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The pharmacologic treatment of the alcohol dependence

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Abstract

The pharmacological intervention can play a crucial role in the reduction of craving and drinking and the maintenance of abstinence. This article reviews pharmacotherapy for alcohol dependence with an emphasis on the naltrexone, dissulfiram and acamprosate. The opioid antagonist naltrexone lowers relapse rate, reduces drinking days and prolongs periods of abstinence. Acamprosate restores the normal activity of glutamate and GABA systems. Disulfiram has been shown to be most effective for patients who believe in its efficacy and remain compliant with the treatment. 0ndansetron, has shown promise in the early-onset alcohol dependence but needs more extensive study. Topiramate (up to 300 mg per day) was more efficacious than placebo in the treatment of alcohol dependence.

Keywords: *Alcoholism. Alcoholism. Naltrexone. Disulfiram.*

Introduction

Inadequate use of alcohol represents a serious worldwide public health problem, what has stimulated innumerable investigations seeking a better understanding of ethanol-related problems and their modes of treatment. Knowing that half of the patients with alcohol dependence syndrome relapse after a short detoxification period and that studies in neurosciences are implying new neurotransmission systems, such as those involved in mesocorticolimbic structures, in their pathophysiology, the development of new pharmacological treatment models has become an area of increasing worldwide interest.

Pharmacological Interventions.

During several years, the pharmacological interventions (PI) were restricted to treatment of alcohol withdrawal syndrome (AWS) and to the use of aversive drugs. In the last 10 years, naltrexone and acamprosate have been proposed for the treatment of alcohol dependence syndrome as important adjuvant interventions for psychosocial treatment. More recently, ondansetrom and topiramate have appeared as promising therapeutical strategies, being in the approval phase.[1,2] This review of the literature will deal with currently-available PI for the treatment of alcohol dependence, focusing on clinically-relevant issues for professionals who deal with these patients.

Disulfiram

Disulfiram (DSF) was the first pharmacological intervention approved by the FDA for the treatment of alcohol dependence. For the success of treatment with DSF all patients should be engaged in some treatment program. Supervised oral DSF is efficient, when incorporated to a treatment which includes a community reinforcement approach, i.e., interventions developed in order to create new social skills, by means of counseling, besides resocialization (e.g., social clubs) and recreational activities which stimulate abstinence.[3,4] It is important the

adoption of strategies to increase the compliance with treatment such as: contingent social contracts - consisting of therapeutical agreements between patients and the people involved in their treatment, aiming that any of the family members supervise the administration of the medication behavioral monitoring of abstinence, besides some form of positive reinforcement for abstinence. Treatment effectiveness increases with these interventions.

1. Mechanism of action

DSF is an irreversible and nonspecific enzyme-inhibitory agent which decomposes alcohol into the stage of acetaldehyde. When inhibiting the enzyme acetaldehyde-dehydrogenase (ALDH), an accumulation of acetaldehyde in the body will occur, leading to the ethanol-dissulfiram reaction (figure1).

2. Contraindications

Among the contraindications, hepatic cirrhosis with portal hypertension may evolve with vomiting-induced visceral hemorrhage, during the ethanol-disulfiram reaction. In pregnancy there is the risk of congenital anomalies. DSF may be used on patients with history of convulsions associated with alcohol withdrawal syndrome, provided it be ruled out the presence of epilepsy. Other contraindication is organic mental syndrome, due to the impairment of the patientsí capability of understanding the risk of the ethanol-dissulfiram reaction. Patients should be explained the toxic effects of DSF before its use, as to not using it without their previous consent. Therefore, patients should abstain completely from alcohol and have a full understanding of the risks and principles of the treatment.

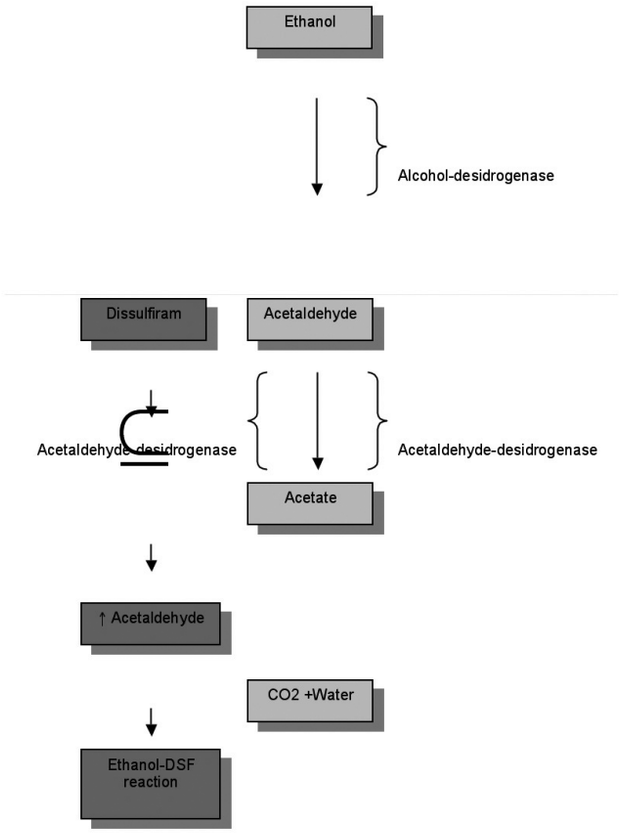

Figure 1 – Mechanism of action of dissulfiram

3. Adverse Effects

DSF is well-tolerated. Hepatitis is a rare adverse effect, which occurs mainly after 2 months of treatment with this medication. Early detection of this clinical condition may be performed, inclu- ding their mildest forms, by means of hepatic function tests. It is recommended to monitor the hepatic function every three months in the maintenance phase. In the first month of treatment, these lab exams may be performed every two weeks.[5]

4. Clinical orientations

The habitual dose is 250 mg/day in a sole daily dose, after at least a 12-hour abstinence interval. Patients may also benefit from 500 mg daily doses. The recommended duration of treatment is one year. Other alternative modes of administration include: use of low maintenance doses during years or intermittent use on high-risk situations. The inhibition of the enzyme ALDH may last for up to two weeks, after the suspension of DSF.[6] Patients should be oriented to avoid all alcohol sources (e.g., vinegar).

Naltrexone

Naltrexone is an opiate antagonist, used as an adjuvant of psychosocial interventions in outpatient treatment of alcoholism. In 1995, the FDA approved naltrexone for the treatment of alcoholism. It is the first medication to be approved, since the introduction of DSF. According to Srisurapanont and Jarusuraisin,[7] pre-clinical studies suggest that opioid antagonists attenuate the pleasant effects of alcohol consumption. Based on these animal studies, the efficacy and effectiveness of naltrexone have been investigated in the treatment of alcohol dependence.

1. Mechanism of action

Alcohol would stimulate indirectly the endogen opioid activity, by promoting the release of endogen peptides (encephalins and endorphins), in the synaptic cleft. The pleasant sensations of alcohol would be mediated by the release of dopamine if the synaptic clefts of the nucleus accumbens. Other mechanism proposed is the inhibitory acti- vity of endogen peptides over the gabaergic inter-neurons situated in the ventral tegmental area, which exert inhibitory effects on area A10 dopaminergic neurons. Naltrexone acts as a competitive antagonist on opioid receptors. Therefore, the administration of opioid antagonists would reduce the consumption of alcohol by means of the post-synaptic blocking of the and opioid receptors in the mesolimbic pathways.

2. Contraindications

The main contraindications to the use of naltrexone are acute and chronic hepatic diseases. Among opioid users it is advisable to perform a test with naloxone to discard recent heroine use. The use of opioid antagonists in heroine-dependent patients may trigger withdrawal syndrome symptoms, which start 5 minutes after the administration of the medication, lasting for approximately 48 hours. In these patients a minimum period of seven days of abstinence is needed before prescribing naltrexone chlorhiydrate. Among those treated with methadone, a longer abstinence period is recommended: 10 to 14 days.

3. Adverse effects

The main adverse effect of naltrexone is nausea, which generally is coincident with the plasmatic levels reached in a period of up to 90 minutes after the ingestion of the medication. Hepatotoxicity based on the increase of hepatic transaminases (3 to 19 times the normal values) was observed on patients treated with high doses of naltrexone (above 300 mg daily). In doses below 200 mg/day, no increase in hepatic enzymes was found. However, it is important the monthly monitoring of bilirrubine values (total and fractions) and of serum transaminases in the first three months, and afterwards every three months. More frequent monitoring is indicated, when transaminases are high. Naltrexone should be withdrawn when the rising of transaminases persist, except if they are mild and attributed to alcohol consumption.

4. Clinical orientations

The recommended dose of naltrexone in the treatment of alcoholism is 50 mg/day. The therapeutic scheme consists of the prescription of 25

mg/daily in the first week of treatment, aiming to decrease the incidence and severity of the adverse effects. After this period, the dose may be raised to 50 mg/daily. The clinical trials with naltrexone propose a 12-week treatment. According to O'Malley et al.,[8] naltrexone keep the reduced relapse rates up to the fifth month after its discontinuation. Anton et al.[9] have evidenced similar relapse rates among the treatment groups, four months after discontinuation of naltrexone chlorhydrate and placebo. Latt et al.[10] found that the therapeutic effects on relapse rates are stronger in the first 42 days of treatment.

Acamprosate

Acamprosate (calcium acetyl-homotaurinate) has been prescribed for more than one decade in several countries and has proven efficient in the treatment of alcohol dependence.[11] Despite its approval for use in the treatment of patients with Alcohol dependence syndrome in several European and Latin-American countries, up to now it has not been approved by the FDA for this indication.

1. Mechanisms of action

This medication inhibits the glutamatergic excitatory activity, acting, probably, on a subclass of Glutamate (NMDA) receptors, especially when there is hyperactivity of these receptors. Acamprosate has been considered a partial coagonist of the NMDA receptor.[12] There is evidence that this medication reduces glutamate-induced calcium reuptake on neurons, suppresses the conditioned responses to ethanol in dependent animals, even on those with protracted abstinence, reduces the aversive effects of alcohol withdrawal, inhibits the brain hyperexcitability of glutamate and inhibits the c-fos gene expression.[13] The activity on the gabaergic system has been described, mainly involving subcortical pathways. In an experimental study, Daoust et al.[14] have described that acamprosate improves the reuptake of GABA in the thalamus and hypothalamus of inebriated rats. Stromberg et al.[15] claim that there are NMDA-type receptors in the nucleus accumbens which receive stimuli from the amygdale, hippocampus, pre-frontal cortex and ventral tegmental area. These receptors, thus, seem to modulate the dopaminergic activity of the nucleus accumbens, reducing the ethanol-related positive reinforcement.

2. Contraindications

Acamprosate has a good oral absorption, which is, however, impaired by the concomitant ingestion of food. It is not metabolized, being completely eliminated by the kidneys. Besides, it has no protein link. All these characteristics suggest that this medication has no preoccupying interactions with other drugs. Patients with hepatic insufficiency are able to receive acamprosate, as it suffers no pharmacokinetic alteration. However, some authors proscribe the drug for patients with hepatic insufficiency CHILD-PUGH C, but not for CHILD-PUGH A or B. Pregnant women should not receive the medication, as there are no reliable data about its safeness for the fetus.[16]

3. Adverse effects

In the clinical trials performed, there was no report of death attributed to the medication.[17] Acamprosate is well tolerated, however, Tempesta[18] reported that two patients had discontinued the treatment due to the appearance of edema on inferior limbs after the drug started being used. Poldrugo[11] reported that 1.6% of patients who received acamprosate dropped out due to side-effects (nausea and vomiting in one case and diarrhea in other one). In general, the adverse effects reported are headache, gastrointestinal symptoms (abdominal pain, nausea and vomiting) or dermatological (pruritus, maculo-papular rash and blistering reactions. Sickness, mental confusion, somnolence and alteration of libido were also reported. Five cases of overdose associated with acamprosate were described (>43g), and all patients recovered after gastric lavage. Monitoring of hypercalcemia is recommended for patients with ëintoxicationí by this drug.[19]

4. Orientations

Acamprosate should be administered in alcohol-dependent patients with more than 60 Kg, in three daily doses, being two capsules with 333 mg in the three periods of the day, always before meals. For patients with less than 60 Kg, most of the studies suggest the administration of lower doses, i.e., a capsule with 333 mg in the three periods of the day. Maintenance time of the medication is variable. The clinical trials performed used the drug for 6 to 12 months.[20]

Future Perspectives

Currently, two medications, topiramate and ondansetrom, have shown promising in the treatment of alcohol-dependence.

Topiramate is an antagonist of the Glutamate AMPA receptor, which reduces the propriety of positive reinforcement related to the consumption of ethanol. Johnson et al. (2003) have demonstrated, in one double-blind, placebo-controlled study, the efficacy of topiramate in alcohol-dependent patients, in terms of abstinence rates, reduction of craving and decrease in the serum levels of serum gama-glutamil transpeptidase (GGT).

Ondansetron, a 5-HT^3 antagonist, is a drug which has been proposed for the treatment of subjects with early-onset alcohol dependence. These patients present significant family history for alcohol dependence and anti-social behavior. It is supposed that the neurochemical substrate of these clinical characteristics is abnormalities of the serotoninergic system. Johnson et al. (2000) have evidenced decrease of alcohol consumption among patients receiving 4g/kg of ondansetron along the 11 weeks of treatment.[21]

Conclusions

Acamprosate and naltrexone are important pharmacological resources in the treatment of alcohol dependence syndrome. Under certain paired conditions, disulfiram is also an efficient intevervention. We highlighted promising results with topiramate and ondansetron which should be replicated by further clinical trials. The pharmacological research in this area remains always guided by the neurobiological alterations triggered by the intense consumption of ethanol, revealing new and promising breakthroughs. The pharmacological treatment of chemical dependences as a whole should not be the main therapeutical strategy, as innumerable other factors, besides the biological, compose these diseases, but should be thought as an important medical tool for better approaching patients.

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Table 1 – Clinical Description

	DISSULFIRAM	NALTREXONE	ACAMPROSATE
Definition	Alcohol sensitization	Opioid antagonist	Coagonist of Glutamato receptors (NMDA)
Mechanism of Action	Inhibitor of the enzyme aldehyde- dehydrogenase	Blocking of opioid receptors	Blocking of the glutamatergic excitability
Posology	Initial dose: 500 mg/day during 14 days Maintenance dose: 125 to 250 mg/day	Initial dose: 25 mg/day during two days Maintenance dose: 50 mg/day	Dose for patients with more than 60 Kg: 1998 mg/day Dose for patients with less than 60 Kg: 999 mg/day
Contraindications	Cirrhosis, hepatic insufficiency, epilepsy, pregnancy	Cirrhosis, Hepatic insufficiency opioid dependence, pregnancy	Hepatic insufficiency Child Pugh C, pregnancy
Adverse effects	Cutaneous rash, sexual dysfunction, acne, fatigue, metallic taste in the mouth	Nausea, vomiting, headache, loss of weight	Headache, diarrhea, cutaneous rash, nausea
Recommendations	Monitoring of the hepatic function; Introduction only after an abstinence period from 24 to 48 hours Avoid alcohol sources (including for topic use)	Monitoring of the hepatic function	Insisting in the correct taking of medications The hepatic monitoring is recommended, due to consumption of ethanol

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