Editorial

Pharmacotherapies for Alcoholism: The Old and the New

Abstract: Alcoholism and other alcohol use disorders are major public health problems, and the success rates of non-pharmacological treatment of these disorders such as psychotherapy, cognitive-behavioral therapy, group therapy, or residential treatment programs, remain only modest at best. High rates of recidivism (relapse) in alcoholics attempting to remain abstinent are prevalent worldwide. In recent years abundant evidence has accumulated demonstrating that alcoholism is a complex and multifaceted disease of the brain caused by numerous genetic, neurobiological, developmental, environmental, and socioeconomic factors that are still not yet fully understood. There is thus a great need to improve the success rates of all forms of treatment of alcoholism not only in preventing relapse, but curbing active alcohol consumption and craving. The development of improved pharmacotherapies that could be used as adjuncts to the aforementioned non-pharmacological treatment approaches is one avenue of great interest to the scientific community and the general public. Currently there are only three medications approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of alcohol abuse and alcoholism – disulfiram, naltrexone, and acamprosate. Yet medication compliance issues and the modest efficacy of these compounds leave substantial room for improvement. This special issue is devoted to reviewing the current status of these FDA-approved medications in the treatment of alcoholism. In addition, preclinical and clinical evidence suggesting that other classes of medications might also be of potential use are reviewed, including anticonvulsants, $GABA_B$ receptor agonists, cholinergic receptor partial agonists, corticotropin-releasing factor and cannabinoid CB_1 receptor antagonists, nociceptin receptor ligands, and the novel antipsychotic aripiprazole.

THE SCOPE OF THE PROBLEM OF ALCOHOLISM

Alcoholism can be briefly defined as compulsive and uncontrolled alcohol consumption despite negative consequences and failed attempts at abstinence, a loss of social, occupational, or other normal functioning, and signs of physical dependence. It is now apparent that alcoholism and other alcohol use disorders are complex disorders of the nervous system that result from a combination of genetic, neurobiological, environmental, and socioeconomic factors. In addition to causing the loss of billions of dollars from society due to treatment and health care costs, lost productivity due to impaired functioning, and destruction of family and peer relationships, alcoholism-related deaths are estimated to account for approximately 3.2% of all deaths worldwide [1]. In addition, abuse of or addiction to alcohol by pregnant women results in one of the most common forms of mental disability – Fetal Alcohol Syndrome – which has an incidence of approximately 0.7% [2].

To date, most non-pharmacological approaches to the treatment of alcoholism, such as individual psychotherapy and cognitive-behavioral therapy, group therapy including 12-step programs, and inpatient residential treatment programs have demonstrated only moderate success rates. In addition, the three medications that are currently approved by the FDA – disulfiram, naltrexone, and acamprosate - which are often used as adjuncts to the aforementioned non-pharmacological treatment approach, have also demonstrated only moderate efficacy in curbing alcohol drinking, craving, and reducing the incidence of relapse. The use of these medications is further hindered by poor medication compliance, adverse side effects in some individuals, and a lack of affordability due to health care insurance restrictions. The development of anti-alcoholism medications is further complicated by the unclear molecular targets of alcohol itself, and the high degree of polysubstance abuse and co-morbidity of alcohol dependence with other psychiatric conditions such as depression and anxiety-related disorders. To add insult to injury, it is clear that chronic heavy alcohol use causes significant impairments in brain function and lasting neuroadaptions and neurodegeneration that tilt the motivational scale of the afflicted individual towards a lack of proper impulse control and decision-making, hypersalience of alcohol-related environmental stimuli, maladaptive psychological and behavioral response to stress, and a high propensity to relapse [3]. Together, these phenomena set the stage for an uphill battle against developing safe and newer effective medications to treatment alcoholism and related alcohol use disorders.

As of early January of 2010, the National Library of Medicine's Pubmed search engine yielded more than 66,000 citations spanning a time period of over a century when the sole search keyword "alcoholism" was used, and almost 7,000 of these citations were review articles. These numbers underscore the significant amount of scientific effort that has been, and continues to be, devoted to the study of alcoholism and other alcohol use disorders. In this special issue of *CNS & Neurological Diseases – Drug Targets*, 10 reviews written by noted experts in the alcohol field have been compiled to recapitulate the current status of the three FDA-approved medications for the treatment of alcoholism (the "old" – disulifram, naltrexone, and acamprosate), as well as review preclinical and clinical evidence supporting a potential role for "new" medications that may be of use in the treatment of alcoholism, including anticonvulsants, the $GABA_B$ receptor agonist baclofen, nicotinic acetylcholine receptor partial agonists, corticotropin-releasing factor and cannabinoid CB_1 receptor antagonists, nociceptin receptor ligands, and the novel antipsychotic aripiprazole.

OVERVIEW OF REVIEWS IN THIS SPECIAL ISSUE

Barth and Malcolm review the clinical history, mechanisms of action, safety, and current status of the oldest FDA-approved medication for the treatment of alcoholism – disulfiram - commonly marketed under the trade name of Antabuse™. Disulfiram, first approved by the FDA for as a deterrent to alcohol consumption almost 60 years ago, inhibits the activity of aldehyde dehydrogenase, which normally metabolizes acetaldehyde (the active metabolite of alcohol) to acetate. As a consequence of inhibition of aldehyde dehydrogenase activity by disulfiram, consumption of alcohol in the presence of this drug produces an accumulation of acetaldehyde in the periphery and central nervous system, which results in aversive reaction characterized by nausea, vomiting, severe headache, flushing, and other unpleasant autonomic and central nervous system disturbances. Thus, disulfiram is primarily used as a psychological deterrent to the consumption of alcohol. As discussed by the authors, however, disulfiram also inhibits the conversion of dopamine to norepinephrine *via* inhibiton of the activity of dopamine-beta-hydroxylase. This latter mechanism of action suggests that disulfiram may also be of benefit in the treatment of addiction to other drugs of abuse which act directly on monoaminergic transmission, such as cocaine.

Ray, Chin, and Miotto provide a review of the clinical efficacy, safety, pharmacokinetics, related compliance issues, and the neurobiological mechanisms of action of naltrexone, a mixed opioid receptor antagonist with high affinity for mu opioid receptors. The numerous positive findings on the ability of naltrexone to suppress alcohol consumption, craving, and rates of relapse have implicated an important role for endogenous opioid peptides with affinity for the mu opioid receptor (i.e., endorphins and enkephalins) in mediating various alcohol-related effects and behaviors. The authors also review the importance of pharmacogenomic analysis of the efficacy of naltrexone, as recent identification of a functional polymorphism in the mu opioid receptor that alters the function of this receptor suggests that this polymorphism may eventually serve as predictive biomarker for a subset of alcoholics that may show a more favorable response to naltrexone than those lacking this polymorphism.

Mason and Heyser review the clinical efficacy of acamprosate, a homotaurine analogue originally identified 25 years ago as having the ability to reduce alcohol consumption in rodents and promote abstinence in human alcoholics. While the precise neurobiological mechanisms of actions of acamprosate have yet to be determined, the authors attribute the efficacy of this compound to reduce alcohol craving and relapse to its ability to act as a "neuromodulator" of the adaptations in glutamatergic transmission that result from chronic heavy alcohol use.

Leggio, Garbutt, and Addolorato summarize clinical studies showing that the $GABA_B$ receptor agonist baclofen, a nervous system depressant originally approved for use as a muscle relaxant and antispastic agent, reduces alcohol consumption as well as symptoms of the alcohol withdrawal syndrome. The authors also present a wealth of previously unpublished secondary analyses of previous clinical trials on the use of baclofen for alcohol dependence. Finally, the authors suggest a host of future directions that are in need of exploration in order to improve the efficacy of baclofen in the treatment of alcoholism, including the usage of different formulations and dosages, combining baclofen with other anti-alcoholism medications, and identification of subtypes of alcoholics that might demonstrate increased responsiveness to the drug.

De Sousa provides a review of clinical studies that have been conducted on the anticonvulsant medication topiramate for the treatment of alcoholism. Possible neural mechanisms of action of topiramate in reducing alcohol consumption and relapse are hypothesized that relate to its ability to facilitate GABAergic transmission and antagonize AMPA and kainate glutamate receptor subtypes. In addition, a brief review of the handful of studies examining the efficacy of other anticonvulsants (carbamazepine, oxcarbazepine, sodium valproate, gabapentin and levetiracetam) in the treatment of alcohol dependence is also included.

Vergne and Anton summarize recent preliminary studies showing that aripiprazole, a third generation antipsychotic, reduces alcohol consumption in both rodents and human alcoholics. Aripiprazole is a unique antipsychotic since it lacks dopamine D_2 receptor antagonist properties, and rather displays partial agonism at D_2 receptors and antagonistic action at various 5-HT receptor subtypes. Aripiprazole is often referred to as a "dopamine stabilizing" agent. The authors hypothesize that aripiprazole's ability to reduce alcohol consumption is a result of its dopaminergic and serotonergic actions in frontal-subcortical circuits that subserve alcohol reward and craving as well as impulsive behavior.

Maccioni, Colombo, and Carai review a host of preclinical studies performed in rodents showing that antagonism of cannabinoid CB_1 receptors reduces alcohol consumption and relapse-like behaviors. Similar to the implication of the endogenous opioid system in mediating alcohol consumption, craving, and relapse effects by virtue of the ability of naltrexone to suppress alcohol consumption, the studies reviewed by Maccioni and colleagues implicate endogenous ligands of the CB_1 receptor, such as anandamide and 2-arachidonoylglycerol, in mediating the rewarding and reinforcing effects of alcohol. The authors primarily focus on studies that utilized the prototypical CB_1 antagonist rimonabant (SR141716), although studies using other CB_1 antagonists are also reviewed. Unfortunately, recent large scale clinical trials on the ability of rimonabant to aid in the treatment of obesity and smoking cessation were discontinued due to adverse psychiatric effects, and thus the clinical efficacy of this CB_1 antagonist will not likely be determined in the near future. Nevertheless, the preclinical studies summarized by Maccioni and colleagues strongly suggest that other CB_1 antagonists may eventually be useful as pharmacological adjuncts in the treatment of alcoholism.

Chatterjee and Bartlett focus their review on the cholinergic system and one of its primary receptor subtypes, the nicotinic acetylcholine receptor (nAChR). nAChRs are the primary molecular target of nicotine, and there is a high rate of co-morbidity of alcoholism with cigarette smoking. Preclinical studies in rodents are reviewed, which show that partial agonists of the nAChR, particularly the recently approved smoking cessation aid varenicline acting at nAChRs containing the $\alpha_4\beta_2$ subunit configuration, may be of potential use in the treatment of alcoholism with or without co-morbid cigarette smoking. The potential underlying neurobiological basis of these findings is also reviewed.

Lowery and Thiele present a summary of preclinical studies indicating that antagonists of primary receptor for the stress-related peptide corticotropin releasing factor (CRF), known as the CRFR1 receptor, are able to reduce alcohol consumption and relapse-like behavior in rodents, particularly in those with a history of ethanol dependence induced by prolonged alcohol vapor inhalation. As CRF plays a critical role in negative hedonic and emotional states and stress-related behaviors, the studies reviewed by Lowery and Thiele underscore the importance of stress- and negative affect-associated neural circuitry, CRF, and CRF-related neuropeptides in mediating alcohol consumption and relapse.

Finally, *Murphy* reviews rodent studies that have implicated the neuropeptide nociceptin (also known as orphanin FQ) and its receptor (NOP1) in mediating behavioral effects of alcohol as well as alcohol consumption and relapse-like behaviors. Nociceptin is the endogenous ligand of the NOP1 receptor, and was discovered in the mid-1990s as a neuropeptide that bears homology to "classical" endogenous opioid peptides such as endorphins and dynorphins, and was therefore thought to be a novel member of the endogenous opioid peptide superfamily. However, in opposition to the effects of pharmacological blockade of classical opioid receptors such as the mu opioid receptor, studies reviewed by Murphy reveal that stimulation, rather than blockade, of NOP1 decreases alcohol consumption and relapse-related behaviors in various rodent models. These findings are in accord with other studies showing that nociceptin exerts behavioral and neurochemical effects that are opposite to those of classical opioid peptides. Thus, nociceptin is often referred to as an endogenous "anti-opioid" peptide. The potential therapeutic applications of nociceptin-related ligands in the treatment of alcoholism, particularly in the context of the ability such ligands to modulate anxiety-like behaviors, learning and memory, and feeding, are also reviewed.

These ten reviews provide a comprehensive coverage of the current status, potential mechanisms of action, and future directions that are in need of exploration for not only previously FDA-approved medications for the treatment of alcoholism, but also the potential for compounds approved for other medical uses such as epilepsy and muscular spasticity to be of utility in the pharmacological management of alcoholism. A subset of these reviews also provide evidence that further development of compounds targeting nAChRs, CRFR1, NOP1 and CB_1 receptors may provide novel pharmacological avenues to aid in the treatment of alcoholism and other alcohol use disorders.

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