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ALCOHOL ADDICTION: Toward a patient-oriented pharmacological treatment

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Abstract

A very few medications (i.e. disulfiram, naltrexone and acamprosate) are approved for the treatment of alcoholism and their effects are sub-optimal. The development of new effective and safe pharmacological agents to treat alcoholic patients is crucial, together with the need of identifying predictors of outcomes in different subsets of patients.

Keywords

Alcohol Use Disorder; Drug treatment

The understanding of the neurobiology of the alcohol use disorder (AUD) has significantly advanced in the last decades. In particular, the growing knowledge about molecular, biological and behavioral aspects of AUD has led to a substantial improvement in the management of alcoholic patients, including the possibility of identifying new pharmacological treatments.

Realizing that alcoholism is a medical disease has clearly changed how health care providers approach alcoholic patients, including the understanding of the importance to help them to reduce alcohol consumption or achieve alcohol abstinence, and prevent relapse. As such, several medications have been tested for the treatment of AUD, combined to psychosocial interventions, and a few drugs have been approved, such as disulfiram, naltrexone and acamprosate (although the exact panel of approved drugs may vary across countries).

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However, the efficacy of these medications is still sub-optimal [1]. Other drugs, such as topiramate, baclofen, ondansetron, sodium oxybate, varenicline and nalmefene have been tested in alcoholic patients with promising results; some of them are sometimes used off label, and indeed nalmefene has recently received approval in Europe.

Data on the efficacy of some of these medications are sometimes conflicting or suggest that the medication only works for a specific subgroup of patients. This is not surprising, however, if we keep in mind that alcoholism is in fact a heterogeneous, complex disorder made up of biopsychological subtypes. The heterogeneity of AUD patients may represent one of the main reasons why some medications may help some patients but not others.

Research aimed to identify and develop a patient-oriented pharmacotherapy approach could represent the start of a personalized treatment approach for alcoholic patients, and indeed some clinical evidence has already been generated. For example, naltrexone and acamprosate have been shown to be effective pharmacological treatments for alcohol dependence. Since individuals with a family history of alcohol dependence showed greater naltrexone-induced attenuation of the stimulatory effects of alcohol, the gene coding for μ-opioid receptors, the primary target of naltrexone (i.e., the OPRM1 gene) was investigated. Consistent with preclinical studies, an association between the A118G SNP of the OPRM1 gene (G allele) and sensitivity to the effects of alcohol in alcoholic patients was reported. In particular, Oslin and coworkers [2] conducted a double-blind clinical trial on AD patients treated with naltrexone showing that patients with one or two copies of the opioid receptor μ 1 (OPRM1) Asp40 allele were less likely to return to heavy drinking and had a longer time to return to heavy drinking compared with their homozygous counterparts. Similar results were evidenced, even if with a small effect size, in the COMBINE study [3]. Although the exact role of the OPRM1 Asp40 allele has still to be exactly defined, the genetic characteristics of patients seems to be important in predicting response to naltrexone. Applying Lesch's typological differentiation, Kiefer and collegues [4] showed that naltrexone revealed best treatment effects in type III and IV, whereas acamprosate was shown to be mainly effective in type I; naltrexone was effective especially in patients with high baseline depression, whereas acamprosate was mainly efficacious in patients with low baseline somatic distress. Moreover the same group recently showed that the single nucleotide polymorphism, rs13273672, an intronic SNP in the gene for GATA-binding protein 4 (GATA4), was associated with relapse. Pharmacogenetic analyses showed that this association was mainly based on patients treated with acamprosate. Moreover the study showed that genetic variations in GATA4 might influence relapse and treatment response to acamprosate via modulation of atrial natriuretic peptide plasma levels. These results could help to identify those alcohol-dependent patients who may not respond to treatment with acamprosate [5].

Serotonine (5-HT) has a pivotal role in the regulation of mood, impulsivity, and appetitive behaviors, including alcohol consumption. Ondansetron, a 5-HT3 receptor antagonist, is thought to work by affecting the function of the 5-HT transporter (5-HTT) resulting in down-regulation of the dopaminergic neurons decreasing the reward from alcohol. Clinical studies provided evidence on the role of ondansetron in reducing alcohol drinking [6]; furthermore, when compared with placebo, ondansetron (4 mcg/kg bid) resulted in a

significant reduction in alcohol craving, in early onset alcoholism (EOA) but not in late-onset alcoholism (LOA) [6]. More recently, in a large study, alcohol-dependent patients were randomized to receive ondansetron (4 mcg/kg bid) or placebo after being divided them by genotype in the 5′ regulatory region of the 5-HTT gene: LL, LS, or SS. Individuals with the LL genotype who were receiving ondansetron significantly improved drinking outcomes compared with LL individuals on placebo, and compared with the LS and SS individuals receiving ondansetron [7]. In a pilot human laboratory study, Kenna and colleagues [8] reported that AD individuals taking ondansetron 0.25 mg b.i.d. with the LL genotype showed a significant reduction in drinking, while no reduction was found in LS or SS genotype patients. In summary, ondansetron seems to be effective only in specific subtypes of patients (EOA, LL genotype), representing an interesting approach for the personalized treatment of AD.

Consistent with several preclinical studies, clinical studies showed that the GABAB receptor agonist baclofen is effective in reducing alcohol intake, promoting alcohol abstinence and preventing relapse in alcohol-dependent patients, [for review see 9]. The drug was effective and well tolerated also in alcohol dependent patients affected by liver cirrhosis [10], where the medication showed a robust effect. On the contrary, a recent US trial failed to demonstrate an effect of baclofen compared to placebo in alcohol-dependent patients [11]; unlike the previous study [10], in this study the placebo response was high and there was a robust overall treatment effect without a significant effect of baclofen compared to placebo. These findings lead to the hypothesis that baclofen is more beneficial for more severe dependent alcoholics (i.e. alcoholic patients with severe alcohol related damage). Genetic characteristic of patients could also play a role in the baclofen response of patients. In a recent double-blind randomized controlled human laboratory pilot study, non-treatment seeking alcohol-dependent heavy drinking subjects received either baclofen 10 mg t.i.d. or an active placebo for a 7-day period and then an experiment consisting of both alcohol cue-reactivity (CR) and alcohol self-administration (ASA) took place. Baclofen increased sedation and stimulation after the alcohol priming, and then reduced self-administration during the ASA. Furthermore, the potential role of D4 dopamine receptor (DRD4) and 5-HTTLPR polymorphisms was studied in these subjects, although the pilot nature of the study prevents from any conclusion. Baclofen increased alcohol sedation and reduced alcohol administration in those individuals with DRD4 ≥7 repeats (DRD4L) and baclofen effects were moderated by 5-HTTLPR LL genotype [12]. However, larger studies are needed to confirm these preliminary and exploratory findings.

Expert Opinion

AUD is a complex disease with multifactorial etiology that includes different genetic, neurobiological, psychological, and environmental components. Despite the progress in understanding the biological mechanisms of AUD and the identification of effective medications, a few drugs are at present available and/or approved for alcoholic patients. Moreover pharmacotherapy is still underutilized in clinical practice. The presence of side effects could play a role in reducing physician willingness to prescribe and patient willingness to take the available medications. Moreover there are few medical schools worldwide with courses on alcohol dependence, so few physicians in practice have been

trained to diagnose or manage alcohol dependent patients. As such, on one hand it could be very useful to train physician to use the available medications; on the other hand there is a strong need to develop new effective and safe pharmacological agents and to identify the clinical predictors of outcomes in subset of AUD patients, in order to personalize the treatment. Moreover, alcohol-related medical consequences virtually involve any organs and system (e.g. cardiovascular, immune, metabolic, nutritional, liver, gastrointestinal etc.). Trials testing medications for AUD usually exclude severely ill patients. Exclusion criteria improve the homogeneity of the sample population but they reduce the external validity of trials because in clinical practice it is more frequent to manage AUD patients with medical comorbidities, rather than “healthy” alcoholic patients. As such, there is a need for identifying safe drugs that can be used in a wide population of patients with AUD, including those with severe medical comorbidities. A specific subgroup is represented by patients with alcoholic liver disease (ALD), commonly present in AUD patients. Patients affected by early-stage ALD (hepatic steatosis, mild alcoholic hepatitis and fibrosis) can be treated with anticraving medications, although caution is recommended, in particular by monitoring liver function tests. On the contrary, pharmacological options are limited in patients affected by advanced ALD with severe impairment of liver function [13]. The most effective clinical goal for alcoholic patients with advanced ALD is to achieve and maintain total alcohol abstinence, as medical and surgical interventions have limited success in these patients if drinking continues. In this regard, baclofen represents at the moment the only medication that has shown safety and efficacy in alcoholic patients affected by advanced liver disease [13], even in those alcoholic cirrhotic patients with HCV coinfection [14].

It is very encouraging that several new medications are at present under investigation and it is possible that new drugs will be available in the next future to treat alcoholic patients. It is an exciting period of the research on alcoholism pharmacotherapy and is consistent with the need for more effective treatments – we need more arrows in our quiver to give more chance to our patients.

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