Pharmacological treatment of alcohol use disorder. Scientific evidence

Trattamento farmacologico del disturbo da uso di alcol. Evidenze scientifiche

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SUMMARY. Pharmacological treatment of alcohol use disorder represents an essential core of the therapeutic project in a multidisciplinary approach. While non-drug treatment is evolving, from a medical perspective few pharmacotherapies are available; in particular acamprosate, naltrexone and more recently nalmefene among anticraving drugs, disulfiram as an antidipsotropic medication. New studies are focusing on off-label drugs. Moreover, scientific evidence has to support any therapeutic indication which should be tailored on patient needs and comorbidity by considering the individual bio-psycho-social profile. Follow-up is essential in order to assess patient compliance to treatment and monitoring outcomes.

KEY WORDS: alcohol use disorder, anticraving drugs, follow-up.

RIASSUNTO. La terapia farmacologica nei pazienti con disturbo da uso di alcol riveste un ruolo centrale nel progetto terapeutico, altamente contestualizzato in un approccio multidisciplinare. Sebbene i trattamenti non farmacologici per la dipendenza da alcol risultino ben strutturati e in continua evoluzione, dal punto di vista medico le possibilità di intervento sono realmente ristrette, con poche molecole a disposizione approvate per il disturbo da uso di alcol: nello specifico, l'acamprostato, il naltrexone e, più recentemente, il nalmefene tra gli anticraving; il disulfiram tra gli avversivanti. Nuovi approcci sperimentali stanno cercando di ampliare tale gamma attraverso l'utilizzo di farmaci off-label. Evidenze scientifiche devono supportare l'indicazione terapeutica, quest'ultima deve dimostrarsi "cucita" sulle esigenze del paziente e sulle comorbilità presenti tenendo conto del profilo bio-psico-sociale individuale. Fondamentale risulta il follow-up per valutare la ritenzione in trattamento e il monitoraggio degli outcome alcologici.

PAROLE CHIAVE: disordine da uso di alcol, terapia anticraving, follow-up.

INTRODUCTION

The goal of drug treatment, during the rehabilitation phase, is the maintenance of abstinence, by preventing relapse or decreasing the number of relapses, to reduce organic damage. A multidisciplinary approach to alcoholism consists of a combination of pharmacotherapy (namely anti-craving drugs and psychiatric drugs when necessary) and psychological support to create the most suitable therapy for each individual bio-psycho-social profile[1]. Thus, the new concept of "tailor-made" therapy responds to these needs. Developments in genetics and the use of off-label drugs are expanding the range of available drugs resulting in new alternative therapies and an improvement of the effectiveness of traditional drugs.

ANTICRAVING DRUGS

Acamprosate

Acamprosate (ACA) is used in alcohol dependence due to its modulation of glutamatergic transmission via its effects on NMDA receptors. Owing to its tolerability and safe profile, Acamprosate is extremely versatile[2,3]. ACA is administered at the dosage of 666 mg three times per day. Dosage reductions are required for patients weighing <60 kg and for those with renal impairment[4]. Since ACA is cleared by the kidneys, where there is a severe renal failure, the drug is contraindicated. Studies on pregnancy and Child-Pugh class C cirrhosis do not exist[5].

The effectiveness of the drug is evident in relapse but not in the case of heavy drinking[2]. (Recommendation A1 of Table 1)[5].

Naltrexone

Naltrexone (NTX) is an opioid antagonist, blocking mu-opioid receptors located in brain areas that have been implicated in reward pathways associated with alcohol. Its effectiveness is related to the reduction of the number of days of alcohol consumption and alcoholic drinks consumed in one drinking episode[6]. NTX has been found to be superior to a placebo in maintaining abstinence and in preventing relapse[3,7]. Its effectiveness increases if combined with psychotherapy[8]. NTX is contraindicated in liver failure while it is used with caution in case of liver disorders, even in mild forms[5]. Furthermore, NTX is contraindicated in patients who use opioids since it may cause withdrawal symptoms. The initial dose is 25 mg for the first 4-5 days, then 50 mg daily. Doses may be increased to 100-150 mg daily[3]. NTX is particularly effective in patients presenting a family history of alcohol use disorder (AUD)[9], and /or those presenting with early onset and antisocial behavior[10]. In individuals presenting the genetic polymorphism G, which codes for the mu opioid receptor (OPRM1), this drug has been found to be to be more effective at a dosage of 100 mg/day[11]. (Recommendation A1 of Table 1).

Nalmefene

Nalmefene is an antagonist at mu- and delta-opioid receptors and a partial agonist to the kappa receptors[12,13]. It decreases reinforcing effects of alcohol, thus helping reduce consumption by modulating the opioid system[14,15]: nalmefene is the first drug to have been approved in Europe with the goal to reduce consumption in heavy alcohol drinkers[12]. Nalmefene represents the "as needed approach" in which the drug must be administered 1-2 hours before the expected alcohol consumption. The maximum dosage is one pill per day. Contraindications are a recent history of opioid use, renal and liver failures, recent episodes of alcohol withdrawal syndrome (AWS) or hallucinations[16,17]. (Recommendation A2 of Table 1).

ANTIDIPSOTROPIC MEDICATIONS

Disulfiram

Disulfiram exhibits an antidipsotropic effect. It has been the first drug available for AUD treatment and still represents the drug of choice in some countries. It inhibits the conversion of acetaldehyde in acetic acid by blocking the aldehyde dehydrogenase 2 (ALDH2) in the liver and in the brain, resulting in an accumulation of acetaldehyde [18].This compound, in high concentrations, creates a specific reaction characterized by nausea, vomiting, headache, flushing on the face and neck and more rarely vertigo, blurred vision, hypotension and syncope[19]. Disulfiram is contraindicated in the case of hepatic impairment, cardiovascular diseases, psychosis, or cognitive impairment, pregnancy or in patients who plan to have children. Absolute abstinence is required some days before the start of treatment and patients must sign the informed consent. The administration of the drug should have placed under the supervision of a relative. Because of its contraindications and its lack of convenience Disulfiram is not commonly used[20,21]. (Recommendation A2 of Table 1).

OTHER DRUGS

Baclofen

Baclofen is an agonist of GABA-B receptors. It inhibits dopaminergic activity and it is used for spasticity[22]. In recent years, studies have been conducted to assess the effectiveness in reducing alcohol cravings in patients presenting AUD; however, data require confirmation for its use[23]. (Recommendation B2 of Table 1).

Varenicline

Varenicline is a partial agonist of $\alpha 4\beta 2$ nicotinic receptors exhibiting high affinity and high selectivity. It is used in nicotine dependence[24-26] and it has been used in AUD only recently[27]. It activates acetylcholine nicotinic receptor $\alpha 7$ which is implicated in the reward pathway associated with alcohol[28].

Table 1. Treatments' efficacy grading of both evidence and recommendations (*adapted from* EASL[5]).

Grading of evidence	**Notes**	**Symbol**
High quality	Further research is very unlikely to change our confidence in the estimate of effect and clinical practice	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate and clinical practice	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate and clinical practice. Any estimate of effect is uncertain	C
Grading of recommendation	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	2

Some studies have detected the effectiveness of Varenicline but further studies are required to assess its therapeutic use[29]. (Recommendation B2 of Table 1).

Sodium oxybate

Sodium oxybate, besides being a medication for AWS treatment, is approved in Italy and Austria in preventing relapse and decreasing craving. Despite its effectiveness, studies conducted thus far are not reliable because of their small sample sizes.

Therefore, future studies should use random sampling and employ large sample sizes with standardized assessment scales to be valid. Moreover, it is important to monitor for abuse in multi-drug abusers and in patients presenting dual diagnosis[30-32]. (Recommendation B2 of Table 1).

NEW APPROACHES OF PHARMACOGENETICS IN THE TREATMENT OF ALCOHOL USE DISORDER

Alcohol addiction is a complex disease that results from a variety of genetic and environmental influences. The variety of factors activates several individual pathophysiological mechanisms leading to the development and progression of AUD. In support of this hypothesis, numerous studies have been conducted demonstrating the existence of slight differences in the population at the genetic level (i.e., polymorphisms) that may increase the vulnerability in developing dependence or determining some characteristics of the disease such as severity of drinking, craving, the age of onset, etc. After such genetic variations were identified, they were used to study the best response to treatment with drugs in terms of therapeutic efficacy and tolerability. Studies have been conducted on both the main drugs used in alcohol dependence (NTX and ACA) and on the off-label drugs (topiramate, ondansetron, sertraline and olanzapine).

Naltrexone

Studies conducted on alcohol dependence and treatment with NTX have shown that some individuals having alcohol problems present a deficit of endogenous opioids[33] along with genetic markers (i.e., polymorphisms) predictive of pharmacological response. In particular, studies have focused on the single-nucleotide polymorphism (SNP) rs1799971 concerning OPRM1 gene, which determines the A118G variation at the nucleotide level[34] resulting in the amino acid substitution Asn40Asp at the protein level. The presence of the G allele is associated with: an increased binding capacity for β-endorphin, a reduction in mRNA levels and in the synthesis of the protein-receptor[35,36], as well as a more efficient response to NTX at a dose of 100 mg/day[37].

Other studies have investigated whether NTX is effective in some patients at a dosage of 50 mg/day and they showed that a response was possible in individuals presenting the variable number of tandem repeat polymorphism (VNTR from 7 to 11) of DRD4 gene[44]. To summarize, since the G allele is more common among Caucasian and Asiatic people, the use of NTX would be most beneficial in these populations.

Acamprosate

It was FDA approved for AUD treatment in 2004. Researchers studying populations have identified polymorphisms able to predict response to treatment with ACA, in particular: the C1412T polymorphism of GABRB2 gene, the SNP rs13273672 polymorphism of GATA4 gene and the PER2Brdm1 mutation of PER2 gene. The first two are associated with the physiological response to alcohol, the latter is associated with the response to ACA. A preclinical study on mice carriers of the gene mutation PER2 showed a reduction of alcohol consumption following the administration of ACA[37]. The same study focused on alcohol consumption in a population of Caucasian individuals treated with ACA, showing that the individual carriers of at least one mutated allele, within a regulatory region of PER2, showed a lower alcohol intake (<300 g/die) than those who do not carry the mutated allele. However, these findings need to be replicated in independent studies to validate the importance of pharmacogenetics to treatment.

Ondansetron

Ondansetron was FDA approved for the treatment of nausea, postoperatively and in chemotherapy. This drug has a high affinity for the 5-HT3 receptors which regulate the release of dopamine. While alcohol induces an increase of dopamine, ondansetron reduces the release of the neurotransmitter by blocking the 5-HT3 receptors. Several studies[38] investigated the effectiveness of ondansetron by dividing alcoholic individuals into two subgroups based on their genotype for the promoter region of the SLC6A4 gene coding for the serotonin transporter (5-HTTLPR L/S polymorphism). The study showed that the patients with the LL genotype treated with ondansetron responded better in terms of alcohol amount and days of abstinence, compared to the other subgroups. Based on these results, researchers have further investigated genotype LL carriers, by analyzing the role of a functional polymorphism of the SLC6A4 gene (rs1042173 [T/G] SNP). The result was that individuals who carry both 5-HTTLPR LL polymorphism and rs1042173 TT polymorphism, treated with ondansetron at the dosage of 0.5 mg/die, present a more effective response to the drug. Unfortunately, the sample of this exploratory study was too small to be validated.

Topiramate

Topiramate was FDA approved for the treatment of epilepsy in 1996 and for the treatment of migraine in 2004. It has been tested in multiple clinical trials since it could be promising in AUD treatment. Topiramate decreases reinforcing effects of alcohol and craving[39]. A meta-analysis[40], based on data from seven random studies (2003-2014), suggested that topiramate might have beneficial effects in AUD treatment but because of its many side effects, the use is limited. The most common side effects are cognitive dysfunction[41], paresthesia[42], and taste abnormalities[43]. Pharmacogenetics studies were conducted on an SNP for the GRIK1 gene coding for one of the main receptors of topiramate: the Gluk1 receptor. The rs2832407 polymorphism is a substitution of the nucleotide C/A. Rav et al.[44] suggested that patients with at least one copy of A allele (AC or AA) treated with 300 mg of

topiramate, presented an increased risk of experiencing adverse events compared to patients with two copies of the C allele (CC). Furthermore, in 2014 Kranzler et al.[45], by dividing patients based on their genetic profile (CC, AA, or AC), compared the efficacy of 200 mg of topiramate versus placebo. This study has shown that only CC patients received a real benefit from topiramate, while no difference was found between the drug and placebo in patients with at least one A allele.

Sertraline

Sertraline was FDA approved for the treatment of depression in 2002 and for the treatment of generalized anxiety disorder in 2003. Sertraline belongs to the selective serotonin reuptake inhibitors (SSRI) drug classification. In 2009 Kenna et al.[46], by randomly administering a placebo, ondansetron and sertraline to 21 patients at a dose of 200 mg/die for three weeks, suggesting beneficial effects resulted from sertraline on some individuals carrying the 5-HTTLPR LL polymorphism. These individuals were the subject of further studies for the investigation of an SNP, a rs25531 substitution of the nucleotide A/G in the upstream promoter region of the SLC6A4 gene. The study showed that patients who responded to the administration with sertraline carried the LALA profile, that exhibits a totally functional serotonin transporter and a late onset of AUD[47]. These individuals showed a good response up to 3 months after the discontinuation of the drug.

Olanzapine

Olanzapine was FDA approved for the treatment of schizophrenia and bipolar disorder only. It is an atypical antagonist of D2 and D4 receptors which determines a decrease in craving for alcohol[48]. The DRD4 gene of dopamine presents a VNTR polymorphism, with a number of repetitions that varies from 2 to 11 which allows for the division of individuals in two subgroups: those with a number of repetitions between 2 and 6, classified as DRD4 S and those with more than 7 repetitions, classified as DRD4 L. Association studies between this variation and AUD have showed that individuals who carry the L allele exhibit greater craving after alcohol intake[49,50]. Another study has investigated the association olanzapine-DRD4 showing that olanzapine reduces craving to the L allele carriers only, while no benefits were observed in S allele carriers[51].

CONCLUSIONS

Scientific evidence must support therapeutic indications appropriate to the needs of each patient and their comorbidities by considering the individual bio-psycho-social profile[52-57]. Thus, the combination of pharmacotherapy, psychological and psychiatric support is necessary, as are the follow-up and the monitoring of clinical outcomes.

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