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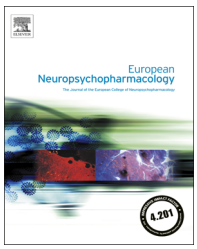

REVIEW

Pharmacological management of alcohol dependence: From mono-therapy to pharmacogenetics and beyond

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Abstract
Almost 10% of the world's population is affected by alcohol use disorders, and the treatment of alcohol dependence (AD) still remains a challenge. Patients with AD can differ in many traits. Three drugs (disulfiram, naltrexone, and acamprosate) have been approved by the FDA for the treatment of AD, and in some European countries sodium oxybate is also approved for this purpose. Combined pharmacological therapy has not provided such convincing results. Considering the fact that the "ideal" and effective drug for all types of alcoholic patients does not exists, the future challenge will be to identify a personalized approach. Recent data has shown that this objective can be achieved by investigating the genetic variability of the patient. Moreover, the use of replacement molecules can probably be considered an advantageous therapeutic opportunity (i.e. sodium oxybate). In addition, reduction of alcohol consumption is increasingly accepted as a viable treatment goal, and the use of nalmefene "as-needed" (a pharmacological approach similar to naltrexone, but, possibly, with lower hepatotoxicity) may help in the treatment of AD. Thus, it is important to stress that a pharmacological approach to treat AD should be preceded by the definition of patient characteristics; this may help in the choice of the most appropriate drug and it can be done more easily when more pharmacological options approved for the treatment of AD are also available.

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Contents

1. Introduction

Around 2 billion people consume alcoholic beverages worldwide (Schuckit, 2009). Alcohol consumption is responsible for approximately 3.8% of all deaths (Rehm et al., 2009) and accounts for 5.5% of the global burden of disease (Lim et al., 2012). Almost 10% of the world's population is affected by alcohol use disorders (Schuckit, 2009; Friedmann, 2013), and the treatment of alcohol dependence (AD) still remains a challenge.

After suppression of the alcohol withdrawal syndrome, the primary goal in the treatment of AD remains complete abstinence from alcohol, even though alcohol intake reduction may also be seen as a positive result (Aubin and Daeppen, 2013). In any case, a multi-professional intervention is needed to achieve these targets (Schuckit, 2009; Friedmann, 2013). The most common treatments for promoting abstinence, reducing alcohol intake, and preventing relapse are psychosocial interventions (i.e. cognitive behavioral therapy, motivational enhancement therapy), self-help groups (i.e. Alcoholics Anonymous), and the use of medications (Schuckit, 2009; Friedmann, 2013), mainly represented by anti-craving drugs.

The aim of this review is to illustrate the typologies of alcoholism and cravings, and describe the efficacy of the currently approved and off-label drugs.

2. Typologies of alcoholism and craving

Patients with AD can differ in many traits, such as age of onset of heavy drinking (early or late), patterns of drinking (e.g. continuous or binge), rate of alcohol metabolism, sensitivity to intoxication, rapidity of progression to medical problems, and presence or absence of co-occurring psychiatric illness (Leggio et al., 2009). Because of the heterogeneity that occurs among AD individuals, there has been an effort to divide them into distinct groups or subtypes that can guide diagnosis, predict prognosis and provide targeted treatments (Leggio et al., 2009; Johnson, 2010). Subtypes are the expression of a patient's gene polymorphism and the phenotypes or endo-phenotypes in different environmental backgrounds; the understanding of this results in a clear identification of different typologies of alcoholism (Gottesman and Gould, 2003; Enoch, 2003). Most importantly, it has been suggested that different subtypes of AD patients could optimally benefit from targeted therapies (Leggio et al., 2009; Johnson, 2010). Therefore, alcoholic patients can be classified into different groups according to their phenotype. Namely, the concept underlying the identifications of AD typologies has evolved from conceiving AD as a disease state (Jellinek gamma and delta) (Jellinek, 1960) to a personality model supported by genetic epidemiological data (Cloninger type I and type II) (Cloninger et al., 1981), and extended into a measure of disease severity determined through cluster analysis, using detailed empirical data derived from in-patient AD patients (Babor type A and type B) (Babor et al., 1992). In addition, consistently with the complex nature of AD, it has been suggested that the "binary" model of AD typologies was not sufficiently inclusive to classify all individuals affected by AD. Indeed, in 1988 Prof. Otto Lesch described factors predicting the development of chronic alcoholism based on the results of a long-term prospective follow-up study (18 years) (Lesch et al., 1988). The resultant identification of four subgroups of alcohol-dependent patients has been validated by biological, psychological and physiological assessment, and therapeutic studies (Pombo and Lesch, 2009). Namely, the main characteristics of Lesch's typologies are: Lesch's type I (or "model of allergy") individuals suffer from severe alcohol withdrawal syndrome, and tend to use alcohol to prevent or weaken their withdrawal symptoms; Lesch's type II subtype (or "model of anxiety or conflict") identify subjects who drink alcohol as a means of self-medication, due to its sedative and anxiolytic effect, and exhibit extensive behavioral changes under the influence of alcohol; Lesch's type III (or "model of depression") is characterized by the use of alcohol as an