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REVIEW

ALCOHOL DEPENDENCE – NEUROBIOLOGY AND TREATMENT

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Abstract: The consequences of alcohol dependence concern serious health care, social and economic problems. The scope of many studies is to better understand mechanisms underlying alcohol addiction in order to work out new, more effective treatment strategies. Alcohol affects many neurotransmission systems within the brain. In general, acute alcohol enhances inhibitory transmission, up-regulating the GABAergic system and impairing glutamatergic function, therefore interfering the balance between excitatory and inhibitory synaptic inputs. Chronic alcohol consumption, meanwhile, in order to restore equilibrium leads to neuroadaptive changes causing both decreased GABAergic and increased glutamatergic activity. Also function of other neurotransmitters and modulators is modified by the presence of alcohol, including glycine, adenosine, serotonin and dopamine. Moreover, a significant impact of alcohol on the endogenous opioid system, nicotinic cholinergic transmission and the endocannabinoids system has been also established. At present, only four medications are approved for the treatment of alcohol dependence in Europe, that is naltrexone, acamprosate, disulfiram and the most recent nalmefene. Among other promising strategies the following drugs are mentioned: baclofen, topiramate, ondansetron, aripiprazole, rimonabant and varenicline. Additionally, the role of appetite-regulating hormones, neuroimmune modulators or the body's stress-response system modulators in reducing alcohol consumption is currently of great interest, however, further investigations are needed.

Keywords: alcohol dependence, γ-aminobutyric acid, glutamate, naltrexone, acamprosate, novel therapeutic targets for alcoholism

According to World Health Organization (WHO) about 2.5 million people die each year from alcohol-related causes. Alcohol is one of the leading risk factor for disease burden including neuropsychiatric disorders, cardiovascular diseases, liver cirrhosis and various cancers. But the harmful impact of alcohol is much more complex, affecting not only the drinker. Alcohol abuse is a global problem concerning road traffic accidents and many social issues such as violence, child negligence, suicides, absenteeism in the workplace, breakdown of the family (1).

In 1956, the American Medical Association (AMA) defined alcoholism as an illness that comes within the scope of medical practice and encouraged hospitals to admit patients with alcoholism (2). Further, a proper definition was provided, describing alcoholism as "a primary, chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations" (3).

Because drug addiction, including alcoholism, remains a great subject of interest to scientists and society, this paper is a review of neuromolecular mechanisms underlying alcohol dependence with emphasis on current available treatments and including novel pharmacological targets.

Neurobiology and treatment of alcohol dependence

Alcohol's effects on neurotransmission

Overall, a balance between excitatory and inhibitory synaptic inputs is critical for normal brain function. Alcohol affects this balance with different response depending on the duration of intake. Short-term alcohol consumption increases inhibitory transmission, whereas after long-term exposure excitatory transmission is enhanced in order to recover equilibrium (4).

GABA

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system (CNS), acting through the GABA receptor.

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There are two types of the GABA receptors: the $GABA_A$ receptor, which is a pentametric ligand-gated ion channel, and the metabotropic $GABA_B$ receptor. Stimulation of the $GABA_A$ receptor allows the entrance of chloride ions into the neuron, which results in sedation and decreased anxiety. The G-protein coupled $GABA_B$ receptor is located presynaptically and its stimulation leads to a decrease in neurotransmitters release (5, 6).

Short-term alcohol consumption increases the $GABA_A$ receptor function, and therefore enhances inhibitory neurotransmission. Alcohol binds to the $GABA_A$ receptor in a specific binding site and induces chloride ion flux in an allosteric modulator manner (4, 7). Alcohol sensitive sites were determined. As $GABA_A$ receptors are composed of α, β, γ and δ subunits, subtypes containing δ and β3 subunits seem to be more susceptible to alcohol (8). Long-term exposure to alcohol, meanwhile, leads to a decrease in GABA neurotransmission, due to a neuroadaptation process called down-regulation. At the cellular level, a decrease in the number of $GABA_A$ receptors as well as changes in the protein composition of the receptor were observed. There are a large number of studies demonstrating above all a decrease in $GABA_A$ receptor α1 subunit in the cortex, cerebellum and ventral tegmental area (VTA). Decreased sensitivity to neurotransmission counteracts the depressant effects of alcohol and helps restore equilibrium (4-6).

Glycine

Researchers put also emphasis on the other inhibitory neurotransmitters, namely glycine and adenosine. Glycine plays a crucial role as an inhibitory neurotransmitter in the spinal cord and brain stem, but simultaneously, it may potentiate the action of glutamate (the major excitatory neurotransmitter) *via* its co-agonist site on the N-methyl-D-asparate (NMDA) receptors. Glycine acts through strychnine-sensitive glycine receptors (GlyRs), which are pentameric ion channels producing their effects through chloride current. It seems that the main mediator of glycinergic inhibition is a subtype consisting of α1 and β subunits. It has been shown that alcohol modulates GlyRs with a greater affinity for α1-GlyRs, which may explain some of alcohol-induced behavioral effects (4, 9, 10). The glycine levels in the synaptic cleft is under the control of glycine transporters (GlyTs), which belong to the Na^+- and Cl^--dependent neurotransmitter transporter family. Recently, data indicate that glycine reuptake inhibitors may reduce alcohol consumption by activating inhibitory transmission through GlyRs (8, 9).

Adenosine

Adenosine modulates neurotransmission in the CNS by suppressing the release of other neurotransmitters. There are four classes of G protein-coupled adenosine receptors (A_1, A_{2A}, A_{2B}, A_3), but the A_1 receptor, whose action is coupled with K^+ channel activation and Ca^{2+} channel inhibition, is presumably the most significantly responsible for reducing neuronal excitability. Adenosine extracellular concentration is mainly controlled by nucleoside transporters, which regulate adenosine passage through the plasma membrane, and therefore modulate adenosine signaling (11, 12). It has been established that acute ethanol administration increases adenosine signaling, and a few potential mechanisms have been suggested for explanation. First of all, adenosine uptake is claimed to be suppressed through inhibition of nucleoside transporters, which leads to an increase in extracellular adenosine. Another possible mechanism may occur *via* metabolism of ethanol to acetate. Ethanol is incorporated into acetyl coenzyme A with the concomitant formation of AMP and its subsequent conversion to adenosine (12, 13). Possibly, ethanol may also affect adenosine receptors coupling (11). Increased activation of the adenosine system, primarily through A_1 receptors, results in the ataxic and sedative effects of alcohol. In similar way to the GABAergic system, chronic alcohol exposure leads to a compensatory decrease in adenosine activity (4, 12).

Because adenosine signaling has a particularly important influence on glutamatergic neurotransmission, adenosine is considered to be strongly involved in alcohol addiction (12).

Glutamate

Glutamate is the most important excitatory neurotransmitter in the CNS, responsible for controlling signal transmission and metabolic activities in the brain. Two main groups of glutamate receptors have been distinguished: metabotropic glutamate receptors (mGluRs) and ion-channel receptors, divided into three following subtypes: NMDA receptors, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA) receptors and closely related to the previous ones kainate receptors. AMPA/kainate receptors allow mostly Na^+ and K^+ into the cell, whereas in case of NMDA receptors the entry of Ca^{2+} occurs as well. In addition, in order to open the channel except for glutamate also the presence of the co-agonist (glycine) and the removal of Mg^{2+} are required. This feature of NMDA receptors seems to be strongly contributed to neuroplasticity and synaptic changes underlying learning and

memory formation (14-16). Although alcohol appears to inhibit all three types of ion-channel glutamate receptors, the greatest impact was determined on NMDA receptors, which results in sedation and such brain dysfunctions as memory loss, cognitive impairments and withdrawal syndrome (4, 14, 17). Moreover, alcohol intake during the prenatal period, both acute and chronic, affects glutamate transmission in fetus. Reduced NMDA function was observed in animals prenatally exposed to alcohol, which presumably leads to the prevalence of fetal alcohol syndrome, characterized among other factors by impairments in memory and learning (14).

In a concentration-dependent manner acute alcohol impairs glutamatergic function, mostly by inhibiting ion flow through the NMDA receptor (8, 14, 16, 17). The NMDA receptor subunit composition is relevant to the response to alcohol. In key publications, it is indicated that critical are subunits NR1, NR2A and NR2B (8, 17). Interestingly, the potency of different alcohols to suppress ion flow is linearly related to their intoxicating potency, implying a strong connection between alcohol intoxication and alcohol-induced inhibition of NMDA receptors. Chronic alcohol intake, on the other hand, induces adaptive changes by increasing the number of the receptors as well as their excitatory activity. This enhanced excitatory neurotransmission is a result of an attempt of the brain to restore equilibrium (8, 16, 17).

Serotonin

Serotonin, (5-hydroxytryptamine, 5-HT), mediates cellular communication within the brain, playing therefore an important role in many brain functions including processes underlying alcohol abuse (18-20).

5-HT is derived from L-tryptophan (Trp), whose availability to the brain is decreased due to acute alcohol exposure. Alcohol activates liver Trp pyrrolase, an enzyme catalyzing the transformation of Trp, and therefore leads to a decrease in brain 5-HT synthesis and turnover (18, 20). On the other hand, increased levels of 5-HT metabolites in the urine and blood may suggest that acute alcohol raises serotonin release in the brain (19). Alcohol influences also serotonergic system *via* 5-HT receptors. Potentiation of the 5-HT_3 receptor function was observed after short-term alcohol consumption. Simultaneously, overexpression of this receptor results in diminished alcohol consumption. Chronic alcohol exposure, meanwhile, leads to adaptive changes in 5-HT_2 receptors, whose number increases in laboratory animals, whereas decreased 5-HT_{1A} has been demonstrate in alcoholics (8, 19, 21).

Moreover, decreased cerebral 5-HT turnover has been suspected as a one of possible mechanisms responsible for aggressive and sociopathic behaviors in drinkers. Alcohol-induced aggression may appear as a result of a lower 5-HT transporter density in the anterior cingulate cortex in alcoholics. In addition, serotonergic deficits in this area are probably also correlated with impairments in judgment, planning and decision making (18, 22).

Dopamine

Dopamine (DA) plays an important role in motivational control and reinforcement processes, modulating regions which belong to reward circuitry of the brain, such as VTA and nucleus accumbens (NAc) (23). Alcohol increases DA levels in the VTA and NAc, which triggers alcohol-seeking behavior and underlies alcohol addiction (24-26). It should be also noticed that DA neurotransmission is closely related to serotonergic system. Owing to this fact, alcohol may influence dopamine release *via* 5-HT receptors. Alcohol-induced 5-HT release through 5-HT_2 and 5-HT_3 receptors increases in the firing rate of dopaminergic neurons in the VTA and NAc, respectively, mediating indirectly alcohol's rewarding effects (19). Interestingly, there are data suggesting that alcohol-dependent subjects may express decreased DA function in the ventral stratum, which manifest as low DA levels or low dopamine D_2 receptor density. The authors indicate that these changes may be attributed to the intensified compulsive and maladaptive patterns of behavior, which can be seen in addicted individuals (26).

nAChRs

Neuronal nicotinic acetylcholine receptors (nAChRs), which are ligand-gated, cation-selective ion channels, consist of five from a variety of α (α2-α10) and β (β2-β4) subunits (15). Alcohol has been proved to affect the function of many ligand-gated ion channels within the brain, including nAChRs. Ethanol-mediated enhancement of nAChRs current has been proposed as a result of stabilization of the open-channel state, increased channel opening rate or increased agonist affinity. Subunit composition of the receptor matters in alcohol-induced response of the cholinergic system, putting emphasis on significance of $\alpha3\beta2$ and $\alpha4\beta2$ subunits. It was established that ethanol raises acetylcholine-induced ion flux through the $\alpha4\beta2$ nAChR (27-29). The $\alpha3\beta2$ nAChR, meanwhile, may be a site at which ethanol modulates dopaminergic neurons in the VTA and NAc. Alcohol stimulates cholinergic transmission in the mesocorticolimbic pathway, which has an input

to the dopaminergic system. This positive interference leads to increased DA release, mediating an alcohol-reward behavior (28, 29). Moreover, prolonged exposure to alcohol may result in a loss of cholinergic neurons and a significant reduction in choline acetyltransferase, which is a synthesizing enzyme of an endogenous agonist – acetylcholine. Considering that cholinergic deficits are strongly associated with memory impairments, these changes may explain cognitive dysfunctions after chronic alcohol intake (29, 30).

Cannabinoids

The endocannabinoids system is thought to be responsible for behaviors related to drug-seeking and drug self-administration, including alcohol seeking and drinking behaviors and modulating reinforcing and motivational effects of alcohol (31, 32). It consists of cannabinoid receptors (CB_1 and CB_2) localized on presynaptic terminals, their endogenous ligands: anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and synthesizing and degrading enzymes of AEA and 2-AG (32-34).

Acute alcohol inhibits endocannabinoid transmission, which becomes hyperactive during chronic alcohol intake as a result of neuroadaptive changes. These changes, which are supposed to have an important impact on the development of alcohol tolerance and dependence, comprise the increased synthesis of AEA and 2-AG in the brain and the widespread down-regulation of CB_1 receptors and their function (8, 31, 33, 34). Moreover, CB_1 receptors are suggested to underlie rewarding properties of alcohol *via* dopaminergic transmission. Acute alcohol was shown to increase dopamine release in the NAc. At the same time, this effect was completely suppressed in CB_1 receptor knockout mice, which confirms the importance of CB_1 receptors in dopamine-mediated alcohol-related behaviors (32, 33).

Opioids

There is a large body of evidence demonstrating that the endogenous opioid system is a key factor mediating reinforcing effects of many drugs of abuse (35-39). Three types of opioid receptors were distinguished: mu (μ), delta (δ) and kappa (κ), which are targets for the opioid peptides, namely enkephalin, β-endorphin, and dynorphin (36, 37). In general, both the μ-opioid receptor (activated mostly by β-endorphin) and the δ-opioid receptor (whose main endogenous ligand is enkephalin) are responsible for rewarding properties and their stimulation produces positive hedonic state, according to an increased DA release in the VTA and NAC. By contrast, activation of the κ-opioid receptor, to which dynorphins bind specifically, results in dysphoria and related decrease in DA levels in the mesolimbic pathway (36-39). Acute alcohol administration stimulates the release of opioid peptides, particularly β-endorphin, leading *via* μ- and δ-opioid receptors to activation of brain reward pathways and promoting further alcohol consumption (36, 37, 39). Meanwhile, prolonged alcohol administration generates a state of opioid withdrawal, which contributes with negative reinforcing effect of alcohol (36). Unlike positive reinforcement, in which a rewarding stimulus increases a potential response, in negative reinforcement alcohol administration reverses unpleasant state connected with withdrawal syndrome (40). It has been established that repeated ethanol intake causes a drop in brain levels of β-endorphin and enkephalin, and at the same time upregulates the dynorphin/κ system. It is suggested that this molecular adaptation is in fact a counteraction to dopaminergic stimulation, and promotes alcohol seeking and consumption in addicted individuals (35, 36, 39). Some authors indicate also that enhanced dynorphin/κ transmission may contribute to learning and memory deficits associated with alcoholism and mediate cognitive control dysfunctions in subjects with alcohol dependence (35).

Alcohol dependence and withdrawal syndrome

Alcohol dependence can be defined as a repeated alcohol self-administration despite adverse medical and social consequences (40). There are four significant characteristics of this disorder: craving, described as a compulsion to use alcohol; loss of control over drinking; tolerance, which manifests as a need to increase in the amount of alcohol to achieve desired effects; and symptoms of withdrawal (41). Alcohol withdrawal syndrome appears in alcohol-addicted subjects after 6-48 h of the last drink consumption and includes a cluster of symptoms, which in extreme cases may be fatal. According to clinical definition, at least two of the following signs have to occur: autonomic hyperactivity, hand tremor, insomnia, nausea or vomiting, hallucinations (visual, tactile or auditory) and illusions, psychomotor agitation, anxiety and tonic-clonic seizures (40, 42). An addicted person is fully concentrated on alcohol seeking and consuming, and continuously relapse into drinking after periods of cessation (40, 43). This alcohol-induced behavior contributes to reinforcement and neuroadapatiation. In greater detail neuroadaptive changes related to prolonged alcohol exposure have been already dis-

cussed in this paper. In summary, the main neuronal adaptation underlying alcohol dependence consists of NMDA receptors up-regulation accompanied by reduced GABAergic transmission and dysregulation of the dopaminergic system. Once a shift in the balance between excitatory and inhibitory neurotransmission in the brain is provoked, the presence of alcohol for proper neuronal functioning is then required (40, 41, 43, 44).

Pharmacotherapy of alcohol dependence

At the moment, four substances are approved by the European Medicine Agency (EMA) to treat alcohol dependence: disulfiram, naltrexone, acamprosate and nalmefene. Nalmefene has not yet been given approval of the Food and Drug Administration (FDA) for the treatment of alcoholism, thereby is not used in this indication in the USA (45).

Disulfiram

Disulfiram was the first medicine used in the treatment of alcoholism, which discourage from drinking by provoking an unpleasant physiological reaction as alcohol is consumed simultaneously. This aversive agent interferes with alcohol metabolism, leading to accumulation of toxic product – acetaldehyde. Normally, alcohol undergoes biotransformation into acetaldehyde, which then is metabolized by aldehyde dehydrogenase to harmless acetate. Disulfiram inhibits the activity of the enzyme increasing the level of the toxic intermediate metabolite. Drinking alcohol during the treatment with disufiram results in high levels of acetaldehyde and hence aversion reaction of the body characterized by sweating, headache, flushing, nausea and vomiting (45, 46). Moreover, disulfiram inhibits also dopamine β-hydroxylase in the brain, which is responsible for the conversion of DA to norepinephrine. This additional mechanism of action supposedly may be important not only in the treatment of alcohol dependence, but also other drugs of abuse such as cocaine (46, 47). Disulfiram may bring potentially severe adverse consequences, and although the current view is that it may be used safely in some groups of patients (47), it is also suggested that the treatment with disulfiram should be avoided in those with liver dysfunctions (45). It is important to note that disulfiram therapy is not a typical example of pharmacotherapy. The response to disulfiram treatment can be described as instrumental conditioning, when an individual learns a connection between the presence of a particular behavior (alcohol drinking) and its unpleasant consequences (signs of intoxication). In this conditioning by punishment disulfiram-induced alcohol overdose functions as aversive (negative) reinforcer. Owing to that, alcoholic patients are discouraged from drinking in order to avoid appalling symptoms of alcoholic poisoning (48).

Naltrexone

Naltrexone is a non-selective opioid antagonist with high affinity for the μ-opioid receptor and to some extent for the κ-opiod receptor (46, 49). Since the opioid system is strongly involved in DA-related rewarding effects of alcohol, inhibition of the μ-opioid receptor with naltrexone prevents DA release in the VTA, and therefore reduces alcohol's positive reinforcing properties and further motivation to drink (47). Additionally, also the blockade of the κ-opioid receptor, which is up-regulated after prolonged alcohol exposure, brings positive therapeutic effects. As increased activation of κ-opioid receptors may contribute to dysphoria induced by alcohol withdrawal, naltrexone inhibiting this receptors will suppress relapse and supports cessation. Moreover, naltrexone was also shown to reduce the number of days when alcohol was consumed and its amount consumed per occasion (49).

There are two formulations of naltrexone approved by FDA: oral and depot. Depot naltrexone, administered *via* intramuscular injection, was demonstrated to block central opioid receptors for a period of approximately 4 weeks. Its undeniable advantage over oral naltrexone, apart from reduced frequency of administration, is that steady therapeutic plasma levels can be reached (45).

Nalmefene

In 2013, the EMA authorized another opioid antagonist - nalmefene, which is an antagonist of the μ- and δ-opioid receptor, but a partial agonist of the κ-opioid receptor. The preclinical and clinical studies indicate that nalmefene causes a significant reduction in alcohol consumption, possibly by modulating mesocorticolimbic function (50). Nalmefene has a few potential advantages over naltrexone including: longer plasma half-life, higher bioavailability, the greatest selectivity for central opioid receptors and lower liver toxicity (45). The drug should be used only as-needed (so-called targeted use), 1-2 hours prior to the anticipated time of drinking, or as soon as possible if the patient has already started drinking (50).

Acamprosate

Acamprosate is a homotaurine derivative with similar chemical structure to GABA, which has

been demonstrated to attenuate relapse in alcohol-addicted patients, and therefore is approved as a drug used for treating alcohol dependence (5, 17). Its precise mechanism of action has not been sufficiently explained yet, however, two hypothesis GABAergic and glutamatergic were proposed (5). Firstly, acamprosate was proposed as a $GABA_A$ receptor agonist, which increases down-regulated GABAergic transmission in alcohol-addicted individuals. Further studies drew attention to the importance of the NMDA receptor in clinical efficacy of acamprosate. It turned out that acamprosate in high concentrations functions as an antagonist of the receptor and blocks the glutamate increases during ethanol withdrawal. Moreover, it was also established that acamprosate induces the release of the inhibitory neurotransmitter taurine in the NAc (5, 51). To sum up, acamprosate seems to recover the chemical balance in the brain, which is disturbed by long-term alcohol consumption.

Among others, acamprosate is thought to be a safe and well-tolerated drug. Some authors suggest that the efficacy of acamprosate is decreased in patients with current alcohol intoxication, therefore complete detoxification before medication is required (51).

Other medicines and novel targets

In this part of the paper, other medicines which can be potentially used to treat alcohol dependence will be briefly discussed, concentrating on those with already documented efficacy.

One of the most promising medications seems to be *baclofen*, which is a presynaptic $GABA_B$ receptor agonist, decreasing DA release in the mesocorticolimbic projection (45). Originally prescribed to decrease the muscle tone and treat spasticity, baclofen was shown in human studies to reduce alcohol craving and consumption, and to increase abstinence periods (45, 46, 52). In general well-tolerated and safe, it barely undergoes liver metabolism, therefore may be considered as an alternative treatment in patients with alcoholic hepatitis (45).

Next relapse-preventing medication belongs to the anticonvulsants. *Topiramate* antagonizes glutamatergic inputs to the mesocorticolimbic system hence decreases dopaminergic activity, and facilitates GABAergic transmission in the brain. Unfortunately, its use may be significantly reduced by high toxicity and severe side effects such as paresthesias or cognitive dysfunctions (45, 46).

Since $5\text{-}HT_3$ receptors have been found to play an important role in alcohol-induced reinforcement, also $5\text{-}HT_3$ antagonists should become more important in the treatment of alcohol dependence. Indeed, clinical studies have indicated that *ondansetron*, used as an anti-emetic agent to prevent vomiting and nausea after chemotherapy and radiation, reduces alcohol drinking in patients with early onset alcoholism, who display serotonergic dysfunction (52, 53).

As discussed above, dopaminergic projections underlie reward and reinforcement of alcohol. Dysregulation of dopamine signaling, which is closely related to serotonergic system, may be a potential target for developing new strategy for reduction and cessation of alcohol use. *Aripiprazole* is an atypical antipsychotic with a complex mechanism of action. It acts as a partial agonist of D_2 receptors, simultaneously antagonizing various 5-HT receptor subtypes. It has been demonstrated that aripiprazole reduces alcohol consumption, probably due to its ability to normalize dopaminergic and serotonergic neurotransmission in the brain (46, 54).

Recently, a strong interest in CB_1 receptor antagonists as a new strategy for alcoholism treatment has been observed. Preclinical studies indicate that *rimonabant* inhibits ethanol seeking and self-administration in rodents (31). It is proposed that reduced alcohol consumption after rimonabant is linked to suppressed DA release in the shell of the NAc (33). Although the cannabinoid antagonists may become important therapeutic agents in alcohol dependence, trials with rimonabant on account of its adverse psychiatric effects were discontinued (32).

Alcohol abuse very often goes hand in hand with cigarette smoking. It is suggested that alcohol-addicted smokers who have achieved abstinence from drinking but continue smoking are more likely to relapse. In those, *varenicline*, already approved by FDA as an agent used in smoking cessation, may become twofold beneficial. It is a partial agonist of nAChRs, which are involved in the rewarding effects of both nicotine and alcohol. Varenicline decreases alcohol-related DA release in the NAc, reducing alcohol seeking and consumption in rodents. Human studies indicate that varenicline reduces alcohol craving and the number of heavy drinking days in smokers confirming a potential new strategy in alcohol dependence treatment (55).

Recently, under investigation are also appetite-regulating hormones, which supposedly may play an important role in modulation of alcohol craving and use. It has been observed that *leptin* blood levels were increased when alcohol was administered chronically, and stabilized during abstinence periods (56). Moreover, central injection of *neuropeptide Y*, which physiologically is inhibited by leptin,

Table 1. Current clinical trials on alcohol dependence.

Drug **Phase**	**Title and Sponsor**	**Description**
Completion Date ***ABT-436*** **Phase II**	**Aug. 2014** *A phase 2, double-blind, randomized, placebo controlled trial to assess the efficacy of ABT-436 for alcohol dependence* National Institute on Alcohol Abuse and Alcoholism	Chronic dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis resulting from stimulation of V1B receptors is common in substance abuse disorders. HPA axis normalization *via* pituitary V1B antagonism is a mechanism for potential ABT-436 efficacy in the treatment of alcoholism.
Citalopram **Phase I** **Dec. 2016**	*Citalopram effects on craving and dopamine receptor availability in alcoholics* Department of Veterans Affairs	Citalopram is a selective serotonin reuptake inhibitor (SSRI). SSRIs in patients with less severe alcohol dependence (type A) were shown to decrease drinking behavior in clinical trials, whereas type B alcoholics showed a trend in the opposite direction. The aim of the study is to assess whether craving for alcohol in type B alcohol dependence is affected by citalopram.
Ibudilast **Phase I** **Jun. 2015**	*Development of ibudilast as a novel treatment for alcohol dependence* University of California, Los Angeles	Ibudilast is a neuroimmune modulator that inhibits phosphodiesterases -4 and -10 and macrophage migration inhibitory factor. Preclinical data suggest that neuroimmune modulation is critical to the rewarding properties of drugs of abuse, therefore ibudilast may be a novel target for the treatment of alcoholism.
Ketamine **Phase I** **Mar. 2016**	*A randomized controlled trial of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine in comorbid depression and alcohol dependence* Yale University	Recently it has been established that ketamine has antidepressant properties with the more effective response in patients with a family history of alcoholism relative. Because major depression and alcohol dependence very often co-occur, the study is conducted in order to evaluate ketamine efficacy in comorbid depression and alcoholism.
Mecamylamine **Phase II** **Oct. 2014**	*Treatment with mecamylamine in smoking and non-smoking alcohol dependent patients* Elizabeth Ralevski, Yale University	Mecamylamine is a noncompetitive nACh receptor antagonist used in smoking cessation, which has been demonstrated to block the effects of alcohol in animals. Authors hypothesize that mecamylamine will be effective in reducing both alcohol consumption and smoking in alcohol-dependent smokers.
N-acetylcysteine + Naltrexone **Phase II** **Dec. 2014**	*N-acetylcysteine plus naltrexone for the treatment of alcohol dependence* Department of Veterans Affairs	The purpose of the study is to evaluate if the combination of N-acetylcysteine and high-dose of naltrexone is more effective in reducing alcohol consumption than high-dose of naltrexone alone.
Pexacerfont **Phase II** **Aug. 2020**	*Corticotropin-releasing hormone receptor 1 (CRH1) antagonism in anxious alcoholics* National Institute on Alcohol Abuse and Alcoholism	Alcohol increases the activity of CRH1 receptors, which are responsible for modulating the body response to stress, hence triggering feelings of anxiety often observed in alcohol-dependent individuals. The aim of the study is to investigate weather pexacerfont, as a CRH1 blocker, can lessen anxiety and craving for alcohol as part of alcohol-dependence treatment.
Pioglitazone **Phase II** **Jan. 2020**	*Role of proinflammatory signaling in alcohol craving* National Institute on Alcohol Abuse and Alcoholism	Pioglitazone is the peroxisome proliferator-activated receptor γ (PPARγ) agonist, which modulates glial activity. The aim of the study is to determine if pioglitazone can inhibit alcohol craving resulting from proinflammatory signaling provoked by low dose lipopolysaccharide administration.
Prazosin **Phase III** **Oct. 2014**	*The use of prazosin for treatment of patients with alcohol dependence (AD) and post traumatic stress disorder (PTSD)* Elizabeth Ralevski, Yale University	Prazosin is an α-1 adrenergic receptor antagonist used in the treatment of trauma nightmares and sleep disturbance in combat veterans. Simultaneously, there is a high of comorbidity with alcohol dependence and post traumatic stress disorder. The objective of the study is to evaluate the efficacy of prazosin at a dose of 16 mg *versus* placebo in reducing alcohol consumption and decreasing symptoms of post traumatic stress disorder in alcoholic patients.

decreases alcohol consumption in ethanol preferring rats, whereas neuropeptide Y knockout mice were shown do increase voluntary alcohol drinking (43). Also ghrelin has received lately much attention. Because it is suggested to stimulate alcohol craving and intake, recent investigations have focused on ghrelin receptor antagonists as a novel compound for treatment of alcoholism. One of them, PF-05190457, has just begun phase I of clinical research, whose completion date has been estimated in June 2017 (57).

Other examples of ongoing clinical trials are summarized in Table 1 based on http://www.clinicaltrials.gov.

Summary

Although alcoholism was defined as a disease over sixty years ago, it seems that pharmacology did not fully succeed in facing this matter of medical practice. After more than a half-century, science managed to endow us only with few drugs , some of which are thought to be controversial. Disulfiram, as it is the subject in question, may cause potentially fatal hepatotoxicity, not to mention serious side effects when combined with alcohol. Taking into consideration the fact that alcohol drinking is frequently related to liver diseases (58), and that disulfiram requires strict adherence to the medication regimen (patients must remain abstinent considering the disulfiram-alcohol reaction), pharmacotherapy with this drug has become useful only for selected alcoholic patients.

More beneficial might be combination therapy including disulfiram and other agents such as acamprosate or naltrexone. It was established that patients suffering from both alcohol and cocaine dependence were more likely to achieve 3 consecutive weeks of continuous abstinence from each substance of abuse when they underwent disulfiram-naltrexone combination therapy (59). Moreover, disulfiram added to acamprosate also improved the effectiveness of alcohol dependence treatment (60). This amelioration is probably due to the fact that disulfiram enhances the cognitive effects of self-control, however, disulfiram-related effects on DA levels in the brain cannot be excluded. Finally, also by combining naltrexone and acamprosate a considerably enhanced efficacy can be observed, but only when compared with acamprosate administered alone not with naltrexone (61). On the other hand, in different studies no significant advantages of the combination of disulfiram and naltrexone as well as acamprosate and naltrexone were found (62, 63). Contradictory results only confirm that further randomized clinical trials are needed not only in order to determine actual advantage of polytherapy but also to select appropriate groups of patients who may respond preferably to specific combination treatment.

Current approach to adequate treatment of alcohol abuse and dependence heads towards individualization, which requires fully knowledge about all co-occurring aspects accompanying alcohol addiction. Therefore, therapy supported by antidepressant or anxiolytic agents may help achieve better therapeutic effects in alcoholic patients, who battle against depression and anxiety disorders. Analogously, drugs used in smoking cessation, i.e., varenicline and mecamylamine, may be more effective in reducing alcohol intake, as well as smoking, in alcohol-dependent smokers. Also a subtype of alcoholism play a crucial role in choosing optimal pharmacotherapy. There are two main categories of alcoholics: type A alcoholics, who demonstrate later onset characterized by psychosocial triggers, and type B alcoholics, whose early onset is strongly associated with biological predisposition to the disease. It has been revealed that serotonergic pharmacotherapy may be differentially effective depending on alcoholic subtype. Hence, type A alcoholics, with presumably more normative 5-HT function, are more likely to respond successfully to treatment with SSRI than type B alcoholics (52).

Difficulties in treatment of alcohol dependence are associated with the fact that alcohol directly or indirectly affects function of almost every neurotransmitter system in the brain. For instance, DA levels can be elevated precisely by alcohol, but also as a result of alcohol-related changes in the serotonergic, cholinergic and opioid system. Despite an extensive knowledge of alcohol's influence on CNS, probably not all mechanisms have been described yet. Some interesting results may provide studies on appetite-regulating hormones, which are of great interest recently. Other latest reports indicate also histamine H_3 receptor antagonists as a potential novel therapeutic strategy in alcohol dependence, suggesting a significant part of this receptor in rewarding effects of alcohol (64). Further studies in this area might give us necessary answers, which will help to optimize pharmacotherapy of alcohol dependence.

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