis. It is the leading cause of advanced liver disease and liver cirrhosis in Europe, including Spain. Together with non-alcoholic steatohepatitis, they are the most frequent causes of chronic liver disease. In contrast, viral hepatitis B and C, thanks to advances in prevention and treatment, are experiencing a decrease in their prevalence as causes of liver disease, especially in our region, so that ALD has now become the most frequent indication for liver transplantation. When advanced liver diseases do not improve with alcohol abstinence, liver transplantation is the only curative option. The assessment of these patients is complicated and involves consideration of the risk of relapse[15].

Relapse in general terms in addiction is the use of the "problem" substance after a period of abstinence, and if AUD is characterized by anything, it is the inability to control the substance; however, there is no evidence that mild relapse, defined as occasional "slips", can have a significant impact on engraftment or patient survival[16].

Post-transplant alcohol relapse rates vary between 15% and 50%, and several studies have investigated the demographic and clinical factors associated with alcohol relapse. In this regard, the importance of psychiatric evaluation and treatment of AUD and comorbid pathology is critical to reduce these figures[17].

For the selection of patients with advanced alcoholic liver disease suitable for liver transplantation, most programmes worldwide require a six-month abstinence period. However, the usefulness of this six-month rule as a predictor of long-term sobriety is controversial18. What has been shown is that early liver transplantation improves survival in patients with a first severe episode of Alcoholic Hepatitis (AH) unresponsive to medical treatment[15].

AUD is a chronic and relapsing disease and therefore the focus should be on an intensive therapeutic approach, including psychotherapy and pharmacotherapy primarily in high-risk patients before and after transplantation. Cognitive behavioural therapy, motivational enhancement therapy together with self-help groups and pharmacotherapy[19], play a crucial role in the treatment of SAD in patients with cirrhotic alcoholic liver disease and patients in need of transplantation. Naltrexone and acamprosate could be an effective and safe alternative (Table 3), although the former should be avoided in severe hepatic dysfunction, and acamprosate in chronic renal failure[17].

DRUG	FDA/ EMA	APA RECOMMENDATIONS	ADVANCED LIVER DISEASE	INTERACTION WITH IMMUNOSUPPRESSANTS	HEPATOTOXICITY	RENAL INSUFFICIENCY
Naltrexone	Approved	First line	Avoid in Child-Pugh C	None	Possible	Allowed
Acamprosate	Approved	First line	Allowed	None	None	Reduce dose if Cr Cl 30–50 ml/min/1.73 m2, avoid if Cr Cl <30 ml/min/1.73 m2

FDA, Food and Drug Administration; EMA, European Medicines Agency; APA, American Psychiatric Association

Table 3. ***Pharmacotherapy in AUD in cirrhotic and/or transplanted patients.***

DOI: 10.37352/2024471.3

Conclusiones

AUD is a chronic and relapsing disease that is managed in the CTAs. Knowing the existing resources, as well as the correct referral to them, facilitates the access of patients to the treatment circuit.

The professionals involved in this long process must know the pharmacological and psychotherapeutic tools; naltrexone, acamprosate and disulfiram are first-line drugs with proven evidence, provided they are prescribed within a psychotherapeutic framework. A correct assessment and diagnosis of dual pathology favours adherence and improves the prognosis of patients with alcoholic liver disease, as well as a lower relapse rate in transplant patients.

Coordination between Hepatology Departments and CTAs should therefore be considered a necessity in the management of these patients, especially in those who have undergone liver transplantation, in whom post-transplant follow-up could reduce the relapse rate by allowing the assessment and treatment of possible comorbid psychiatric pathology.

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