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Recent advances in the treatment of alcoholism

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Abstract

Alcoholism is a major public health problem, and a devastating disorder for affected individuals, their families, and society. We have made great gains in the past 25 years in understanding and treating alcoholism. A recent and important treatment advance is the use of pharmacotherapies that improve treatment response for many patients beyond what they obtain from counseling. We have gained a better understanding of the neurobiology associated with alcoholism, pharmacological treatments can be targeted to numerous pathways affected by chronic and excessive alcohol drinking. Consequently, an increased number of investigational studies of new compounds that are meant to reduce alcohol craving and drinking have emerged in the literature. There are three medications that have been approved in the United States (US) by the Food and Drug Administration (FDA) for the treatment of alcohol dependence: disulfiram, naltrexone, and acamprosate. Many more are being used in Canada, Europe, Australia and other parts of the world for treating alcohol dependence. Studies have also examined best practices in prescribing medications. For example, it has been empirically demonstrated that patient non-adherence to treatment diminishes the treatment's value. In turn, we can improve treatment response if we proactively provide patients with strategies to help them take their medications and attend their counseling visits. Other important advances related to pharmacotherapy are that alcoholic subgroups differentially respond to specific pharmacotherapies, and combining two pharmacotherapies that address different neurobiological systems simultaneously to treat alcohol dependence may prove more beneficial than a single medication in some patient groups.

Keywords: Alcoholism; Pharmacotherapy; Treatment; Medication adherence; Naltrexone; Acamprosate

1. Introduction

Advances in understanding the nature of alcoholism over the last 25 years have stimulated innovative treatment approaches to managing this major public health problem and devastating illness. Historically, alcoholism was regarded as a 'deficiency in self-control' or the 'result of ineffective thinking' [1]. While such perspectives are not widely held today, they did generate a number of useful and important remedial interventions that focused on spirituality, motivation, and cognitive skill learning. The 12-step philosophy, typified by the well-known Alcoholics Anonymous, has long been and remains the most prevalent approach for changing alcoholic behaviors in the United States (US) [2]. Cognitive behavioral therapy (CBT) [3,4] and motivational enhancement therapy (MET) [5,6] have advanced over a number of years and current versions of these approaches are empirically proven psychosocial treatments for alcohol dependence [2–6]. Nonetheless, the successes of our psychosocial treatments and mutual support groups depend heavily on a patient's regular attendance at treatment sessions, and the patient being able to derive the psychological benefits typically associated with therapy. Relapse rates in some settings remain high and further investigation of other and multimodal treatment options is paramount.

In the past decades, the scientific community has come to better understand the neurobiological actions of alcohol in

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the brain, and the potential neurochemical disruptions associated with chronic, uncontrollable and excessive alcohol drinking. The increasing understanding of alcoholism as a biological disease has led to a conceptual mapping of alcohol-related constructs like 'craving', 'reward', and 'high' onto neurological substrates. This, in turn, has driven the investigation of the usefulness of pharmacological agents to 'reduce craving, reward', and/or the 'high', as part of the treatment of alcohol dependence [7–10].

Alcoholism also bears similarity to chronic illnesses such as Type-2 diabetes, hypertension, and asthma. Like alcoholism, the etiology and course of these diseases are influenced by genetic heritability, personal choice, and environmental factors [11]. The resemblance of alcoholism to these chronic illnesses has at least suggested that treatment models similar to those applied in treating hypertension could be employed when treating alcoholics. That is, treatments for chronic illnesses are most effective when self-motivated lifestyle changes are implemented in conjunction with long-term monitoring, educational advice, and a medication regimen [12]. There are a growing number of models for studying long-term maintenance in alcoholism [13], but these typically have not included a medication regimen. The field is still in its infancy in understanding the role of pharmacotherapy in treating alcoholism, so to include pharmacotherapy in long-term models of treating chronic diseases may be premature. However, this area of inquiry will need to keep pace with the growing level of knowledge on how to best treat chronic alcoholism.

Currently, there are three medications approved by the Food Drug Administration (FDA) for the treatment of alcoholism in the US: disulfiram, naltrexone, and acamprosate. Disulfiram and naltrexone have been readily available for treating alcoholism since 1954 and 1994, respectively, but they are not widely used in the clinic due to a number of potential reasons (discussed subsequently) [14]. In July of 2004, a decade after the FDA approval of naltrexone, acamprosate became the third medication approved in the US for the treatment of alcoholism. This recent approval, coupled with a number of ongoing investigations of other promising compounds, brings hope that soon there will be pharmacological options for treating alcohol dependence.

The literature on pharmacotherapy for alcoholism features several classes of medications that are purported to reduce alcohol craving and promote abstinence through different mechanisms of action. Some of these individual pharmacotherapies have been very promising in their own right, but for the most part, effect sizes reported in clinical trial studies have been modest, and, clearly, therapeutic response has not been observed in all patients. A meta-analysis of the literature on naltrexone and acamprosate, for example, suggested that the treatment effect sizes for both drugs compared with placebo was between 7 and 19% [15,16]. One persistent hurdle to overcome in relation to modest effect sizes is to increase medication adherence, which has been shown to improve the therapeutic effect of naltrexone and disulfiram, both of which are shown to be significantly more efficacious in patients who are adherent to treatment [17–19]. In addition, the alcoholic patient population is heterogeneous. It has now been reported in several studies that by tailoring treatments toward alcoholic subtypes, much larger responses to the medication (large effect sizes) are observed than those seen in alcoholic population as a whole. Rather than these medications having a mediocre therapeutic benefit, it is likely that certain medications have robust therapeutic effects in certain patients, and little or no effect in other patients, and hence the average effect over all patients has been moderate**.** Exciting advances in the field of genetics are particularly promising in this regard [20]. Finally, alcohol's complex actions in the brain suggest that combining pharmacotherapies may be needed to fully address the biological mechanisms underlying alcohol dependence.

This paper will bring together the fast growing literature on FDA-approved and potential pharmacotherapies for treating alcoholism. This review will summarize the information on the medications already available to the alcoholism treatment field in the US with a focus on best clinical practices, as well as extending their therapeutic effects. These medications are disulfiram, naltrexone, and acamprosate. Other agents that are not FDA-approved for treating alcoholism but are otherwise being studied for their potential to treat alcoholism will also be described, such as a number of selective serotonin reuptake inhibitors (SSRIs), ondansetron, topiramate, and baclofen. Combination pharmacotherapy and differential response to medication due to alcoholic subtype are also discussed because both of these advances in the treatment research field are likely to change the way that pharmacological treatments for alcoholism are prescribed.

2. Medications approved by the FDA for treating alcoholism

2.1. Disulfiram (Antabuse): an aversive pharmacotherapy

In 1954, the first medication, disulfiram, was approved by the FDA in the US for the treatment of alcoholism. Disulfiram inhibits acetaldehyde dehydrogenase, an enzyme needed for metabolizing alcohol. This leaves an over-accumulation of acetaldehyde, which induces an unpleasant reaction when alcohol is ingested. Typical symptoms patients experience with the disulfiram-alcohol combination include nausea, vomiting, and flushing. Although rare, more severe reactions have been reported. The rationale behind aversive therapies like disulfiram is clear: if alcohol ingestion elicits an unpleasant reaction, the patient will avoid alcohol in order to avoid the aversive experience.

Early clinical studies of disulfiram suggested it was highly efficacious in stopping alcohol drinking, and this led to its FDA approval. However, a subsequent pivotal study