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Pharmacotherapy of alcohol addiction – new reports

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Abstract

Introduction:
Alcohol use disorder is a worldwide problem. It can affect people and their families regardless of culture or age. Yet there is still no one good form of treatment. Each patient requires an individual approach. Unfortunately, for some patients current available treatments is not enough. There is a great need for new drugs that could be helpful in treating alcohol use disorder. Here, we integrate the information about the disease itself, current available treatments which is disulfiram, acamprostate and naltrexone and new possibilities in pharmacotherapy.

The aim of the study:
The purpose of this systemic review was to collect and analyse current and new methods of treatment of alcohol addiction.

Material and method:
Standard criteria were used to review the literature data. The search of articles in the PubMed database was carried out using the following keywords: alcohol, treatment, addiction, pharmacotherapy, psychotherapy.
Description of the state of knowledge:
Currently the basis for alcoholism treatment are psychosocial and behavioral treatments and classic medicines such as disulfiram, acamprostate, naltrexone. New promising off-label medication are baclofen, gabapentin, pregabaline, topiramate, γ-hydroxybutyrate, nalmefene, ondansetron andvarenicline. The use of these drugs may bring more benefits than use of older medicines. There are numerous studies proving the effectiveness of these drugs.
Summary:
Therapy for alcohol addiction could be more effective using other medicines than currently. Further research is needed to confirm the effect of new off-label medicines.

Keywords: alcohol, treatment, pharmacotherapy, addiction

1. Introduction

Alcohol is the most dangerous addictive drug in the Word [1]. Alcoholism has many definitions that vary from social frameworks to a psychiatric framework [2]. Alcoholism consists of heavy drinking periods with intervals of sobriety and then a relapsing phase that means returning to drinking [3]. It does seem like a never-ending circle. Three stages of drug addiction can be observed: composed preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect [4]. Drug addiction has been linked to dysregulation of brain regions that mediate reward and stress [5].When it comes to treatment of alcohol use disorder (AUD), possibilities are varied. Detoxication seems to be the most urgent form of treatment. Psychological help in form of psychotherapy or group therapy is also needed. However, the treatment should also consist of pharmacotherapy. There are drugs well known for this usage like disulfiram, but there is a growing group of new drugs with potentially beneficial effect on AUD treatment.

2. Etiology and effects of alcohol addiction

Many factors such as exposure to early life stress, acute or chronic stress, posttraumatic stress disorder can affect alcohol use disorder [6]. As early life stress we mean incidents such as childhood maltreatment and stressful life events [7]. It can cause changes in the hypothalamic-pituitary-adrenal axis, which lead to changes in gene expression of the mesolimbic reward pathway and brain morphology [8]. Furthermore, cumulative stressful life events experienced in adulthood, also have negative impact on the development of alcoholism [9]. There are several studies that show childhood stressors impact on alcohol use disorder. One study showed that experiencing two or more childhood stressful life events compared with none, highly increased the risk for alcohol disorder[10]. Another study carried out on African American showed increased risk for the development of alcohol, cocaine or heroin addiction in those who experienced childhood maltreatment [11]. A study of 1362 people from six American Indian tribes showed that childhood exposure to physical and sexual abuse was associated with increased risk of alcohol disorder [12]. Research were also conducted on animals. Early life stress has been shown to affect alcohol consumption in adult rhesus macaque monkeys and alcohol, cocaine and morphine consumption in rodents [13,14,15]. In breeding monkeys that were separated from the mother drink significantly more alcohol, than monkeys which were raised with mother, when alcohol were freely available [9]. In addition to stress, the development of alcoholism may also be affected by inflammation, bugs or intestinal dysbiosis [16].

In order to enable the development of efficacious treatments, it is necessary to understand the actions of alcohol at the molecular level. Alcohol affects the bran in different way. It causes changes in levels and function of neurotransmitters, receptors, enzymes and other molecules, leading to synaptic changes in brain circuitry regulating compulsivity and inhibition [17]. After consumption alcohol easily crosses the blood-brain-barrier. It is found at approximately the same concentration in all tissues and most of the metabolism of alcohol occurs in the liver by the mitochondrial cytochrome P450 (CYP2E1), catalase, aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH) [18]. CYP2E1 metabolizes alcohol to acetaldehyde and is main source of acetaldehyde in brain. It can also enter the brain from peripheral conversion of alcohol by ALDH. Acetaldehyde is the primary metabolite of alcohol and is responsible for the flushing effect that encompasses face flushing, nausea, vomiting, headache, tachycardia. One of the drugs acting at this stage is disulfiram, which inhibits aldehyde dehydrogenase enzyme [17].

The sequence and structure of DNA moleculescan contribute to the development, progression, and persistence of alcoholism. Several studies show that epigenetic mechanisms can play an important role in the changes in brain function associated with alcoholism [19]. There are three main epigenetic and enzymatic modifications to chromatin structure:

- DNA methylation
- histone acetylation
- histone phosphorylation

This changes the availability of the DNA for transcription factors and enzymes. In this way, the transcriptional activity of genes is changed. Chronic exposure to alcohol induces changes in the chromatin structure, specifically on gene promoters causing changes in gene expression in alcoholics[17,20].

Alcohol has also influence on neurotransmitter system, mainly glutamatergic, GABAergic, dopaminergic and serotonergic system. The most sensitive receptors are NMDA. Alcohol inhibits this kind of receptors, through protein kinase C [17,21]. However, research has reported that activity of NMDA receptor returns to baseline level after less than one hour of alcohol exposure [17,22]. Short-term use of alcohol inhibits the function of NMDA receptor, but chronic use could upregulate NMDA receptor expression in brain [23]. After removing the alcohol withdrawal syndrome may occure with characteristic clinical signs and cell death. In this situation, drugs with antagonistic action on the NMDA receptor may be used. When it comes to the dopaminergic system, we observe that short-term use of alcohol activates dopamine reward pathways, while chronic use causes hipodopaminergic state [17]. Studies show that alcoholics have less D2 receptors compared to non-alcoholics [24]. Study carried out on rats shows that after one year of administration of alcohol, rats have reduce level of dopamine, tyrosine hydroxylase protein and increased dopamine transporter protein levels [25]. In GABAergic system, we distinguish two kind of receptors GABA(A) and GABA(B). Alcohol is agonist of GABA(A) receptor. Increase of GABAergic system activity takes place in three different mechanisms:

- allosteric modulation of GABA(A)
- releasing GABAergic steroids
- increasing presynaptic release of GABA.

Due to this agonist effect of alcohol, we observe such symptoms as sedation, impaired cognitive function and motor function [17,26]. However, for chronic use of alcohol, there is downregulation of GABA(A) receptor because of the initial overstimulation. This, combined with upregulation of NMDA receptors, in the absence of alcohol, leads to the occurrence of such symptoms as anxiety or dysphoria [17]. Alcohol is also agonist of GABA(B) receptor. It induces the enhancement of the GABAB-mediated synaptic responses on dopaminergic cells.it seems that its action is mainly caused by postsynaptic activities [27].The last system

on which alcohol works is serotonergic system. Of all serotonin receptors only 5-HT3 is the ionotropic receptor and alcohol increases the potency with which the agonist can activate this receptor and increases the time it spends in open state. Studies with animals and humans show that drinking small amounts of alcohol increase serotonergic transmission and drinking large amounts of alcohol decrease it [17,28].

3. Alcoholism treatment

Psychosocial and behavioral treatments play the leading role in the treatment of alcoholism. Primary care physicians can use short tests to capture patients with alcohol problem during 5-10 minute medical office visit. This brief intervention can contribute to reduce drinking of alcohol. The basis is the patient education in the field of problematic drinking, increasing motivation to change behavior, and reinforcing skills to address problematic drinking [29]. Of course for people who are strongly addicted it is not enough, but it can play a supporting role with classical pharmacological therapy. Specialists psychosocial and behavioral therapies include cognitive behavioral therapy, motivational enhancement therapy and twelve-step facilitation [30,31,32]. Cognitive behavioral therapy has very high level of empirical support for the treatment of alcoholism and based on acceptance, spirituality and moral inventories [30,32]. Motivational enhancement therapy is focused on increasing motivation to change behaviors based on - establishing empathy, developing discrepancy, rolling with resistance, and supporting self-efficacy [32]. Some authors suggest that it is a better method of treating addictions than others [33].

Classic pharmacotherapy

For pharmacological treatment, meds such as acamprosate, disulfiram, naltrexone are used [30]. Acamrpostate is the most effective at maintaining abstinence in patients who are not currently drinking alcohol [34]. It is a dimer of acetyl-homotaurine linked by a calcium salt and is structurally close to taurine and ɤ-aminobutyric acid [35,36]. After absorption, it is immediately converted into acetyl-homotaurine and in this form exceeds the blood-brain barrier. It has a time at the maximal concentration of 6.3 h in enteric-coated form. Acamprostate is completely dissociated in plasma, it is not protein bound, metabolized and is excreted unchanged in the urine [35,37]. Therefore, a dose reduction is indicated in mild renal impairment and it is contraindicated in renal failure but it is safe in patients with damaged liver [34,35]. Mechanism of action of acamprostate is not fully understood. Acamprosate may influence GABA(A) transmission by inhibition of presynapticGABA(B) receptors. It also modulates function of NMDA receptors by interaction at the polyamine site. Acamprosate may also modulate the NMDA receptor response by metabotropic glutamate receptor subtype 5 antagonism [35]. It can be said that its operation corresponds to the following mechanisms: antagonism of the amino acids that stimulate the CNS and stimulation of neurotransmission in the GABAergic system to decrease glutamate during alcohol withdrawal, to increase β-endorphin in those with high alcohol exposure and possibly modulate the hypothalamus-pituitary–adrenal axis. Action of acamprostate may prevent hyperglutamatergic, potentially excitotoxic state during alcohol withdrawal [35,38]. The main side effects are: diarrhea, anorexia, flatulence, nausea, paraesthesia, fatigue [39]. Acamprostate should never be used alone but in combination with psychotherapy.

Disulfiram is used in the treatment of alcohol dependence with consistently successful results. It does not reduce the craving for alcohol. Its mechanism of action for maintaining alcohol abstinence is thought to be primarily psychological [34,40]. It causes unpleasant symptoms after alcohol consumption because it inhibits the enzyme aldehyde dehydrogenase. After alcohol intake it causes accumulation of acetaldehyde [35,40]. The disulfiram-ethanol reaction consists in the appearance of such symptoms as tachycardia, flushing, nausea, and vomiting [35]. Mechanism of action of disulfiram is about domination of psychological or cognitove threat and thus dissuade the use of alcohol [41]. There are limited trials to support

the effectiveness of disulfiram [34]. Problem with using disulfiram is that it does not reduce the urge or propensity to drink, which newer medications such as naltrexone, ondansetron, and topiramate have [42]. Disulfiram is more effective when taken under supervision and has no proven effect on the long-term outcome of alcoholism [34,43].

Naltrexone is semi-synthetic opioid. It is effective in treatment of alcohol and opioid addiction. Naltrexone is a competitive antagonist at μ-opioid receptors in the central nervous system. It has also partial agonist activity at kappa receptors in the brain and spinal cord. Naltrexone is rapidly absorbed after oral administration and undergoes the first-pass effect in the liver. Its active metabolite is 6-beta-naltrexol [44]. The use of naltrexone is best when controlled drinking is desired. The use of oral naltrexone is relatively safe and has good clinical effects [45]. Naltrexone is metabolized in the liver, it could be hepatotoxic and it should be used cautiously in patients with alcoholic liver disease [30,34]. One study suggests that the effectiveness of naltrexone treatment is the highest during active drinking alcohol [46]. The most common side effects of naltrexone are: nausea, vomiting, abdominal pain, headache, sedation, and the most dangerous is hepatotoxicity. Naltrexone, in combination with psychosocial support, has beneficial effect on relapse rates, and in reducing alcohol intake [39].

Off-label medications

Baclofen is a selective gamma-aminobutyric acid-B (GABA-B) receptor agonist. Baclofen is known as a drug for muscle spasticity treatment and is used for the spasticity of spinal origin that is a common to spinal cord injury and multiple sclerosis [47,48]. However, there are some signs that baclofen may also be helpful in the treatment of AUD [49]. This drug is often used due to off-label prescribing by general practitioners, mostly in Europe and Australia, to treat AUD [50].One of the trials which aim was to find out about efficacy and safety of using high-dose of baclofen to treat AUD shows that the drug was generally well tolerated. Despite consuming alcohol by many patients there were no significant alcohol/baclofen interactions. Also no serious adverse events were reported [51].Some studies found that baclofen reduces anxiety levels in patients addicted to alcohol [51,52].Addolorato and colleagues were the first to investigate the efficacy of baclofen in reducing alcohol consumption in AUD patients [53]. In this study there were ten male current alcoholic patients. They took baclofen for 4 weeks, at a dose of 15 mg/day three times a day, then the dose increased to 30 mg/day for the remaining 27 days. Seven of those patients maintained abstinence through the experimental period. Also the craving was significantly reduced and the thinking about alcohol disappeared so this feature may suggest that baclofen is useful during AUD treatment [53].Another study was run by a physician with alcohol dependence and comorbid anxiety, who prescribed himself high-dose baclofen. He started with 30 mg/day and increased the dose with 20 mg every third day. As a result he observed that cravings decreased. The conclusions of this study was that high-dose baclofen suppressed symptoms of alcohol dependence and relieved anxiety [54].But not all studies are compatible. The largest meta-analysis about the efficacy and tolerability of baclofen compared to placebo in long-term treatment of alcohol dependence showed that firstly, baclofen is not significantly superior to placebo and secondary, that there is variability among the trials which results as a significant diversity. However, it is worth saying that baclofen was well-tolerated and small superiority of baclofen over placebo is conceivable [55].There is a great need of official regulations or guidelines how to prescribe baclofen, to who, in which doses and what are the maximum doses. Meantime, without these kind of directions, prescribers need to find out all those informations themselves as baclofen is suggested as a second-line treatment [56]. While prescribing this drug, firstly the patient needs to be informed about the drug and physician need to know if there are any contraindications. Also it is recommended to evaluate the renal

function before treatment as insufficiency of those can lead to drug accumulation. Nevertheless, baclofen is a promising medication in treatment of AUD [47].

Gabapentin (GBP) is another well known drug with a potential in AUD treatment. In animal models of alcohol dependence, gabapentin decreased the amplitudes of GABA receptor mediated inhibitory post synaptic currents in the central nucleus of the amygdala, and decreased dependence-induced alcohol drinking. Notably, the effects of gabapentin were identical to the effects of a corticotropin releasing factor antagonist (decreased inhibitory post synaptic currents in dependent rats). These results suggest an important GABA-CRF interaction in GABAergic neurotransmission [57].A randomized, double-blind, placebo-controlled trial with 60 male alcohol-dependent subjects that was performed in Brazil showed that gabapentin is a potential drug for the treatment of alcohol withdrawal and dependence. The results of gabapentin group were significantly different compared to those of placebo group. The conclusion of this trial was that gabapentin reduces alcohol consumption and craving [58].There is also a retrospective study about the impact of gabapentin in conjunction with benzodiazepines for the management of alcohol withdrawal. Although the results suggest that gabapentin has no beneficial features in this treatment [59]. That shows that more trials need to be done in order to find the role of gabapentin in alcohol-dependence treatment. GBP is also used to manage alcohol withdrawal and dependence in recovering alcohol-dependent individuals as it has a beneficial impact on sleep, anxiety, and mood disturbances very often seen in early abstinence and also reduces alcohol craving [60].

Pregabalin is a newer gabapentinoid drug, but with greater potency [57]. One of the trials was comparing pregabalin and naltrexone for their efficacy. Patients treated with pregabalin have shown greater improvement of specific symptoms in the areas of anxiety, hostility and psychoticism, and survival function. However, overall pregabalin was the same range of efficacy as the one of naltrexone [61].

In Australia there is a randomised, placebo-controlled clinical trial currently in the recruitment phase that refers to topiramate. The popularity of topiramate In AUD treatment is increasing. So the aim of this study is to examine the drug comparing to naltrexone [62].

γ-Hydroxybutyrate (GHB) is a partial agonist at the gamma-aminobutyric acid B ($GABA_B$) receptors. Clinically is known for treating narcolepsy. In some European countries the drug is approved for AUD treatment. GHB is supposed to reduce craving for alcohol [63].

Nalmefene is also a subject of study In terms of AUD treatment. In a randomized, double-blind, placebo-controlled trial patients treated with nalmefene had significantly less heavy drinking days than placebo group [64].

Ondansetron may be another potentially helpful drug in AUD treatment. A trial that studied its effects showed that ondansetron is effective for patients with early-onset alcoholism [65].

Varenicline is a partial agonist for α4β2 nicotinic acetylcholine receptor subtype. Clinically is known for smoking cessation [66]. The study of potential usage of varenicline in AUD treatment suggests that this drug may have a beneficial effects. Reduction of alcohol craving and less heavy drinking days were observed in group of patients who received varenicline comparing to placebo group [67].

4. Summary

Alcohol use disorder is very common disease. As it affects life of patients and their families on many different levels, there is a great need for accurate treatment. Drugs currently used that were mentioned above bring positive effects but not for all of the patients. This is why potential of new drug is so important. Results of the trials on these drugs are not unambiguous and it suggest that more this subject requires more research.

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