NEW DEVELOPMENTS IN THE TREATMENT OF ALCOHOL USE DISORDER

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Abstract

Alcohol dependence is a chronic disorder with frequent relapses. Even the most motivated individuals have difficulties in maintaining abstinence, and require pharmacotherapy, apart from psychotherapy. Current anti-craving medications (acamprosate, naltrexone, nalmefene, disulfiram) have only limited efficacy. The present paper aims to review both the agents developed within the last 10 years (novel opioid and vasopressin antagonist, dopamine, cannabinoid, glucocorticoid and orexin receptors modulators) and the drugs already prescribed for other uses (anticonvulsants, muscle relaxants, antihypertensives, antiemetics, and even neuroimmune modulators and antiparasitic drugs), which were proven beneficial for controlling heavy drinking.

Rezumat

Dependența alcoolică este o patologie cronică, recăderile fiind frecvente. Chiar și indivizii motivați mențin cu dificultate abinența, necesitând psihoterapie, dar și terapie medicamentoasă. Medicația *anti-craving* actuală (acamprosate, naltrexonă, nalmefen, disulfiram) are eficacitate limitată. Prezentul articol își propune o trecere în revistă a compușilor descoperiți în ultimii 10 ani (noi antagoniști opioizi și de vasopresină, modulatori ai sistemelor dopaminergic, cannabinoid, corticoid și orexinic), dar și a medicamentelor utilizate deja în practica clinică cu alte indicații (anticonvulsivante, antiparazitare, miorelaxante, antihipertensive, antiemetice și chiar modulate neuroimune), care s-au dovedit utile în controlul consumului de alcool.

Keywords: dependence, alcohol, anti-craving agents

Introduction

Addiction, a chronically relapsing condition, involves significant perturbations of the most important neurotransmitter pathways [22]. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) reunites alcohol abuse and dependence in a single entity, Alcohol use disorder (AUD), adding craving as a diagnostic criterion. Thus, an individual receives this diagnosis if, in a 12 month period meets 2 out of the 11 criteria: inability to stop drinking, failed attempts to abstain, long periods of intoxication or recovery after heavy drinking, social, professional and family difficulties, declining pleasant activities in order to imbibe, involvement in risky behaviour while intoxicated, continuing drinking despite negative physical and psychiatric consequences, increasing the consumed amounts to obtain the same effects (tolerance), developing withdrawal and an intense desire to drink (craving) [2]. The variation between AUD symptom combinations generates numerous different phenotypes, which require targeted treatment and could explain the contradictory results of the clinical trials [24].

The main cerebral molecular targets of alcohol are the pentameric ligand-gated ion-channels (pLGIC), N-methyl-D-aspartate (NMDA) receptors, L-type Ca^{2+} ion channels and G protein-activated inwardly

rectifying K^{+} channels (GIRKs). The pLGIC receptors include the inhibitory glycine receptor (GlyR), γ -aminobutyric acid type A (GABA_A) and the excitatory nicotinic acetylcholine receptor (nAChR) and 5-hydroxytryptamine₃ (5-HT₃), on which alcohol has an agonist effect [42].

The approved drugs for AUD therapy are disulfiram, naltrexone, nalmefene and acamprosate. The first approved agent was disulfiram, an irreversible inhibitor of aldehyde dehydrogenase which generates a potentially dangerous aversive reaction, limiting its use only to healthy individuals, a requirement difficult to meet in AUD patients. Also, disulfiram decreases craving by inhibiting dopamine-beta-hydroxylase which leads to elevated levels of dopamine [3].

At the ventral tegmental area (VTA), a part of the mesolimbic reward circuit, alcohol stimulates the μ -opioid receptors located on dopaminergic neurons both directly and indirectly, through elevated levels of endogenous opioids. Consecutively, the opioid neurons increase dopamine release in the nucleus accumbens, generating euphoria [44].

Koob and Volkow describe the three stages of dependence, with the correspondent neural circuits: the binge/intoxication stage stimulated by the basal nuclei and maintained through positive feedback due

to pleasure (reward seeking), the withdrawal/negative affect stage controlled by the amygdala (seeking relief) and the preoccupation/anticipation stage (craving) with the activation of the prefrontal cortex [22]. The progression of the disorder implies the predominance of one of the 3 pathways. Based on this theory, the recently published PREDICT study proved a better response to naltrexone, a μ and κ -opioid receptor antagonist, for the “relief drinkers” subgroup, with a significant decrease of heavy drinking (more than 5 drinks per day for men and more than 4 drinks per day for women; a “standard drink” or “unit” varies between 8 to 23.5 grams of alcohol, depending on the country) [18]. The hypothesis of the same clinical trial that acamprosate would be more effective on the “relief drinking” subgroup wasn’t confirmed [29]. Ethanol potentiates GABA induced inhibition and reduces glutamate stimulation. During withdrawal, excessive glutamate becomes neurotoxic, especially since GABA is insufficient. These events are countered by acamprosate, a taurine derivative which acts like “artificial alcohol” by inhibiting the glutamate system (blocking the metabotropic glutamate receptors, mGluR), thus indirectly inhibiting the GABAergic system [12]. The latest approved treatment (only in Europe) for AUD is the μ , δ and κ -opioid antagonist nalmefene.

With the advantage of an “as needed” administration, some studies declare it superior to naltrexone [43]. The present article briefly reviews the latest attempts to discover safer and more effective therapeutic alternatives for AUD, focusing on major neurotransmitter systems (Table I).

Materials and Methods

We searched papers published between 2008 and 2017 in PubMed, Medline, SpringerLink and Elsevier databases. The search terms were therapy/treatment, alcohol dependence/alcoholism. Both preclinical and clinical studies were included.

Results and Discussion

The GABAergic system. Gabapentin, an antiepileptic which modulates GABA transmission by interacting with voltage-gated calcium channels (VGCCs), reduces craving, dysphoria and insomnia and is useful both for the treatment of mild withdrawal and, in the long term, for relapse prevention [28, 31]. A GABA derivative, γ -hydroxybutyric acid or sodium oxybate (GHB) was proven effective both for alcohol withdrawal and for maintaining abstinence and is already approved for AUD in Italy and Austria [17].

Table I

A summarized outlook of the new agents for AUD and the neurotransmitter systems involved in their action

Neurotransmitter system	Agent	Current use
γ -aminobutyric acid (GABA)	gabapentine	anticonvulsant
	γ -hydroxybutyric acid or sodium oxybate (GHB)	alcohol withdrawal, “date rape drug”
	ivermectines	antiparasitic
	baclofen	muscle relaxant
Glutamate	topiramate	anticonvulsant
	zonisamide	
	D-cycloserine	tuberculosis
	Guanfacine	ADHD
Opioid	LY2196044	new
	GSK1521498	
Dopamine	OSU6162	
Acetylcholine	varenicline	smoking cessation
Norepinephrine	prazosin	hypertension, benign prostatic hyperplasia
	doxazosin	
Serotonin	ondansetron	antiemetic
	D-Lysergic acid diethylamide (LSD)	hallucinogenic
	psilocybin	
Glucocorticoid	CP376395	new
	CRF6-33	
Cannabinoid	rimonabant	smoking cessation, obesity (preclinical)
	AM4113	new
Vasopressin	ABT-436	
Orexin	SB-334867	

Nevertheless, the potential for abuse and misuse (a so called “date rape drug”) makes it risky especially for patients with psychiatric comorbidities [6]. The antiparasitic drugs ivermectines limit ethanol ingestion

in mice by stimulating GABA_A receptors and by blocking the effects of alcohol on purinoceptor 4 (P2X4R). This class of receptors, ion channels activated by adenosine triphosphate (ATP), could

become a target for the development of new treatments for AUD [10]. Baclofen, a GABA_B agonist approved for muscle spasticity, decreases alcohol consumption (ethanol is a presynaptic GABA_B antagonist), but only on low (< 90 mg/day) or high doses (> 150 mg/day) and is already frequently prescribed off-label for AUD in European countries like France [34, 38].

The glutamate system. The glutamate antagonists and anticonvulsants topiramate and zonisamide have moderate effect for the treatment of AUD, but their cognitive side effects are a major reason for non-compliance [21]. D-cycloserine, an antituberculosis medication, was shown to diminish craving by acting as a glutamatergic NMDA partial agonist at the glycine site [20]. Guanfacine, a α_2 adrenoceptor agonist approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) can modulate the glutamatergic neurotransmission in the medial prefrontal cortex (mPFC), thus reducing alcohol intake in rats, but clinical trials are in order to validate this effect in humans [11].

The opioid system. New compounds such as LY2196044, a μ , δ and κ -opioid antagonist and GSK1521498, a μ -opioid antagonist were shown useful for abstinence maintaining, the latter was even more effective than naltrexone in decreasing alcohol consumption in mice [36, 47].

The dopaminergic system. A new monoamine stabilizer that modulates dopamine levels in the nucleus accumbens, OSU6162 diminished craving and the pleasure related to alcohol consumption in highly impulsive individuals in a phase II human laboratory study [19].

The cholinergic system. The prevalence of tobacco use disorder among individuals with AUD is approximately double than in the general population, with half the persons with heavy alcohol use being smokers [46]. Varenicline, prescribed for smoking cessation, is a nicotinic partial agonist, selective for the $\alpha_4\beta_2$ sub-type present on dopaminergic neurons from the VTA. It was shown to decrease drinking both in smokers and non-smokers alcoholics [7, 37].

The adrenergic system. In animal models, prazosin and doxazosin, α_1 -adrenoceptor antagonists usually prescribed for hypertension and benign prostatic hyperplasia, prevented stress induced alcohol consumption [13]. Furthermore, the combined blockade α_1 - and 5-HT₂ by adding cyproheptadine could reverse alcohol preference [45]. Although promising, these effects have yet to be validated in humans.

The serotonergic system. The antiemetic ondansetron, a selective 5-HT₃ antagonist, combined with topiramate, decreases the relapse rate [32]. D-Lysergic acid diethylamide (LSD) is a partial 5-HT_{2A} agonist, a 5-HT_{1A} agonist in the Dorsal Raphe and a D₂ agonist in the VTA, at high doses, might trigger psychotic-like effects [9]. A meta-analysis of six clinical trials concluded that

a single dose of LSD was an effective augmentation to several AUD therapy programs [25]. Comparable long term results were obtained with psilocybin, another hallucinogenic very similar structurally to 5-HT [5]. *The glucocorticoid system.* Corticotropin-releasing factor (CRF) is considered to control the anxiety/stress-like effects of withdrawal and abstinence, the so called “dark side” of dependence [22]. Type 1CRF-receptor antagonists (such as CP376395) infused into the VTA of mice, decreased stress-escalated alcohol intake [15]. Type 2 CRF-receptor antagonists (astressin-2B) and CRF binding protein (CRFBP) antagonist CRF fragment 6-33 (CRF6-33) combined reduced binge-like drinking in a similar experiment [1]. While the preclinical studies were encouraging, currently, the results were not translated to humans.

The cannabinoid system. The two types of presynaptic cannabinoid receptors on GABA and glutamate neurons could be another target for ethanol binding, promoting sedation [8, 40]. Rimonabant is a cannabinoid receptor 1 (CB1) inverse agonist, was proven beneficial for smoking cessation, obesity and also for controlling drinking in preclinical studies. Nevertheless, clinical studies on heavy alcohol drinkers showed no effect in humans [14]. On the other hand, AM4113, a CB1 antagonist diminishes binge-like drinking behaviour in mice, without any apparent adverse effects [4].

Other mechanisms. A recent vasopressin type 1b (V1b) receptor antagonist, ABT-436 increased the number of days of abstinence, especially in high stress alcoholics in a phase 2, double-blind, placebo-controlled randomized trial [39]. Another similar study determined that the supplement benfotiamine, a S-acyl synthetic derivate of thiamine, diminished alcohol intake notably in women [30]. Animal studies showed the role of SB-334867, a type 1 orexin receptors antagonist present in the nucleus accumbens and the mPFC, in the control of compulsive alcohol consumption [26, 27]. In a randomized, placebo-controlled, human laboratory trial, ibudilast, a neuroimmune modulator, reduced cue-induced craving, particularly in alcoholics with comorbid depression [35]. One of the epigenetic mechanisms involved in the development of addiction is histone deacetylation with chromatin remodelling. The counteraction of this phenomenon by new agents, such as MS-275 and sodium butyrate reduced the impulse to drink, the amounts of ethanol ingested and relapses [16, 41]. This model suggests that intermittent exposure to alcohol during adolescence could induce long term histone alterations in the amygdala which could lead to anxiety and AUD [32].

Conclusions

The literature contains extensive research on new agents for the treatment of AUD, involving most of the neurotransmitter systems (GABA, glutamate, serotonin, dopamine, cannabinoid, orexin or vasopressin). Each

mechanism could be more effective for certain groups of patients, according to their phenotype.

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