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REVIEW

Contribution of Visceral Systems to the Development of Substance Use Disorders: Translational Aspects of Interaction between Central and Peripheral Mechanisms

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Abstract—Substance use disorders are associated with structural and functional changes in the neuroendocrine, neuromediator, and neuromodulator systems in brain areas involved in the reward and stress response circuits. Chronic intoxication provokes emergence of somatic diseases and aggravates existing pathologies. Substance use disorders and somatic diseases often exacerbate the clinical courses of each other. Elucidation of biochemical pathways common for comorbidities may serve as a basis for the development of new effective pharmacotherapy agents, as well as drug repurposing. Here, we discussed molecular mechanisms underlying integration of visceral systems into the central mechanisms of drug dependence.

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INTRODUCTION. PSYCHOACTIVE SUBSTANCE DEPENDENCE IS NOT ONLY THE CENTRAL NERVOUS SYSTEM DISEASE

At least 1% of the world's population suffers from substance use disorders. When taken in or administered, psychoactive substances (PASs) affect the central nervous system (CNS) and alter mental state, up changes in the state of consciousness. Substance use disorders are a heavy socioeconomic burden; their prevalence, morbidity, as well as associated economic losses consistently increase [1]. Disorders caused by the use of PASs are characterized by chronic relapsing course, loss of control, and PAS abuse despite obvious adverse effects. The pathogenesis of these disorders involves changes in the functioning of neuroendocrine, neurotransmitter, and neuromodulator systems in specific brain areas associated with the mechanisms of reinforcement and stress response [2]. Since chronic exposure to PASs and related pathological processes are also accompanied by the adaptive response of CNS, substance dependence is considered as a type of aberrant neuroplasticity [3] with the imbalance of neurotrophins playing the key role in this process [4].

Despite a relative success in understanding the patterns of chronic exposure to PASs, the possibilities

Abbreviations: ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CVS, cardiovascular system; FGF, fibroblast growth factor; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide-1; HPA, hypothalamic-pituitary-adrenal axis; PAS, psychoactive substance; PPAR, peroxisome proliferator-activated receptor.

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and efficacy of pharmacotherapy in the treatment of addiction remain quite limited. Thus, only a few drugs have been approved by the FDA (Food and Drug Administration) for the treatment of substance use disorders. For example, disulfiram (acetaldehyde dehydrogenase inhibitor), naltrexone (opioid receptor antagonist), and acamprosate (neuromodulatory drug) are the only therapeutic agents that have been approved for the treatment of alcohol use disorders [5]. The only drugs approved for the treatment of opioid use disorder are naltrexone and opioids buprenorphine and methadone used in maintenance treatment [6]. Currently, there are no drugs approved for the treatment of addiction to psychostimulants (psychotropic substances that stimulate mental and, to a lesser extent, physical activity) on the market. Pharmaceutical agents used in the therapy of substance dependence act primarily on the central neurotransmitter systems and corresponding receptors. Because of a high social and biological significance of these disorders and a limited number of therapeutic approaches, studying biological mechanisms involved in the formation and course of substance use disorders at all levels (from molecules to the entire body) remains extremely relevant.

Substance use disorders are characterized by a recurrent or chronic course with an increase in the dosage of used substance as a result of tolerance development, loss of control, development of withdrawal syndrome, compulsion to seek and take the drug, and inability to stop using it despite obvious psychological, physical, and social consequences [7, 8]. In fact, risky drug consumption, addiction, and drug dependence are integrated into a single psychopathological structure, with brain being its key substrate [9, 10]. Existing classifications of substance use disorders typically do not take account the contribution of physical health in the formation of substance dependence, which is undoubtedly a serious omission. Substance use disorders are considered to be diseases of the CNS by default, thus ignoring involvement of almost all body visceral systems in their development, which will be discussed in this review.

PASs are xenobiotics and, therefore, also have a significant effect on the functioning of internal organs other than the CNS. It is not surprising that the PAS abuse is often accompanied by comorbid diseases, for example, cardiometabolic syndrome [11], endocrinopathies [12], eating disorders [13], and many others. Approximately half of subjects dependent on PASs have at least one chronic somatic disease [14]. The risk of developing somatic pathologies increases dramatically in individuals with the substance use disorders [15]. The comorbidity of somatic pathologies and substance dependence significantly increases mortality in many diseases, including disorders of the gastrointestinal tract (GIT) and cardiovascular system (CVS), endocrine disorders, and pathologies associated with metabolic disorders [16]. The prevalence of substance use disorders in people with eating disorders reaches 40%, and the prevalence of eating disorders in people with dependence can reach 30%, which is considerably higher than in the total population [17]. The comorbidity of eating disorders with PAS dependence increases the risk of developing somatic diseases [18]. PAS abuse is accompanied by disturbances of circadian rhythms, sleep structure, and sleep quality and duration in 90% people with alcohol addiction [19] and up to 80% of people with addiction to illicit PASs [20], which is significantly higher than the prevalence of sleep problems in the total population. Eating and sleep disorders belong to neuropsychiatric diseases and are closely related to the physical health of an individual.

Mental health and physical health are closely interrelated [21], which is clearly evident, in particular, for affective spectrum disorders. It has been proven that the development of stress-induced mental disorders, e.g., psychotic depression, is based on the close interaction between the central and peripheral mechanisms [22]. This example is especially important if we consider development of substance dependence, since psychopathological addiction is formed as a way to achieve a feeling of well-being against the background of chronic stress and mental tension [23]. In other words, psychopathological addiction in some way is an attempt of adaptation to stress. Indeed, an imbalance in the stress response systems often accompanies the development of a pathological pattern of PAS intake [2]. Stress response systems and their mediators (corticosteroids) play a key role in both development of brain pathology under chronic stress and formation of depressive phenotype [24, 25]. The risk of developing depression increases significantly in chronic somatic pathologies. In turn, depression is an independent risk factor for increased morbidity and mortality in many somatic diseases. Moreover, effective therapy of depression not only contributes to the restoration of mental health, but also improves the clinical prognosis of concomitant somatic diseases [26].

Therefore, substance use disorders and comorbid somatic diseases aggravate each other's clinical course. Chronic substance abuse is a risk factor in somatic pathologies and *vice versa*. Identification of their common molecular mechanisms can help in the development and implementation of new effective methods of pharmacological correction of the corresponding comorbidities.

The main goal of our review was conceptual analysis of the relationship between peripheral systems and central biochemical mechanisms underlying substance use disorders. This article is a traditional critical review of the published articles. The search queries included the following keywords: [name of the

compound/mediator or process AND PAS dependence OR substance use disorder] in the Russian-language resource Scientific Electronic Library (eLIBRARY.ru) and English-language MEDLINE (PubMed) and Google Scholar databases. The search was conducted among the reports published within the last 5 years; some significant studies that had been published before that, were also included. The discussed peripheral mediators were grouped by their anatomical location and belonging to a particular organ system or by involvement in a corresponding physiological process (although classification by systems and organs is rather conventional, since all described biologically active molecules exhibit pleiotropic effects).

MEDIATORS OF CARDIOVASCULAR SYSTEM AND WATER-SALT BALANCE

Endothelin is synthesized in many types of endothelial cells, vascular smooth muscle cells, macrophages, fibroblasts, and brain neurons [27]. Endothelin acts through the activation of the subtype A (ETA) and B (ETB) transmembrane G protein-coupled receptors (GPCRs). Stimulation of ETA receptors is accompanied by vasoconstriction and inflammation, while stimulation of ETB receptors typically has the opposite effect [27]. Activation of endothelin receptors located in the brain ensures their involvement in many pathophysiological processes of the CNS. ETA receptors modify the antinociceptive effect of opiates, as well as the development of tolerance [28]. It was suggested that the blockade of ETA receptors potentiates the antinociceptive activity of opiates and reduces development of desensitization and tolerance by restoring the association of Gi proteins with the opioid receptors and preventing their desensitization mediated by β-arrestin [28]. Administration of the ETA receptor antagonist BQ123 to the brain ventricles attenuated oxycodone and morphine withdrawal syndrome in mice, which indicates endothelin involvement in the mechanisms of dependence formation [29]. Despite an obvious potential of endothelin receptor antagonists for treating opioid dependence and appearance of approved antihypertensive drugs with such pharmacological activity on the market, no clinical studies have been conducted so far.

Atrial natriuretic peptide (ANP) is a hormone produced by cardiomyocytes in response to myocardial strain. By binding to a receptor with the guanylate cyclase activity, ANP stimulates formation of cGMP, which mediates biological functions of this peptide. ANP produces a pleiotropic effect, including relaxation of vascular smooth muscles, regulation of water-salt balance due to its influence on sodium excretion, suppresses the renin-angiotensin-aldosterone system, stimulates lipolysis and lipid oxidation, and regulates insulin sensitivity [30]. In general, increased ANP plasma levels are associated with a reduced risk of cardiometabolic syndrome. Beside regulating the water-salt balance, ANP is also integrated in the activities of the hypothalamic-pituitary-adrenal (HPA) axis and immune system [31]. Despite the fact that preclinical studies have demonstrated ANP involvement in the development of mental disorders, there are almost no studies dedicated to this topic, although their relevance has been well recognized. Alcohol intoxication leads to electrolyte imbalance accompanied by changes in the content of substances regulating electrolyte homeostasis in blood plasma during withdrawal syndrome. In the acute withdrawal phase, the activity of renin and the plasma levels of aldosterone increase and then return to the initial values as the symptoms of withdrawal reduce [32]. It has been shown that in patients with alcohol-related psychosis, the level of ANP increases at the onset the psychosis. In mice maintained on an alcohol-liquid diet, intracerebroventricular injection of ANP attenuated, whereas injection of an antiserum against ANP intensified the severity of handling-induced convulsions (a symptom of alcohol withdrawal) [32]. In patients with alcohol dependence, the level of ANP in the blood plasma after two weeks of abstinence under stationary conditions correlated negatively with alcohol craving, severity of perceived stress, and anxiety. Moreover, the ANP level was found to be a reliable predictor of anxiety and stress [33]. Therefore, ANP is only a peripheral marker of clinical manifestations of alcohol addiction, but might also exhibit the central activity in the case of alcohol withdrawal syndrome.

The renin-angiotensin system is involved in the CVS functioning through the regulation of vascular tone and water-salt balance. Angiotensin also participates in the mechanisms of PAS dependence development. Using a pharmacological approach and functional MRI, it was demonstrated that angiotensin regulates the functional activity of human brain via activation of type 1 receptors [34]. Several signaling cascades triggered by the activation of type 1 angiotensin II receptor, are integrated into the HPA axis and participate in the stress response, which can explain angiotensin participation in the mechanisms of addiction [35]. It is known that the angiotensin system is able to alter the motivation for alcohol consumption in rodents [36]. Early experiments on rodents showed that captopril and enalapril, which are angiotensin-converting enzyme (ACE) inhibitors that suppress formation of active angiotensin II and are used in the therapy of hypertension, reduced voluntary alcohol consumption without affecting hemodynamic parameters [37]. Interestingly, ACE involved in proteolytic maturation of angiotensin in the nucleus accumbens mediates the

degradation of endogenous opioid peptides, which underlies the interaction of opioid, glutamate, and dopaminergic neurotransmitter systems [38]. Moreover, systemic administration of captopril reduced the activity of dopaminergic striatal neurons and attenuated the reinforcing properties of fentanyl [38]. It is believed that such pharmacological agents can be repurposed for the pharmacotherapy of substance use disorders. The role of angiotensin II in the CNS in alcohol consumption has been studied in detail [39]. Transgenic rats with the downregulated expression of angiotensin II and lower dopamine content in the ventral tegmental area demonstrated reduced voluntary alcohol consumption compared to the wild-type animals [39]. Experiments in knockout mice showed that alcohol consumption depended on type 1, but not type 2 angiotensin receptors [39]. A single administration of angiotensin II receptor antagonist telmisartan to brain ventricles reduced alcohol consumption in alcohol-preferring rats without affecting food and water intake [40]. Administration of valsartan, another angiotensin II receptor antagonist, during morphine intoxication prevented development of tolerance to the antinociceptive effect of morphine and lessened the severity of withdrawal syndrome [41]. Candesartan, an antagonist of type 1 angiotensin receptor, attenuated the reinforcing properties of methamphetamine in the rat self-administration model [42]. Moreover, despite the fact that both ACE inhibitors and angiotensin receptor blockers are widely used in the treatment of hypertension, we failed to find the data on clinical studies of their effectiveness in PAS use disorders in the analyzed publications.

Aldosterone is a steroid hormone produced by the adrenal gland in response to the stimulation with angiotensin, extracellular potassium, and adrenocorticotropic hormone (ACTH). By binding to mineralocorticoid receptors (nuclear receptors acting as transcription factors) in distal nephrons, aldosterone increased the reabsorption of sodium and water and stimulated potassium efflux, thus modulating the water-salt balance and blood pressure [43]. Mineralocorticoid receptors are also expressed in the brain, in particular in the hippocampus, amygdala, and prefrontal cortex, i.e., brain regions involved in the cognitive functions and formation of addiction [44]. Animal studies have shown that exposure to PASs alters the content of aldosterone and expression of its receptors in the brain. The blockade of mineralocorticoid receptors attenuated the reinforcing properties of PASs and alleviated the symptoms of withdrawal [45]. It is believed that antagonists of mineralocorticoid receptors are promising agents in the treatment of alcohol dependence. Thus, in primates, expression of the mineralocorticoid receptor mRNA in the amygdala correlated negatively with alcohol consumption, while the level of aldosterone in the plasma increased after alcohol intake [44]. Similarly, downregulation of the mineralocorticoid receptor mRNA in the amygdala of rats was associated with an increase in anxiety-like behavior during acute withdrawal and compulsive alcohol consumption [44]. In patients dependent on alcohol, plasma aldosterone levels correlated positively with the amount of alcohol consumed, as well as severity of cravings and anxiety [44]. Spironolactone (mineralocorticoid receptor antagonist) reduced alcohol consumption in mice. Moreover, retrospective analysis of pharmacoepidemiological records showed that administration of spironolactone to alcohol drinkers was also accompanied by a decrease in the level of alcohol consumption [46]. Steroid antagonists of mineralocorticoid receptor (e.g., spironolactone) have been approved for the treatment of hypertension and heart failure. At the same time, there are no reports on the clinical studies of their efficacy against substance use disorders.

Vasopressin is an antidiuretic hormone involved in the regulation of vascular tone and water-salt balance, which determines its influence on blood pressure [47]. Vasopressin peptide is expressed in the hypothalamus and acts as a hormone and neurotransmitter in the brain. Several subtypes of vasopressin receptors have been discovered, all of them being GPCRs [47]. Subtype V1a receptors are expressed in blood vessels, adrenal glands, and kidneys and stimulate vasoconstriction, aldosterone and glucocorticoid secretion, and renin production. Central V1a receptors contribute to the regulation of the sympathetic nervous system. Vasopressin receptors of the V1b subtype are expressed in the hypothalamus, pituitary gland, and limbic structures and play a key role in the stress reactivity. Through activation of V1b receptors, vasopressin potentiates the action of corticoliberin by stimulating ACTH secretion of by the pituitary gland and activation of the HPA axis. Subtype V1b receptor antagonists are promising compounds for suppression of the HPA axis activity in the development of substance dependence, in particular, on alcohol. For example, selective V1b receptor antagonist SSR149415 inhibited alcohol intake in rats [48, 49]. In mice, SSR149415 suppressed conditioned place preference associated with morphine administration [50]. Another V1b receptor antagonist, ABT-436, suppressed the activity of HPA axis in humans by decreasing cortisol levels in the blood serum [51]. In phase II clinical trials, ABT-436 increased the duration of abstinence without affecting the alcohol craving, the greatest effect being observed in the subgroup with a higher baseline stress level [52]. ABT-436 is among the most promising candidates for developing agents for treatment of alcohol use disorders [53].

Oxytocin. Another neuropeptide hormone that has to be mentioned is oxytocin. Assigning oxytocin

and vasopressin to compounds associated with the CVS functioning might seem controversial, but, considering an incredible pleiotropic action of both hormones, they can be attributed to the regulators of any body system. Both oxytocin and vasopressin are produced in the hypothalamus. Along with the regulation of various aspects of brain functioning and behavior, oxytocin controls many body systems [54, 55], including CVS [56]. Metabotropic receptors for oxytocin are expressed in the limbic structures and regulate the reinforcing effect of various stimuli (including PASs), stress sensitivity, and socialization [57]. The neurobiological activity of oxytocin is realized through direct or indirect action on the dopamine and serotonergic neurotransmitter systems and HPA axis [58].

According to the data of preclinical studies, stimulation of oxytocin receptors has a protective effect in substance dependence. It reduces the severity of anxiety and depressive-like behavior, attenuates reinforcing properties of PASs, and reduces the risk of relapse during withdrawal [57, 58]. Injectable oxytocin is used in obstetrics for labor induction. Oxytocin (mostly as nasal spray) has been actively investigated for the therapy of mental disorders, in particular, those associated with substance use. Oxytocin attenuates manifestations of the PAS withdrawal syndrome, including its affective component, and can suppress cravings and consumption of PASs [59].

MEDIATORS OF METABOLISM AND EATING BEHAVIOR

PASs alter fundamental processes of energy metabolism. Chronic morphine intoxication in mice downregulated expression of subunits of pyruvate and NADH dehydrogenase complexes and lactate dehydrogenase 2, reduced ATP synthesis, and impaired glycolysis in the hippocampus, while systemic and intrahippocampal administration of D-glucose attenuated symptoms of morphine withdrawal [60]. Based on these results, Jiang and Ma [61] suggested, although with a certain degree of skepticism, that hypoglycemia may be one of the causes of physical dependence on opiates. Interestingly, the effect of morphine on energy metabolism can be direct, as morphine has been shown to bind to creatine kinase B and inhibit its activity both *in vitro* and *in vivo* [62].

Insulin is synthesized by pancreatic β-cells; its key function is regulation of energy metabolism, particularly, carbohydrate metabolism, by stimulation of glucose transport into the cells. In addition to regulating energy metabolism in almost all organs and tissues, insulin also crosses the blood-brain barrier (BBB) and participates in the regulation of cognitive functions and eating behavior [63]. Central insulin resistance, which typically accompanies peripheral insulin resistance, disrupts synaptogenesis, neurogenesis, and many aspects of neuroplasticity. A decrease in the sensitivity of insulin receptor to insulin is associated with morphological and functional disturbances in the CNS, formation of affective (depressive) phenotype, and impaired cognitive abilities [63].

Antidiabetic drugs, especially BBB-penetrating metformin, have a potential in the treatment of mental disorders, including those associated with substance use. Metformin normalizes blood glucose levels by inhibiting gluconeogenesis in the liver, reduces glucose absorption in the GIT, stimulates glucose uptake by peripheral tissues, and improves insulin sensitivity [64]. Metformin is a biguanidine compound; its mechanism of action is based on the ability to inhibit mitochondrial complex I, reduce production of reactive oxygen species, and exhibit the anti-inflammatory properties. Metformin reduces the severity of neuroinflammation and stimulates neuroplasticity and excitability of neurons. Its neurotropic effects are based on the ability to activate AMPK (AMP-activated protein kinase) and CREB (cAMP responsive element binding protein) transcription factor, leading to the upregulation of BDNF (brain-derived neurotrophic factor) expression followed by the stimulation of neurogenesis and antidepressant effect [64].

Competitive administration of metformin and morphine interfered with the formation of tolerance to the anti-nociceptive effect and morphine dependence in rats [65]. Metformin administration prevented development of anxiety- and depressive-like behavior, as well as memory and learning impairments during chronic methamphetamine intoxication in rats (which was accompanied by CREB activation and increased BDNF levels in the hippocampus) [66]. Metformin injection to the nucleus accumbens reduced cocaine self-administration [67]. Nevertheless, no controlled clinical trials on the effect of metformin or other drugs normalizing glucose level in PAS dependence have been conducted so far.

Cholecystokinin is a peptide hormone produced by the small intestine mucosa in response to stimulation by food proteins and lipids. By binding to GPCRs, it regulates appetite and satiety, stimulates gallbladder contractions, and promotes secretory activity of the stomach and pancreas, thus participating in digestion [68]. Cholecystokinin is also synthesized in the CNS, where it is colocalizes and interacts functionally with the dopamine, GABA, serotonin, and opioid systems in limbic structures and modulates positive reinforcement and emotional state [69].

In animal models, administration of cholecystokinin receptor agonists or antagonists modified consumption of different classes of PASs, but the results of these studies remain contradictory [69].

Russian scientists synthesized and characterized original tetra- [70] and dipeptide [71] analogues of cholecystokinin that reduced alcohol consumption and alleviated alcohol and morphine withdrawal syndromes. Nevertheless, only a few works suggested the prospects for the clinical use of cholecystokinin receptor ligands. RPR102681, an antagonist of the CCK-B (CCK2) cholecystokinin receptor, stimulated dopamine release in the ventral striatum and reduced cocaine self-administration in rodents. In a clinical study, administration of RPR102681 caused a trend toward reduction in cocaine craving [72].

Ghrelin is a peptide hormone produced primarily by enteroendocrine cells in the stomach. Acylated ghrelin interacts with the corresponding GPCR (GHSR1a, growth hormone secretagogue receptor 1a), which is expressed in the CNS and peripheral organs and tissues, such as intestine, pancreas, adrenal glands, and adipose tissue [73, 74]. The main function of ghrelin is regulation of eating behavior. It also plays an important role in energy homeostasis by controlling the intake and consumption of nutrients and participating in the basic metabolism of glucose and lipids [75]. Ghrelin is a stress-reactive molecule that closely interacts with the HPA axis in stress response [76].

Ghrelin has become a focus of attention as a promising pharmacological target in the treatment of substance use disorders. For example, systemic administration of the ghrelin receptor antagonists JMV2959 and HM-04 or inverse agonists PF-5190457 and PF-6870961 attenuated alcohol consumption regardless of sex [77]. Similarly, systemic administration of a JMV2959 reduced conditioned place preference and self-administration of fentanyl, which was accompanied by a decrease in the extracellular dopamine content in the nucleus accumbens [78]. According to preclinical studies, ghrelin stimulated craving for and consumption of PASs, apparently, due to its ability to influence the dopaminergic system by inducing formation of heterodimers of ghrelin receptors with the D1 and D2 dopamine receptors [79, 80]. In many clinical studies, ghrelin modifies alcohol craving. Intravenous administration of ghrelin to alcohol-abusing patients stimulated alcohol cravings [81], while oral administration of PF-5190457 reduced the stimulus-driven cravings [82]. The clinical effect of ghrelin might be due to its ability to influence the cytokine profile. Combined intravenous administration of ghrelin (but not PF-5190457) during intravenous self-administration of alcohol reduced the level of interleukin-6 (IL-6) but increased the content of IL-10 in alcohol abusers with alcohol dependence [83]. The effect of PF-05190457 on alcohol craving was investigated in phase 2 clinical trial (https://clinicaltrials.gov/study/NCT02707055). Unfortunately, due to the COVID-19 pandemic, the study was terminated. In the case of chronic intoxication, ghrelin plays a decisive role in the development of alcoholic liver disease by decreasing insulin secretion and directly affecting the transport, *de novo* synthesis, and esterification of fatty acids, which results in hepatic steatosis [84]. Therefore, development and introduction of ghrelin antagonists in the clinical practice for the treatment of alcohol use disorders is important for the treatment of both alcohol dependence and concomitant liver pathologies. Ghrelin receptor antagonists are among the most promising drugs in the treatment of disorders associated with the consumption of alcohol [53] and opioids [85].

Glucagon-like peptide-1 (GLP-1) in an incretin hormone that is expressed in the intestine and pancreas. It is secreted in response to food intake and regulates satiety. The physiological activity of GLP-1 is mediated through the activation of peripheral GLP-1 GPCRs, resulting in the suppression of intestinal peristalsis, stimulation of insulin secretion, and inhibition of glucagon secretion, which normalizes glucose levels [86, 87]. GLP-1 can penetrate the BBB and is also expressed in the brain stem. GLP-1 receptors are expressed in brain structures associated with reinforcement circuits [86, 87].

Experiments in animals have shown that stimulation of central GLP-1 receptors suppressed the reinforcing properties of alcohol, opioids, and psychostimulants, as well as reduced the motivation to consume them and symptoms of dependence [86, 87]. Among the mechanisms of action of GLP-1 receptor agonists that underlie their modifying effect on the activity of PASs, we should mention the relationship of GLP-1 with the stress reactivity system and ability of hypothalamic neurons to express corticoliberin [88], as well as the ability of these compounds to modulate the activity of dopaminergic and glutamatergic neurons in limbic structures [86]. The GLP-1 receptor agonist exenatide, which is used in diabetes therapy, reduced alcohol consumption in a subgroup of obese individuals [89]. Exenatide reduced alcohol-dependent activation of the ventral striatum and availability of dopamine transporter [89]. Severely obese patients consuming alcohol and treated with semaglutide or tirzepatide (GLP-1 receptor agonists) for diabetes or obesity for at least 30 days reported decrease in alcohol intake, which was accompanied by reduction of the symptoms of alcohol use disorder according to the AUDIT (Alcohol Use Disorder Identification Test) scores compared to values in the control group (people that had not received the drugs) and before the treatment [90]. Treated patients noted a subjective decrease in alcohol cravings, which can be considered as an indirect evidence of the efficacy of these drugs against alcohol dependence [90]. Retrospective analysis of patients treated with semaglutide for weight loss also showed a significant reduction in alcohol use disorder

symptoms based on the AUDIT score [91]. The efficacy of GLP-1 receptor activation by agonists, especially semaglutide, has been demonstrated in independent studies in rodents and primates, so that the use of these drugs in the clinic seems extremely promising [92].

Leptin is a peptide hormone secreted by the adipose tissue. It regulates food intake by influencing appetite; moreover, leptin is involved in the regulation of reinforcement-related behavior associated with various stimuli [93]. Leptin acts through a receptor belonging to class I cytokine receptors expressed in the hypothalamus, hippocampus, and amygdala. In the ventral tegmental area, leptin attenuated the firing rate of dopaminergic neurons projecting to the nucleus accumbens [93].

The data obtained on the studies of the effect of alcohol on the leptin blood levels in animals are contradictory. In mice bearing mutations in the genes encoding leptin or its receptor, leptin administration stimulated alcohol intake [93]. In contrast, leptin administration attenuated motivation for cocaine use in rats [94]. Injection of leptin receptor antagonist into the ventricles or local knockout of leptin receptors in the mesolimbic structures increased dopamine levels and stimulated cocaine-associated conditioned place preference [95]. Leptin peripheral levels in patients with alcohol dependence varied significantly, as well as the relationship between the leptin levels and clinical manifestations of alcohol dependence, especially, alcohol craving [93].

Neurotensin is a peptide produced in the CNS and GIT. Neurotensin is difficult to attribute to any body system, since it exhibits its biological activity in nervous tissue, CVS, adipose tissue, and GIT. Among others, it regulates food and water intake, body temperature, blood pressure, metabolism, energy balance, and sleep-wake cycle [96]. Neurotensin also plays an important role in the mechanisms of reinforcement and formation of adaptive response to stress. The positive reinforcing properties of neurotensin are due to the activation of the high-affinity NTSR1 (neurotensin receptor 1) GPCR in the structures of the mesocorticolimbic system [96].

The influence of neurotensin on the reward circuits and, therefore, mechanisms of psychostimulant and alcohol preference, as well as on the motivation for drug and alcohol consumption, is based on its ability to interact with the dopaminergic system through the formation of NTSR1 heterocomplexes with D2 dopamine receptor [97, 98]. Neurotensin interaction with the dopaminergic system indirectly modulates the activity of glutamatergic and GABAergic systems. Russian scientists synthesized and characterized a dipeptide analogue of neurotensin capable of attenuating morphine withdrawal syndrome in rodents, which was accompanied by changes in the dopamine metabolism [99]. The results of studies in rodents are often contradictory [97, 98]. Despite the efficacy of neurotensin receptor ligands (especially, NTSR1 ligands) in modulation of PAS consumption demonstrated in preclinical studies, no clinical studies on this topic have been conducted yet.

Fibroblast growth factor (FGF) family includes 23 secreted proteins. In humans, FGFs are produced by keratinocytes, fibroblasts, chondrocytes, endothelial cells, smooth muscle cells, and mast cells and display a wide range of biological activities. Impairments in the functioning of these factors are associated with metabolic disorders, cardiovascular diseases, and oncogenesis. It is known that at least two members of this family, FGF2 [100] and FGF21 [101], are involved in substance use disorders. FGF2 has a paracrine mechanism of action; it binds to FGF receptors (FGFRs) with the tyrosine kinase activity, participates in cell migration and proliferation, regulates vascular tone and angiogenesis, and displays the anti-apoptotic and anti-inflammatory properties [100]. FGF2 is also expressed in the brain, where it exhibits the neuroprotective properties, participates in neurogenesis and memory formation, and regulates stress reactivity and emotional background by activating FGFR1 [102]. FGF21, on the contrary, is an endocrine regulator. Beside FGFR, it requires the Klotho transmembrane protein for its activity. Klotho regulates insulin sensitivity and increases FGF21 affinity for the receptor [100]. FGF21 is expressed in liver, adipose tissue, and pancreas and is involved in fat and glucose metabolism.

In rodents, FGF2 influenced the sensitivity to amphetamine and cocaine self-administration. At the same time, FGF2 expression in dopaminergic neurons is affected by psychostimulants. Moreover, in these experiments, FGF2 participated in the morphological changes of neurons of the ventral tegmental area [100]. Systemic administration of FGF2 or its injection into the striatum in rodents stimulated alcohol consumption, while the knockout of the *Fgf2* gene or inhibition of FGFR1 reduced the reinforcing properties of alcohol and motivation to consume it [103-105]. Using systemic and central administration of FGF21 or its analogue (PF-05231023), as well as the tissue-specific deletion of FGF21 in the liver, it was shown that FGF21 expressed in the liver in response to alcohol intoxication, is involved in the negative feedback that suppresses subsequent alcohol intake through the Klotho coreceptor in the basolateral amygdala, as well as in the regulation of dopaminergic neurons activity in the nucleus accumbens [106]. According to the clinical data, alcohol drinking is accompanied by the upregulation of circulating FGF21 [107, 108]. Transgenic mice with an increased level of circulating FGF21 showed attenuation of the morphine antinociceptive tolerance development, reduced morphine dependence,

and reduced preference for morphine in the conditioned place preference test [109]. Therefore, the blockade of FGF2 signaling attenuates addictive properties of alcohol and psychostimulants, while FGF21 stimulation suppresses formation of alcohol and opioid dependences. However, no clinical studies have been conducted to verify the effects of FGF2 or FGF21 in the consumption of alcohol and PASs. Because FDA has approved erdafitinib and pemigatinib (FGFR inhibitors) for the therapy of malignancies with the activating mutations in FGFR2 and FGFR3, this might raise the question of potential repurposing of these drugs in pharmacotherapy for the treatment of substance dependence.

COMPONENTS OF THE IMMUNE SYSTEM

An important aspect in PAS activity and formation of dependence is the effect they exert on the immune system and neuroimmune communication. In general, resident CNS macrophages respond to pro-inflammatory stimuli. TLRs (Toll-like receptors) trigger cascades leading to the activation of transcription factors, primarily NF-κB (nuclear factor κB), and subsequent expression of proinflammatory cytokines by the microglia [110]. In response to cytokines, astrocytes reduce expression of the glutamate transporter, resulting in the impaired functioning of the glutamatergic system [110]. Hence, the microglia and astrocytes can control the excitability of glutamatergic neurons. The disturbances in the balance between the pro- and anti-inflammatory systems can cause neuroinflammation development that often accompanies PAS abuse. Immune mechanisms play an important role in the development of diseases comorbid with chronic PAS abuse, such as affective mental disorders, pain syndrome, and infectious process [111].

Studies in animals deficient by the key mediators of immune response, such as TLRs, TNFs (tumor necrosis factors), IL-1 (interleukin 1), and IL-6, showed that these molecules can modify the addictive properties of PASs or manifestations of the withdrawal syndrome [111]. Preclinical studies have demonstrated that the neuroimmune system modulators, e.g., phosphodiesterase inhibitors and ligands of peroxisome proliferator-activated receptors (PPARs), can modify the course and symptoms of dependence [110, 111]. It is important that these agents demonstrate their activity in clinical studies as well [110, 111].

cAMP and cGMP. As secondary mediators, cAMP and cGMP play an important role in the immune system signaling, while isoform-specific inhibitors of phosphodiesterases (enzymes breaking the phosphodiester bond in cyclic nucleotides) exhibit the immunomodulatory activity and suppress the inflammatory response [112]. The non-selective phosphodiesterase inhibitor ibudilast, which is approved in some countries for the treatment of asthma, acts as an immunosuppressor that inhibits the activation of microglia [113]. Ibudilast efficiently reduced alcohol intake in many rodent models [114]. In a clinical study, ibudilast attenuated alcohol cravings and normalized mood [115], as well as reduced the volume of alcohol consumed, which, according to MRI, was accompanied by a decrease in the activity of the ventral striatum [116]. Systemic administration of ibudilast potentiated the analgesic effect of morphine and oxycodone and attenuated the symptoms of withdrawal syndrome in rats [117]. In clinical studies in patients with opioid dependence, ibudilast weakened the reinforcing properties of oxycodone and attraction to heroin, but potentiated the antinociceptive effect of oxycodone [118], and also partially attenuated the symptoms of opioid withdrawal syndrome [119]. At the same time, ibudilast did not affect the amount of methamphetamine consumed in a 12-week clinical study involving patients undergoing outpatient treatment for addiction [120]. Promising results have been demonstrated for the anti-alcohol properties of apremilast (phosphodiesterase 4 inhibitor) that has been approved for the treatment of psoriasis. Apremilast reduced motivation to consume alcohol in a mouse model, presumably through modification of dopaminergic neurons in the nucleus accumbens, and decreased alcohol consumption by dependent patients in phase 2 clinical trial [121].

PPAR family of transcription factors exhibits a wide range of biological activities by controlling expression of proteins regulating metabolism and inflammatory and immune responses [122, 123]. PPARα isoform stimulates endocytosis, esterification, and transport of fatty acids and regulates the genes of lipoprotein metabolism. PPARδ stimulates lipid and glucose catabolism. PPARγ promotes fatty acid uptake and triglyceride formation, thus providing insulin sensitivity and glucose metabolism. PPAR agonists are widely used in the clinic. Thus, glitazones (PPARγ agonists) are used for the treatment of insulin resistance. Fibrates (PPARα agonisms) are the therapeutic agents in dyslipidemia [122, 123]. Due to the PPAR involvement in essential metabolic processes (e.g., oxidative phosphorylation), These receptors are expressed in almost all tissues and organs.

Due to their involvement in the key processes, such as oxidative stress and inflammation, PPARs also participate the development of CNS pathologies. Many PPAR agonists approved for the use in clinic, penetrate the BBB and show central activity, which opens up the prospects in their repurposing for the treatment of brain diseases [124]. PPAR isoforms are expressed in the dopaminergic neurons of limbic structures

involved in the dependence formation; hence, PPAR agonists can modify the activity of these neurons, which makes their investigation a relevant topic in the studies of addictions [125]. Agonists of PPARα and PPARγ isoforms were found to attenuate motivation and PAS consumption and to reduce the symptoms of withdrawal in experimental models [125]. It should be noted that most studies have been conducted in alcohol consumption models, in which agonists of both isoforms suppressed voluntary and operant intake [125]. Despite their potential, PPARα agonists are unlikely to be effective in the treatment of alcohol dependence, since fenofibrate had no effect on alcohol intake and alcohol craving in a clinical trial [126]. At the same time, in a small sample of diabetic alcohol drinkers, pioglitazone helped to reduce alcohol consumption [127]. In contrast, in another clinical trial (which had been terminated), pioglitazone stimulated rather than inhibited alcohol cravings [128]. Therefore, results of clinical studies do not allow to make unambiguous conclusions regarding the effectiveness of PPARα agonists.

Intestinal microflora (microbiota) makes a significant contribution to the development of inflammatory response in organs and tissues, including the CNS. Regarding communication between the GIT and the brain in the formation of the PAS dependence, it should be taken into account that chronic PAS consumption affects the microbiome, which in turn affects the brain [129]. As xenobiotics, many classes of drugs (including PASs) have a direct impact on the intestinal bacteria [130, 131]. PAS, such as opiates and opioids, indirectly affect the peripheral nervous system and regulate intestinal peristalsis, which can also alter the microbiota composition [132]. The most studied mechanism by which intestinal microbiota affects the CNS is production of neuroactive metabolites, primarily short-chain fatty acids (SCFAs), which enter the portal circulation and reach the brain [133]. Also, lipopolysaccharides, which are pro-inflammatory factors, can enter the bloodstream due to impaired intestinal permeability [134]. SCFAs affect the microglia and immune cells by activating the corresponding receptors. They can also act as substrates for histone modification, as well as regulators of activity of enzymes, for example, histone deacetylases [135].

Studies in animal, early phases of clinical trials, and retrospective analysis have shown that PASs affect the microbiota composition, which can be important in the formation of drug dependence. At the same time, manipulating the composition of the microbiota using antibiotics or its transplantation can modify the course or manifestation of dependence [129, 135]. Despite the fact that the nature of microbiota interactions with the brain under the influence of PASs depends on many factors, which can be seen from diverse and often contradictory study results, the modulation of the microbiota or its metabolites has serious prospects of becoming a part of substance dependence treatment program in the future [129, 135].

CIRCADIAN RHYTHMS

Circadian rhythms and sleep are controlled by the central mechanisms. Dysregulation of these mechanisms affects somatic health, resulting in a wide range of internal diseases [136]. In this regard, we decided to discuss this topic in the review, especially since disturbances in the quality and duration of sleep often accompany the PAS abuse. Sleep disorders increase the risk of relapse, aggravate the course of substance use disorders, and worsen physical health [137, 138].

Melatonin (N-acetyl-5-methoxytryptamine) is secreted by the pituitary gland and regulates circadian rhythms by binding to the MT1 and MT2 GPCRs in the suprachiasmatic nucleus. Administration of melatonin reduced the consumption of alcohol, opiates, and cocaine in rodent models [139]. Melatonin is involved in the mechanisms of dependence at the cellular and systemic levels through the modulation of the glutamate, dopamine, and GABA neurotransmitter systems. It also possesses pronounced anti-inflammatory properties [139]. In contrast to numerous experimental studies, the clinical studies are much less common and the effect of melatonin in these studies strongly depends on the pharmacological class of PAS. For example, in heroin-dependent patients undergoing substitution therapy, melatonin significantly improved sleep quality, as well as reduced anxiety and depression, which was accompanied by a reduction in the insulin serum levels and decrease in the insulin resistance [140]. At the same time, clinical studies have failed to show the effectiveness of melatonin in the treatment of sleep disorders associated with alcohol dependence [141].

Orexins regulate the sleep-wake cycle and eating behavior, i.e., processes often disrupted in individuals with substance dependence. Orexins A and B are peptides produced by neurons in the lateral hypothalamus that act through binding to the cognate Ox1R and Ox2R GPCRs expressed in various brain regions. Unlike classical neurotransmitter systems involved in the reinforcement, orexins do not participate directly in the regulation of primary reinforcement. Orexins regulate motivation to consume PASs, which is a key symptom of addiction, by influencing the neuronal plasticity in limbic structures upon chronic intoxication [142]. In animal models, both non-selective and subtype-selective Ox1R and Ox2R antagonists reduced the reinforcing properties of stimulants (alcohol and opiates), thereby reducing consumption and risk

of relapse [143]. Thus, SB-408124 (Ox1R antagonist) blocked alcohol-induced conditioned place preference in rats [144]. Non-selective Ox1R and Ox2R antagonists, such as suvorexant, have been approved for the treatment of insomnia. These drugs also have a potential in the reduction of cravings in the comorbidity of sleep disorders and alcohol dependence [145]. In a clinical study, suvorexant ameliorated sleep disturbance and relieved symptoms of depression and opiate withdrawal syndrome [146, 147]. Hence, orexin receptors are promising pharmacological targets in the therapy of sleep disorders and comorbid substance use disorders. Antagonists or negative allosteric modulators of orexin receptors are believed to be among the most promising drugs in the treatment of disorders associated with the use of alcohol [53] and opioids [85].

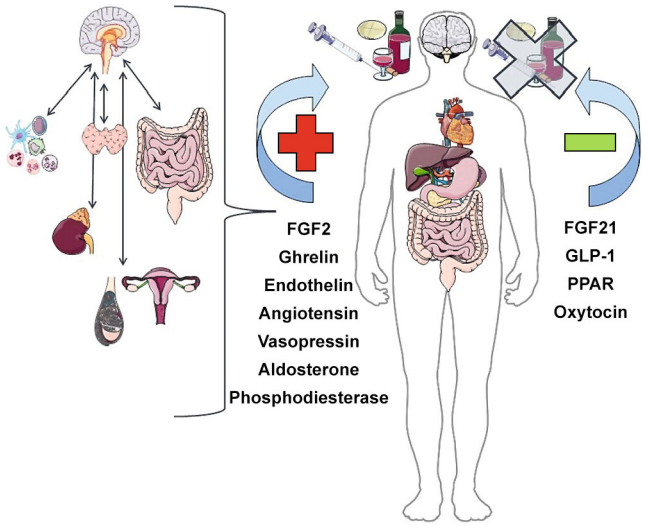

Fig. 1. Interaction of visceral systems and CNS in PAS use disorders. When exposed to PASs, hormones, peptides, neurotransmitters, and growth factors produced in the brain and/or peripheral organs and tissues, have a pleiotropic effect by participating in the pathology development in internal organs, on one hand, and modulating the reinforcement and stress response systems as components of the central mechanism of substance dependence, on the other hand. Mediators have a negative (–) or stimulating (+) effect on various factors in the formation of PAS dependence (right panel). The HPA, hypothalamic-pituitary-thyroid, and hypothalamic-pituitary-gonadal axes, as well as immune system and intestinal microbiota, coordinate the process (left panel). The figure was created using Servier Medical Art (Servier) templates licensed under Creative Commons Attribution 3.0 unported license

CONCLUSION

Realize that everything
connects to everything else.

Leonardo da Vinci (1452-1519)

A body can function in a changing environment due to the maintenance of metabolic homeostasis achieved through cooperation between the CNS and internal organs. Myriads of hormones, peptides, and neurotransmitters in a whimsical ensemble ensure the functioning of systems and organs, as well as communication between them. All compounds described in our review have the following fundamental characteristics: (i) pleiotropic action, i.e., ability to influence different body systems and exert different effects; (ii) interaction with signaling systems and participation in the metabolic events that also involve other described compounds; (iii) close relationship with the main neurohumoral body system regulating stress response and adaptive processes. This is why an imbalance in the mediators in one part of the system, which might reach a critical level when the compensation is no longer possible, leads to a development of a complex disorder. Substance use disorders are a psychopathological phenomenon mostly affecting mesocorticolimbic structures and stress response circuit, whereas interaction with internal organs regulates these processes.

According to the analyzed data, the main effect of visceral system mediators with the pleiotropic functions on the PAS-associated mechanisms is their involvement in the limbic reinforcement system and stress response circuit originating in the hypothalamic-pituitary system. The reward system has a central location, while the system responsible for the stress sensitivity is connected with internal organs via hormonal communication. In addition to the HPA axis, which has been repeatedly mentioned here, axes linking the hypothalamic-pituitary system with the activity of thyroid gland and gonads might be essential in the substance dependence. Due to the complexity of the subject, we opted not to discuss this topic in the current article. Interested readers can refer to the comprehensive reviews [12, 148, 149].

Therefore, PASs themselves, as well as cycles of intoxication and withdrawal, directly or indirectly disrupt neurochemical and hormonal homeostasis, which aggravates the course of chronic somatic diseases. In turn, this promotes pathological dependence, thus forming a vicious circle exacerbating both substance use disorders and concomitant comorbidities. Figure 1 shows interactions between some visceral and CNS mediators, which, according to the published reports, have an effect in substance use disorders.

An important direction in the development of clinical psychopharmacotherapy of substance use disorders should be design and introduction of new drugs, as well as repurposing, i.e., the use of drugs that had been approved for the treatment of other class of diseases [53, 85, 150, 151]. The review describes

Table 1. Promising pharmacological groups of drugs in the treatment of substance use disorders

Pharmacological group	Efficacy in the context of PAS action				Indications for approved drugs
	Group representatives	PAS	Test models	Clinical trials	
Endothelin receptor antagonists	BQ123	opiates/opioids	potentiation of analgesia, attenuation of tolerance and withdrawal syndrome [28]	–	hypertension
ACE inhibitors	captopril, enalapril	alcohol	suppression of intake [37]	–	hypertension
	captopril	opiates/opioids	reinforcement attenuation [38]		
Angiotensin receptor antagonists	telmisartan	alcohol	suppression of intake [40]	–	hypertension
	valsartan	opiates/opioids	attenuation of tolerance and withdrawal syndrome [41]		
	candesartan	psychostimulants	reinforcement attenuation [42]		
Mineralocorticoid receptor antagonists	spironolactonum	alcohol	suppression of intake [46]	–	hypertension heart failure
Vasopressin V1b receptor antagonists	SSR149415, ABT-436	alcohol	suppression of intake [48, 49]	suppression of intake [52]	–
	SSR149415	opiates/opioids	reinforcement attenuation [50]	–	
Oxytocin receptor agonists	oxytocin	alcohol, opiates/opioids, psychostimulants	reinforcement attenuation, reduced relapse risk [57, 58]	suppression of craving and intake, attenuation of withdrawal syndrome [59]	labor induction
Hypoglycemic agents (biguanides)	metformin	opiates/opioids	attenuation of tolerance and withdrawal syndrome [65]	–	type 2 diabetes
		psychostimulants	suppression of intake, attenuation of intoxication [66, 67]		

Table 1 (*cont.*)

Pharmacological group	Efficacy in the context of PAS action				Indications for approved drugs
	Group representatives	PAS	Test models	Clinical trials	
Ghrelin receptor antagonists	JMV2959, HM-04	alcohol	suppression of intake [77]	-	–
	JMV2959	opiates/opioids	reinforcement attenuation [78]		
Ghrelin receptor inverse agonists	PF-5190457, PF-6870961	alcohol	suppression of intake [77]	suppression of craving [82]	–
GLP-1 receptor agonists	exenatide, semaglutide, tirzepatide	alcohol, opiates/opioids, psychostimulants	suppression of intake [86, 87]	suppression of alcohol craving and alcohol intake [90, 91]	type 2 diabetes, obesity
FGF21 receptor agonists	FGF21, PF05231023	alcohol	suppression of intake [106]	–	–
		opiates/opioids	attenuation of reinforcement, tolerance, and withdrawal syndrome [109]		
Phosphodiesterase inhibitors	ibudilast	alcohol	suppression of intake [114]	suppression of alcohol craving and alcohol intake [115, 116]	asthma
		opiates/opioids	analgesia potentiation, attenuation of withdrawal syndrome [117]	analgesia potentiation, suppression of craving, attenuation of withdrawal syndrome [118, 119]	
	apremilast	alcohol	suppression of intake [121]	suppression of intake [121]	psoriasis
PPARα and PPARγ agonists	fibrates, glitazones	alcohol	suppression of intake [125]	results regarding intake are inconsistent [126-128]	metabolic syndrome

main mediators of peripheral systems involved in the central biochemical mechanisms of substance use disorders. The comorbidity of somatic pathologies and chemical dependence, which is due to the existence of common biological mechanisms, can be the basis for the development and introduction into clinical practice of new effective tools of pharmacological correction. At the same time, potential repurposing of many drugs already used in the pharmacotherapy of addiction based on the existence of common pathogenetic mechanisms, can be fundamentally important, since it allows to reduce the stage of safety trials and introduce these drugs in a short time and with minimal funding into clinical practice for a new therapeutic application. The most promising pharmacological targets, whose involvement in the formation of drug dependence was described in this review, are summarized in Table 1.

PAS consumption is not necessarily comorbid with somatic pathologies, although it significantly increases the risk of developing such pathologies and *vice versa*. Creation of a high-tech methodological base for genotyping allows to analyze the data at a genome-wide level and makes possible identification of genetic and epigenetic markers of comorbid pathologies. This can be used in addiction medicine for identification of risk groups, prognostics and diagnostics, and identification of individuals responsive to pharmacotherapy [8].

Due to the science development, an incredibly large amount of experimental data have been accumulated, which determines the need for their analysis and creation of new concepts of physiological and pathological processes. Indeed, considering the multifactorial nature, polygeny, and pleiotropy of mediators involved in the mechanisms providing formation of pathological dependence, it seems that implementation of new effective therapeutic methods has no prospects. Nevertheless, modern tools of data analysis inspire some hope. For example, the use of integrative bioinformatic approaches has led to the identification of protein kinase mTOR (mammalian target of rapamycin) as one of the most promising targets in the treatment of addictions and repurposing of already approved drugs [152]. mTOR inhibitors are used in cancer chemotherapy. mTOR is a key molecule regulating fundamental physiological processes; there is also evidence of mTOR involvement in the mechanisms of PAS action [153].

Keeping with the general trend in modern medicine, drug treatment in addiction medicine should also use a personalized approach, in particular, include clinical examination of patients for detection of comorbid somatic diseases. It has been repeatedly noted that in order to increase the efficiency of treatment of substance use disorders, it is necessary to take into account somatic pathologies in the patient's anamnesis and to integrate therapeutic programs aimed at improving both mental and somatic health [21, 154].

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