Pharmacological approaches to the management of alcohol addiction

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Abstract. - Alcohol abuse and alcoholism represent a world-wide problem, both from a medical and a social point of view. In the past the therapy for patients affected by alcoholism was based mainly on the psychological approach. In recent years the use of pharmacotherapy together with psychosocial interventions have enhanced the percentage of success in maintaining alcoholic patients in remission. The present review discusses the main drugs experimented both in preclinical and clinical studies. Pharmacotherapy of alcohol dependence seems to be effective in both alcohol-related emergencies and prevention relapse. However, pharmacotherapy should not be considered as the only form of treatment but as an integrated part of a multimodal approach including psychological and social support.

Key Words:

Alcoholism, Acute alcohol intoxication, Alcohol withdrawal syndrome, Benzodiazepine, Craving, Relapse prevention, Disulfiram, Gamma-hydroxybutyric, Acamprosate, Naltrexone, Baclofen, Serotonin reuptake inhibitor.

Introduction

Alcohol abuse and alcoholism represent a world-wide problem, both from a medical and a social point of view. Alcohol dependence affects nearly 10% of the general population both in the United States¹ and in Europe² and the high prevalence rate of the alcohol-related problems highlights the pub-

lic health importance of this disorder. Alcohol dependence can be defined as a progressive chronic disease, as recognized by the American Medical and Psychiatric Associations³. Pharmacological treatment of patients affected by alcohol abuse and alcoholism is an emerging means of enhancing alcohol-abstinence and preventing relapse, complementing psychosocial interventions that have been used for many years. Treating alcoholism therefore requires physicians, in both general practice and referral centres, to have an appropriate knowledge of drugs that can be used for alcohol-related emergencies and relapse prevention. In the last few years, many drugs have been experimented both in preclinical and clinical studies.

Emergencies

These are represented by acute alcohol intoxication and alcohol withdrawal syndrome.

Acute Alcohol Intoxication

This is characterized by both psychological and physical/behavioural symptoms, as a result of acute ingestion of high/toxic doses of ethanol. A first phase of euphoria is followed by a phase of mental confusion that can progress up to the coma, because of the alcohol-depressive effect on the central nervous system. Therefore, the patient may present to the doctor with sedation or, conversely, with agitation and self/hetero-aggressive behaviour.

Aggressive patient: the patient should be calmed, reassured and directed towards a correct perception of reality. Nevertheless, this approach is not usually effective and the patient may require sedatives (e.g. Diazepam i.v. 10-20 mg or Droperidol i.v. 5 mg) to protect himself against potential traumatic events or to protect the medical staff. It should be kept in mind, however, that this approach can cause progression of acute alcohol-intoxication toward a major alteration in consciousness, hypotension and respiratory depression, above all in patients with concomitant cerebral or hepatic functional disorders. The use of metadoxine has shown some efficacy because of its effect on ethanol metabolism and, therefore, a faster elimination of ingested alcohol⁴.

Respiratory depression: this needs urgent therapeutic intervention and represents the more frequent cause of death; the patient requires artificial respiration until most of the ingested alcohol undergoes hepatic metabolism.

Alcoholic coma: prompt gastric lavage can be useful to prevent further gastrointestinal absorption of ethanol. The procedure puts the unconscious patient at some risk of gastric content aspiration, but it becomes increasingly important if concomitant ingestion of drugs is suspected. Key determinants in the case of alcoholic coma are close monitoring of respiratory depression, hypoxia, cardiac arrhythmias, hypotension and correction of metabolic, electrolyte and fluid imbalances; therefore, besides re-hydration with glucose and hypotonic solutions since alcohol increases blood osmolality, laboratory parameters should guide bicarbonate and electrolyte infusions. Vitamin supplementation (folates and thiamine) is also indicated to prevent Wernicke's encephalopathy. Drugs such as Naloxone (opiate antagonist) and Flumazenil (benzodiazepine antagonist) and other medications able to influence ethanol metabolism (alcohol dehydrogenase and acetaldehyde dehydrogenase activity) such as Fructose 1-6 biphosphate and Metadoxine (4) can be used to speed up the regaining of consciousness.

Alcohol Withdrawal Syndrome and Delirium Tremens

Alcohol withdrawal syndrome: besides fluid and electrolyte administration, benzodi-

azepines (e.g. Diazepam 100-120 mg/day) and Chlordiazepoxide (300-500 mg/day) have proved particularly effective⁵. Gamma-hydroxybutyric acid – GHB – (10 ml/4-6h po) has also been proposed as an effective drug in the treatment of alcohol withdrawal syndrome⁶. GHB's efficacy is similar to that of diazepam⁷; GHB has also shown fast control of some withdrawal symptoms such as anxiety, agitation and depression⁷. Finally, the effectiveness of baclofen in rapidly reducing (10 mg/8 h) symptoms of alcohol withdrawal syndrome has been recently reported. Baclofen, currently utilized as a relaxant, appears particularly easy to manage and is under investigation in clinical trials.

Treatment with alcoholic solutions is no longer recommended because of the worsening of unstable metabolic conditions and the availability of effective medications to control the withdrawal symptoms.

Delirium tremens: if the alcohol withdrawal syndrome develops into "delirium tremens", patients should be admitted to an Intensive Care Unit. Common causes of death are hyperthermia and cardiac arrest. Therefore, it is extremely important to monitor fluid and electrolyte homeostasis, blood sugar levels and body temperature; patients should be reassured and kept away from sensorial stimulations; duration and intensity of hallucinations should be closely checked. If agitation is not kept under control through the above mentioned medications, alternative pharmacological approaches are the administration of Tioridazine (50-100 mg tid), Haloperidol (1-2 mg/4 h im) or Tiapride (1-6 fl/day im).

Relapse Prevention

Detoxification from psychotropic substances means short, medium and long term intervention which includes elimination of the physical dependence and the achievement and maintenance of long-term abstinence. This program must include the combination of both pharmacological and psychosocial approaches⁹⁻¹¹.

As regards the pharmacological approach, besides several non-specific medications (vitamins, anxiolytics, antidepressants, and major sedatives), the pharmacotherapy of alcohol

dependence currently includes specific drugs that can be classified as adversion-causing drugs and drugs with anti-reward and anticraving effects.

Adversion-Causing Drugs

Disulfiram: Disulfiram blocks the catabolic pathway of alcohol, by inhibiting aldehyde dehydrogenase and increasing acetaldehyde levels. Increases in acetaldehyde levels produce a variety of clinical manifestations, including vasomotor symptoms (flushing), cardiovascular symptoms (tachycardia, hypotension), digestive symptoms (nausea, vomiting, diarrhoea), headache, respiratory depression, malaise. These symptoms appear within 5 to 15 minutes after alcohol is consumed and may last for 30 minutes to a few hours. Alcohol-Disulfiram related manifestations are generally transient, but hospital admission should be considered for serious cases¹². Therefore, subjects have to be aware of alcohol-Disulfiram reactions. Disulfiram treatment (400 mg/day for the first week and 200 mg/day as maintenance) can be started when the patient has been abstinent from alcohol for at least twelve hours¹². Disulfiram implants are an alternative method of ensuring compliance. Nevertheless, informed patient consent should be obtained.

Disulfiram therapy by itself does not, however, represent the only strategy for treating alcoholism. It should be used when a patient needs "external" control to maintain longterm abstinence, in association with other treatment and follow-up programs¹². It would be better to avoid this therapy during concomitant treatment with barbiturates, Diazepam, Chlordiazepoxide, Antipyrine (drugs requiring oxidative metabolism), and when dementia, psychiatric disturbances, neuropathies or poor compliance are present. Conversely, Disulfiram can be associated with GHB and Acamprosate¹³). Absolute contraindications are drug allergy/hypersensitivity or pregnancy; severe organic diseases (cardiopathy, diabetes, hepatopathy, pneumopathy, nefropathy). Finally, Disulfiram may have teratogenic effects.

"Craving" Treatment

The Oxford Dictionary defines the term "craving" as a powerful desire for something. If the desire is not satisfied, physical and psy-

chological suffering (with asthenia, anorexia, anxiety, insomnia, aggressiveness, depression) may appear. Some years ago, craving was erroneously considered as a symptom of alcohol withdrawal; in fact, it has been recently shown that alcoholism-related compulsion can appear after long-term abstinence; this irresistible urge to drink is typically provoked by "the first drink" or by situations associated with alcohol use¹⁴. The role of craving in the pathogenesis of alcohol dependence and of relapse in patients affected by alcoholism has been recently highlighted. Most clinical observations on alcohol craving have been carried out on alcohol-dependent patients during abstinence and who have overcome the withdrawal syndrome. These patients periodically present with asthenia, anorexia, anxiety, irritability, aggressiveness, insomnia, hyperactivity and a search for pleasant sensations or, conversely, with boredom and depression. Patients often associate these symptoms with the increase in compulsive desire to drink alcohol; this condition generally leads to the first drink, loss of control and relapse. If the patient does not relapse, craving tends to resolve spontaneously after a variable period of time (a few hours to several days). This reported phenomenon usually occurs during the first months of detoxification; its frequency and intensity then tend to decrease, although complete disappearance is rare. The appearance of craving sometimes seems to be linked to stressful or sorrowing events; however, it often appears out of the blue. Diagnosis and treatment of this particular clinical condition (marker of the risk of relapse) is, therefore, extremely important.

Prior to the introduction of anticraving drugs for the treatment of alcohol dependence, the Disulfiram administration and surveillance by relatives of the patient and/or by therapeutic groups (i.e. Alcoholics Anonymous), waiting for spontaneous craving exhaustion, were the only treatment strategy to control craving. In the last decade several drugs, able to interfere with the neurotransmitters involved in craving mechanisms, have been studied in both animals and humans. These drugs may be divided into:

 alcohol-mimetic drugs; they attenuate craving by mimicking alcohol effects; anti-reward drugs; they attenuate craving by reducing the pleasant sensations of alcohol.

Gammahydroxybutyric acid (GHB): GHB is an endogenous compound with functions of neuromodulation and neurotransmission. Because of its alcohol-mimetic effect on the central nervous system, studies currently available have shown that GHB is effective in the treatment of alcohol dependence¹⁵⁻¹⁸. Besides its effectiveness in preventing the withdrawal syndrome^{6,7}, GHB decreases alcohol craving by reproducing "rewarding effects" ¹⁹.

The mechanisms of action of GHB are not completely known; this substance interferes with some neurotransmitter systems, in particular with the mesolimbic cortical system, by inducing variation in dopamine, serotonine and GABA cerebral concentrations¹⁹. Recent studies have shown that oral administration of GHB (50 mg/kg body weight, divided into three daily doses) was very effective in inducing short term¹⁵ and medium-long term¹⁶ alcohol abstinence in alcoholic patients. GHB is well tolerated^{20,21}; side effects including dizziness, hyporeflexia and somnolence have been reported, but they are usually tolerated. Non-therapeutic use of GHB can produce an anabolic side effect, but it has not been reported in alcoholic patients at the recommended dose²². Because of its alcoholmimicking effect, cases of craving for GHB, and the consequent risk of GHB abuse¹⁷ and dependence²³, have been reported in the course of GHB treatment. Even though this phenomenon is modest¹⁷, these observations suggest that GHB use should be carried out under close medical surveillance within a multidisciplinary treatment, including psychological support and cooperation of relatives in order to avoid any possible drug abuse²³. It should be emphasized that, in the case of GHB abuse, prompt drug discontinuation does not cause appearance of severe symptoms. Moreover, in case of GHB dependence, the administration of low-moderate doses of benzodiazepine seems to be effective for the regression of GHB withdrawal syndrome²³.

Up to 30-40% of alcohol-dependent patients do not respond to GHB treatment, the short half-life of the drug (about 2 hours) be-

ing considered a possible cause²⁴. Recent studies have shown that non-responders to the conventional fractioning in 3 daily doses of GHB seem to benefit from subdivision in 6 daily doses at the same total amount (50 mg/kg body weight/day)^{25,26}. In these patients the increase of the fractioning of the dose seems to be able to cause a significant reduction in craving, increasing the therapeutic efficacy and decreasing the risk of abuse^{25,26}.

Baclofen: GABAB receptor agonist. This is currently used as a relaxant. Recent studies have shown its efficacy in decreasing alcohol intake²⁷, in preventing the acquisition of alcohol drinking behaviour²⁸ and in suppressing the extra-amount of alcohol consumed some days of alcohol deprivation²⁹ in alcohol-preferring rats. In alcohol-dependent patients, baclofen has been shown to be effective in inducing and maintaining alcohol-abstinence at the dose of 15 mg/day for the first three days and 30 mg/day for the subsequent four weeks^{30,31}. This substance has proved to be effective in reducing alcohol craving in both obsessive and compulsive components^{30,31}. Finally, baclofen proved to be easily manageable and without any risk of abuse and important side effects. This data, however, are preliminary and further studies are needed to confirm the efficacy of baclofen in the treatment of alcohol-dependent patients.

Naltrexone: opioid-receptor antagonist. At a dose of 50 mg/day, it has shown its efficacy in decreasing the compulsive component of alcohol craving and in increasing the compliance of alcohol-detoxification programs³². Naltrexone has been used for a long time in the treatment of heroin dependence; the rational use for alcohol-dependent patients is the involvement of the opioid system in the compulsive desire for alcohol. A double-blind placebo-controlled study³³ has shown that the administration of naltrexone to alcoholic patients decreases relapses by means of the reduction in the number of "heavy alcohol days". Most of the studies found no significant difference between patients treated with naltrexone and with the placebo in the occasional intake of alcohol ("slips"); however patients treated with naltrexone showed a significantly lower percentage of full relapse with respect to patients treated with placebo^{33,34}. Obviously the efficacy of the drug is increased by the association of specific psychological support (in particular counselling and coping skills therapy)³⁵. A recent comparative study between GHB and Naltrexone showed that GHB is more effective that naltrexone in treating alcohol addiction once remission of the withdrawal syndrome has been achieved if the main outcome is to mantain abstinence; on the other hand the study confirmed that naltrexone is useful in preventing alcohol relapse in heavyy drinking³⁶.

Naltrexone is also effective in decreasing alcohol desire caused by images of alcoholic beverages³⁷. Moreover it decreases alcohol intake in social drinkers³⁸, in hazardous drinkers³⁹ and in "problem" drinkers subjected to risk situations⁴⁰.

However, two recent well-performed studies have shown low efficacy⁴¹ or no efficacy of naltrexone with respect to placebo⁴² in treating patients with alcohol problems. Further research is needed to clarify the role of naltrexone in the treatment of alcohol-dependence.

Side effects include nausea (10% and self-limiting), and, less frequently, headache, dizziness, insomnia, vomiting, anxiety and sleepiness⁴³. The incidence of side effects increases if the patient is not abstinent from alcohol. Naltrexone is contraindicated in patients with acute hepatitis or hepatic insufficiency.

Acamprosate: the mechanism of action is not completely known, but it seems that acamprosate affects calcium channels with a subsequent decrease in activity of the excitatory system in the central nervous system. Acamprosate administration in alcohol-preferring rats causes a significant increase of glutamate, taurin and GABA basal concentrations in the hypothalamus and nucleus accumbens. Double-blind clinical trials in alcoholic patients (1.3-3 gm/day) have shown the efficacy of acamprosate in decreasing alcohol craving and in maintaining abstinence^{44,45}. The route of administration is oral at a dose of 1.3-2 gm tid. However also in this case a recent study showed a low efficacy of the drug in treating alcoholic patients⁴¹. Future studies are necessary to verify the efficacy of this drug.

Tiapride: this drug, at a dose of 300 mg/day divided into three daily doses, has been shown to promote abstinence, to increase patient functional capability and self-esteem, to

decrease psychological stress and alcohol-dependence complications⁴⁶. Tiapride seems to be well tolerated, although four cases of tar-dive dyskinesia have been reported⁴⁷.

Fluoxetine: this is a serotonin reuptake inhibitor (SSRI) and seems to act also through GABAergic action other than with serotoninergic mechanisms; it is administered at a dose of 20 mg/day for the first two days with a subsequent dose of 60 mg/day, taking care to note the possible occurrence of manic reactions⁴⁸. Recent studies have shown the efficacy in alcoholic patients affected by major depression; Fluoxetine, at a dose of 20 mg/day for the first two weeks then 40 mg/day if necessary, has proved effective in decreasing depressive symptoms and alcohol consumption in these patients⁴⁹. Its efficacy, however, seems to decrease in alcoholic patients without important mood disturbances⁵⁰.

Other serotonin reuptake inhibitors and Ondansetron: there are some contrasting data on the efficacy of Sertraline, Citalopram (SSRI agents) and Ondansetron (5HT3 receptor antagonist); in particular it seems that SSRI might be useful in those patients with a late-onset of alcohol dependence, while the other serotonergic agent Ondansetron at a dose of 0.5 mg/day⁵¹, could be effective in patients with an early-onset of alcohol dependence (for review see reference⁵²).

Finally, Buspirone (a serotonin agonist, selective for 5-HT 1A receptor) at a dose of 10-20 mg divided into two/three daily doses, was shown to be useful in alcohol-detoxification of anxious subjects⁵³. A recent study, however, has not confirmed the efficacy of buspirone vs placebo in decreasing alcohol consumption in alcohol-dependent patients⁵⁴.

Further studies are needed to assess the importance of these medications in the integrated treatment of alcoholism.

Methadone: it is a potent syntetic opioid agonist commonly used in the treatment of heroin addiction. Rates of alcoholism vary from 5% to 49% in methadone maninenance treatment (MMT). Data on alcohol consumption during MMT have been controversial⁵⁵; however a recent study suggest a possible effect of short-term methadone administration in reducing alcohol consumption in a population of heroin-addicted patients⁵⁶. It is well documented that when patients stop heroin

use, their alcohol intake increases, probably due to the use of alcohol as a substitute substance; the findings by Caputo et al⁵⁶ indicate that physicians and practitioners could be more inclined towards the use of methadone, particularly in heroin addicts with a concurrent alcohol abuse.

Other pharmacological substances that have proved useful in the treatment of alcohol dependence can be associated with the above mentioned anticraving drugs.

Metadoxine: (Pirrolidin-carboxyilate): Besides of its effect on hepatic enzyme systems with subsequent acceleration of ethanol metabolism⁵⁷, metadoxine increases the cerebral release of GABA and acetylcholine and the cerebral levels of ATP. Metadoxine is therefore an antagonist of alcohol-metabolic effects and helps to restore normal neuropsychological behaviour. Experimental studies on alcohol-dependent patients have shown that metadoxine (at a dose of 1 gm/day divided into two daily doses) helps to decrease compulsive desire, aggressiveness, psychomotor agitation and to improve relationships, emotions and work efficiency^{58,59}.

S-adenosyl-l-methionine (SAMe): a ubiquitous molecule and extremely important for transmethylation reactions. SAMe participates in the synthesis, activation and metabolism of hormones, neurotransmitters, nucleic acids, phospholipids and some drugs. It is a well tolerated molecule and prevents drug and chemical related hepatotoxicity. In alcohol-dependent patients, SAMe (at a dose of 200 mg/day for three weeks) decrease alcohol intake. This effect seems to be related to a decrease in both craving and depression⁶⁰. The exact mechanism, however, is unknown.

Benzodiazepines: few and conflicting data are available about their use for long-term treatment of alcoholic patients. This controversy probably depends on the facilities for the treatment of alcohol-dependence in different countries or different areas in the same country and on different typologies of alcohol-dependent subjects. Some authors think that if total alcohol-abstinence is considered as the only outcome then parameter results are not encouraging. In that case, only 12.5% of patients maintain six-months abstinence. On the other hand, if evaluation criteria of treatment efficacy also include the decrease of alcohol intake, the rate of positive re-

sponse rises to 45% in the first six months of treatment and to 70% in the second six months⁶¹.

Benzodiazepine inefficacy in maintaining medium-long term alcohol abstinence has also been reported by a six-month follow up study on the comparison between chlor-diazepoxyde and metronidazole (an antimicotic drug with disulfiram-like action). Both the drugs were ineffective in maintaining total alcohol-abstinence, with 80% relapse at six months⁶².

A new approach to alcoholism treatment by means of benzodiazepine use could be founded on the hypothesis that anxiety disorders, contributing to the risk of developing alcohol-dependence, are present in a subgroup of alcoholic patients⁶³. Although the hypothesis has not yet been confirmed, this possibility should be ascertained in each alcohol-dependent patient. The anxiety disorder may represent a risk factor for alcoholism: alcohol abuse, in such cases, is considered as a selfmedication because of its pronounced anxiolytic effect. Alcoholism and anxiety may reflect a common genetic predisposition, as shown in animal models⁶⁴. In other cases anxiety and alcoholism may not be correlated, but concomitant: in that case, the anxiety disorder is induced by the alcohol-dependence⁶⁵. Anxiety can increase alcohol-dependence severity or become a sign of craving. These considerations would suggest that a well selected group of alcohol-dependent patients may benefit by a medium-long term treatment with benzodiazepines for relapse prevention. It should be kept in mind, however, that benzodiazepine use must be limited because of the risk of drug abuse and dependence.

In conclusion, pharmacotherapy of alcohol dependence seems effective in both alcohol-related emergencies and compliance to therapeutic programs. However, pharmacotherapy should not be considered as the only form of treatment but as an integrated part of a multimodal approach including psychological and social support.

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