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New and Old Drugs to Treat Alcohol Use Disorders

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Around 2 billion people consume alcoholic beverages worldwide, and almost 10% of the world's population is affected by Alcohol-Use Disorders (AUDs) [1]. Alcohol consumption is responsible for approximately 3.8% of all deaths [2] and accounts for 5.5% of the global burden of disease [3]. So far, only three drugs [Naltrexone (NTX), Acamprosate (ACM), and Disulfiram (DF)] have been approved by the Food and Drug Administration for the treatment of alcohol dependence [4]; however, emerging data from clinical trials suggest that these medications are relatively ineffective in maintaining the abstinence from alcohol.

The predict study conducted in Germany by Mann et al. [5] clearly documented that neither ACM nor NTX are more efficient than placebo in reducing the number of relapses throughout the complete treatment period and the subsequent 18 months of follow-up. The results of the predict study have been compared with those of the COMBINE trial performed in the United States (US) [6]. The main outcome of the predict study was the time elapsed before the first episode of heavy drinking, and, contrary to the positive NTX effect reported by the combine study, neither ACM nor NTX provided an additional benefit compared with placebo. It is worth noting that patients drank a significantly greater amount of alcohol before enrolment and more often fulfilled DSM-IV criteria for alcohol dependence in the predict than in the combine study, suggesting that the patient populations included in these trials were substantially different. A similar lack of efficacy also emerged from a previous European trial where NTX plus ACM were more effective than placebo and ACM alone in reducing episodes of heavy drinking, but not NTX alone [7]. A meta-analysis published a few years ago [8] stated that neither NTX nor ACM were able to maintain complete abstinence from alcohol; rather, these agents are effective in reducing relapses and the number of drinks per drinking days, and, consequently, the organ damage caused by alcohol consumption.

The main aim in treating alcohol dependence is complete abstinence. In the light of the results of the studies reported above, ACM and NTX should be rationally indicated only when this purpose cannot be achieved, with the aim of reducing alcohol intake and, therefore, achieve a "harm reduction". Indeed, total abstinence was obtained in an equivalent proportion of patients both in predict and combine studies, i.e. 39.3% and 38.9% respectively. Nevertheless, NTX and ACM remain the first line of pharmacological treatment for alcohol dependence. Are there any other pharmacological possibilities? An interesting position was expressed by Jonathan Chick and David Nutt in their "perspective" paper which appeared in 2011: "For a condition where existing therapies are only effective in a proportion of patients, and which has high morbidity and mortality, the time now seems right for reappraising the use of substitute prescribing for alcohol dependence" [9].

In Italy and Austria, a "substitute" medication with alcohol-mimicking properties has been used since 1992. The drug is the Sodium Oxybate (SMO) [10-13], a physiological neurotransmitter derived from Gamma-Amino Butyric Acid (GABA) that was approved for the treatment of Alcohol Withdrawal Syndrome (AWS) and relapse prevention in Italy and Austria several years ago [13]. Only 6 controlled clinical trials on SMO have been performed so far and the number of patients recruited (about 300) is limited [13]. However, a substantial proportion of patients, ranging from 50% to 60% of cases, maintained a continuous short (3 months) or medium-term (6 months) abstinence from alcohol in all these studies [13]. These results are better than those obtained with NTX and ACM, where the continuous abstinence rate approximates 30-40%. In addition, if motivation to abstain from drinking is enhanced by a more helpful pharmacological approach, the rehabilitation program should likely be more straight-forward both for patients and clinicians [14]. Last but not least, the advantage of using the same pharmacological approach for both the treatment of AWS and the maintenance of abstinence, only assured by SMO, should not be disregarded. Indeed, changing form one drug to another in alcohol dependent patients often creates discomfort, while continuing with the same medication would help in establishing a "therapeutic alliance" between patients and operators, which remains a cornerstone to achieve a favourable outcome.

Taking into account the treatment of Alcohol Withdrawal Syndrome (AWS), Benzodiazepines (BDZs) remain the first-choice for its treatment [15]. Nevertheless, they present a huge abuse potential [16], and we all know that the discontinuation of BDZs in a patient who has become addicted to these drugs is very difficult to achieve. Once AWS has been resolved using BDZs, almost 1/3 of patients who chronically continue their use develop a condition of dependence [17] which often requires hospitalization to discontinue these drugs [18]. It has been demonstrated that SMO presents an efficacy similar not only to diazepam [19,20] but also to clomethiazole [11] in suppressing AWS; in particular, SMO is superior to diazepam in reducing the anxiety and depression associated with AWS [19]. Therefore, due to its excellent tolerability, easy-handling, short half-life (about 30-60 minutes), and oral formulation, SMO has become extensively used by Italian physicians involved in the treatment of alcohol addiction in both in- and out-patients [12]. Unlike BDZs, treatment of AWS with SMO, used at therapeutic doses of 50-100 mg/kg/day from 3 to 7 days, does not induce dependence, does not -contrarily to methadone- need a tapering procedure before discontinuation, and its discontinuation does not induce withdrawal symptoms [12,21]. These pharmaco-dynamic and pharmacokinetic properties of SMO have made it possible to treat AWS in in-patients without prolonging their hospitalization once the syndrome is over, without the need to refer patients to Addiction Centres or to general practitioners to supervise a tapering program of

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reasonable duration to prevent chronic abuse. Moreover, a crucial issue during the treatment with SMO is the development of craving for or abuse of the drug. However, this event is almost negligible in Italy and Austria. Approximately 10% of patients treated with SMO develop a craving for the drug with very limited episodes of abuse [13]. If this occurs, it can be simply resolved by discontinuing the medication, as drug withdrawal leads to moderate side effects (i.e. anxiety, restlessness) that regress without sequelae a few hours later and without the need for additional medications (i.e. BDZs). As highlighted in a Cochrane review [13], only alcoholic patients with poly-drug addiction or psychiatric co-morbidities (such as Axis II borderline personality disorder) present a significantly higher risk of developing an addiction to or abuse of SMO [22,23]. Some advice on the "clinical" use of SMO, in the light of literature data and practical experience, is likely useful: a) SMO should be prescribed by clinicians working in Addiction Centres to patients regularly attending check-up visits; b) SMO should usually be prescribed at a dose ranging from 50-75 mg/kg/day which does not induce sedative effects; c) SMO should be entrusted to a family member who can supervise its administration. These modalities are very different from the "non-clinical" use, when the product is purchased through the "Internet" or from a pusher as a "street drug", without exactly knowing the quantities supplied. Even in these cases, however, it should be pointed out that two publications [24,25] have reported that, although the toxic effects of SMO led to hospitalization in intensive care units, most cases of intoxication/overdose appeared to be precipitated by the use of other illicit substances in combination with SMO rather than SMO alone. It is obvious that a substantial difference exists between "clinical" and "non-clinical" use, the latter being characterized by easy accessibility, lack of purity, uncontrolled dosage and high risk of abuse episodes [25]. In the United States, the prevalence of illegal use, abuse, intoxication and overdose with SMO has undergone a drastic reduction since the year 2000, and is now much lower than with other legal and illegal drugs [25]. Therefore, to avoid even the low risk of developing a craving for and consequent abuse of SMO, a preliminary identification of potential abusers of SMO is important, in order to offer them alternative pharmacological treatments. Thus, even though further data from controlled clinical trials would be welcomed, it can be stated that SMO is not only efficient, but also tolerable, with rare side effects (<10%) that do not require discontinuation.

Furthermore a new approach for the treatment of alcohol dependence is emerging: the reduction of alcohol intake. At this regard, nalmefene is a µ and δ-opiod antagonist and κ-opioid partial-agonist, which has been associated with a reduction of heavy drinking in several studies in patients with AD, could be proposed and it has been recently introduced in the Italian market. The first reported effects of nalmefene on alcohol consumption were conflicting: while one study failed to achieve a significant result [26], others reported a reduction in heavy drinking [27-29]. This has been recently confirmed by two randomized, double-blind, placebo-controlled trials (ESENSE 1 and ESENSE 2) where patients with AD received "as-needed" (defined as self-identified high risk situations, using nalmefene when drinking is imminent or no more than 1 or 2 hours later after drinking) nalmefene (18 mg) for 6-months [30,31]. In addition, a post-hoc analysis of these two studies, only including patients with at least a high drinking risk level (defined as ≥ 60 g/day for men and ≥ 40 g/day for women of alcohol intake) [32] both at screening and randomization ("target population"), showed that nalmefene reduced the number of heavy drinking days (treatment difference: -3.2 days; p<0.0001) and the total alcohol consumption (treatment difference: -14.3 g/day; p<0.0001) at month 6 more significantly than placebo [33].

Thus, the treatment of alcohol dependence, which requires a deeply integrated multi-disciplinary approach, should be provided by specialized Centres. As far as the pharmacological treatment is concerned, the most appropriate therapy should result from tailoring therapy on every individual patient, in order to offer him/her the best chances of achieving and maintaining alcohol abstinence, which remains the primary aim of the treatment of alcohol addiction. This challenge is becoming more and more important, as alcohol use has reached the third position among the risk factors for all diseases after arterial hypertension and cigarette smoking [3].

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