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NEUROCHEMICAL ALTERATIONS DURING ALCOHOL WITHDRAWAL: A REVIEW OF BRAIN NEUROTRANSMITTER DYNAMICS

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ABSTRACT

Alcohol withdrawal syndrome (AWS) is a complex neurobiological condition that arises from the abrupt cessation or reduction of chronic alcohol consumption. This review comprehensively examines the neurochemical alterations in central neurotransmitter systems that underpin the clinical manifestations of AWS. Chronic alcohol exposure induces neuroadaptive changes in key systems, including γ-aminobutyric acid (GABA), glutamate, dopamine, serotonin, norepinephrine, corticotropin-releasing factor (CRF), the endocannabinoid system, endogenous opioids, and acetylcholine. During withdrawal, a shift toward excitatory dominance is observed, with reduced GABAergic inhibition and elevated glutamatergic transmission contributing to anxiety, seizures, and agitation. Concurrently, dysregulation in dopaminergic and serotonergic pathways results in affective disturbances such as depression, anhedonia, and irritability. Hyperactivity of the noradrenergic and CRF systems further exacerbates autonomic and stress-related symptoms. Additionally, deficits in endocannabinoid and opioid signaling compromise reward processing and stress regulation. This review also outlines pharmacological strategies targeting these systems, including both conventional treatments (e.g., benzodiazepines, acamprosate, naltrexone) and emerging therapies (e.g., cannabidiol, CRF1 antagonists, and plant-based agents). By integrating preclinical and clinical findings, this article highlights the importance of neurotransmitter-specific interventions in both acute withdrawal management and long-term relapse prevention, advocating for a more personalized and multi-targeted approach to treating alcohol use disorder.

KEYWORDS: Alcohol Withdrawal Syndrome, Neurotransmitters, GABA, Glutamate, Dopamine, Pharmacotherapy.

INTRODUCTION

Alcohol, commonly known as alcohol, is a central nervous system depressant that profoundly affects the brain's neurochemical architecture. Consumable alcohol refers primarily to ethanol (ethyl alcohol)**,** the only type safe for human consumption, found in beverages like beer, wine, and spirits. In contrast, non-consumable (toxic) alcohols include methanol**,** isopropanol**,** butanol, and denatured alcohol, which are used in industrial products, disinfectants, and fuels. These are highly toxic if ingested and can cause severe health effects such as blindness, organ failure, or death. Only ethanol intended for drinking should ever be consumed; all other forms of alcohol are dangerous. While acute alcohol intake primarily exerts sedative and anxiolytic effects through potentiation of inhibitory neurotransmission, chronic and excessive alcohol use leads to compensatory neuroadaptive changes that disrupt the delicate balance between excitatory and inhibitory systems in the brain. These changes form the neurobiological basis of dependence and withdrawal. Alcohol withdrawal syndrome (AWS) occurs when an individual with prolonged, high-dose alcohol exposure suddenly reduces or stops consumption. This abrupt cessation unmasks the neuroadaptive responses developed during chronic intake, leading to a hyperexcitable neural state. Clinically, AWS ranges from mild symptoms such as tremors, sweating, irritability, and insomnia to severe manifestations including hallucinations, seizures, and delirium tremens a potentially life-threatening condition.

According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), alcohol is the most commonly used substance in the United States, with over 75% of individuals aged 12 and older reporting lifetime consumption.[1] Withdrawal symptoms are very common in alcoholics. Manifestations of alcohol abstinence may vary from simple tremulousness to the most dramatic and severe form, with confusion, hallucinations, agitation,

and autonomic nervous system overactivity with delirium and tremens.[2] When untreated, patients with AUD experience frequently alcohol withdrawal syndrome (AWS). Severity of AUD is associated with increased risk of AWS, however this does not mean that all the patients with severe AUD will experience AWS after reduction or cessation.[3] AUDs are common in patients referred to neurological departments, admitted for coma, epileptic seizures, dementia, polyneuropathy, and gait disturbances.[4] In chronic alcohol users, glutamate neuromediation is over-activated (i.e. upregulation) in order to maintain a balance with the GABA activity that is increased by alcohol consumption. However, during the few hours after reduction or cessation of alcohol intake, there is an acute reduction of GABA activity creating an imbalance with glutamate activity. Thus, alcohol withdrawal symptoms occur as a result of subsequent glutamate overactivity.[5] Alcohol can modulate the activity of several neurotransmitter systems and signalling pathways. These effects can induce molecular and synaptic adaptations that over time, are consolidated in brain circuits that reinforce drug-seeking behavior, contribute to the development of withdrawal symptoms during abstinence and increase the susceptibility to relapse.[6] The neuropathology of AWS involves decreased GABA-A inhibitory function and increased glutamatergic excitatory activity leading to rebound hyper-neuroexcitability, irritability, and in some cases seizures.[7] Alcohol has been shown to affect a variety of different neurotransmitter systems. These include adenosine, glycine, acetylcholine, as well as monoamines and neuropeptides. Alcohol also exerts important effects on membranes, voltage-gated ion channels and second messenger systems. The interaction of alcohol with two major amino acid neurotransmitter systems, gaminobutyric acid (GABA) and excitant amino acids (EAAs) has received extensive interest in recent years.[8] The model of the neurochemical events of chronic exposure to alcohol will be AWS, which defines chemical dependence on this substance, contains common mechanisms such as the functional or pharmacodynamic tolerance and involves some of the processes which result in cognitive impairment of chronic alcoholics.[9] Alcohol alters the majority of the neurotransmission and neuromodulatory systems. Its action goes from a decrease or an increase in the concentration of the neurotransmitter due to changes in biosynthesis, degradation or transportation, to the desensitization or activation of its diverse receptors.[10] Alcohol, EtOH and its metabolites affect many central nervous system neurotransmitter systems e.g. γ - aminobutyric acid, GABA, glutamate, endogenous opioids and acetylcholine, with dopamine, DA, and endogenous opioids playing a major role.[11]

In these review, the properties of several neurotransmitter receptors were determined to look for possible changes in these neurotransmitter systems during alcohol administration and withdrawal.

PATHOPHYSIOLOGY OF AWS

To maintain homeostasis in the CNS, inhibitory signals from the GABAergic system are balanced by excitatory neurotransmitters such as glutamate. Alcohol, a CNS depressant, stimulates the GABAergic system and, in acute intoxication, causes a range of clinical manifestations such as disinhibition, euphoria, and sedation. The effect of alcohol in the acute setting is dose-dependent, with lower doses having a stimulating effect and higher doses having a sedating effect.[12] Chronic alcohol use results in neuroadaptive changes to the balance of GABA-glutamate by causing an upregulation of glutamate to compensate for alcohol-related increase in GABA. At the same time, endogenous GABA is downregulated.[13] Thus, when alcohol is withdrawn, a relative deficit of GABA may occur and simultaneous excess in glutamate, resulting in the excitatory symptoms seen in alcohol withdrawal syndrome.

Alcohol withdrawal syndrome exhibits a phenomenon known as kindling or sensitization, meaning successive withdrawal episodes tend to increase in severity, specifically concerning epileptic potential.[14] Repeated episodes of alcohol withdrawal syndrome lower the seizure threshold, making it more likely a person in withdrawal will experience a seizure. For those who have previously had alcohol-withdrawal seizures, their likelihood of experiencing another is quite high.[15]

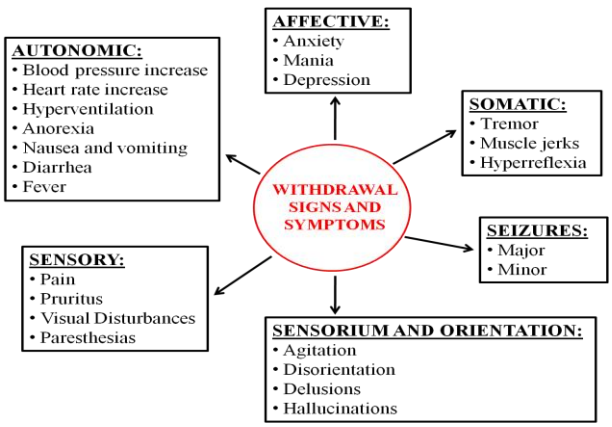

Figure 1: Withdrawal Signs and Symptoms.

ALTERATION IN BRAIN NEUROTRANSMITTERS LEVEL

Prolonged excessive alcohol consumption sets in motion a host of neuroadaptive changes initially triggered to compensate for, and mitigate effects of, continued presence of alcohol in the brain. This section will provide an overview of adaptations in a wide array of neurochemical and neuromodulatory systems associated with alcohol dependence, with particular emphasis on their relationship to various signs and symptoms of the alcohol withdrawal syndrome, as well as their postulated role in underlying enhanced relapse susceptibility and perpetuation of excessive, unhealthy alcohol consumption.

1. GABA

GABA acts through two receptor types: ionotropic $GABA_A$ and metabotropic $GABA_B$. Chronic alcohol exposure causes adaptive changes in GABAergic transmission, altering receptor subunit expression in a brain region- and subunit-specific manner. Notably, alcohol reduces α_1 and increases α_4 subunits of synaptic $GABA_A$ receptors, decreases tonic inhibition via containing extrasynaptic receptors, and diminishes inhibitory postsynaptic currents, contributing to neural hyperexcitability and withdrawal symptoms like anxiety. These changes are partly regulated by protein kinase C and clathrin-mediated endocytosis. Chronic alcohol exposure also alters $GABA_B$ receptor function, particularly presynaptically, reducing sensitivity in the central amygdale.[16, 17]

2. GLUTAMATE

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and Nmethyl-D-aspartate (NMDA) subtypes of glutamate receptors are among the most widely distributed and abundant receptors in the brain. AMPA receptors are heterotetramers comprising GluR1–4 subunits and mediate most fast synaptic neurotransmission. NMDA receptors are also heterotetramers and are composed of an obligatory GluN1 subunit coassembled with a least one type of regulatory GluN2A–D subunit. The majority of NMDA receptors in the adult brain are composed of GluN2A and GluN2B subunits. NMDA receptors mediate the slow component of excitatory postsynaptic potentials. Glutamate also operates at two metabotropic receptor subtypes: mGluR1-like (mGlur1 and mGluR5) and mGluR2-like (mGluR2, mGluR3, and mGluR4). Both ionotropic (AMPA and NMDA) and metabotropic (mGluRs) receptors have been implicated in a wide array of alcohol-associated phenotypes, including those related to dependence and withdrawal.

Chronic alcohol exposure leads to compensatory neuroadaptations that result in a hyperglutamatergic state in the brain, contributing to increased neurotoxicity, synaptic plasticity changes, and withdrawal symptoms like seizures.[18,19,20] This involves complex alterations in NMDA and AMPA receptor function, including increased synaptic GluN1/GluN2B NMDA receptors and GluN2B phosphorylation via Fyn kinase, enhancing receptor activity.[21,22,23] Additionally, AMPA receptor upregulation occurs in several brain regions, contributing to withdrawal-related anxiety[24,25] Imaging and microdialysis studies in both humans and animals show altered glutamate levels during dependence and withdrawal.[26,27,28,29] Dysregulation of mGluR2/3 and mGluR5 receptors also affects alcohol-seeking behavior.[30,31] Despite some promising findings, clinical outcomes with glutamate-modulating drugs like acamprosate and anticonvulsants remain mixed, indicating a need for further research.[32,33]

3. DOPAMINE

Dopamine plays a key role in alcohol addiction, particularly through the mesolimbic and mesocortical pathways that mediate reward.[34,35] It acts via D_1 and D_2 receptors, which have opposing effects on adenylate cyclase activity. Chronic alcohol use enhances dopamine neuron firing in the ventral tegmental area (VTA), increases extracellular dopamine in the nucleus accumbens,[36,37,38] and alters receptor function.[39,40] In contrast, withdrawal reduces VTA activity and dopamine levels in the striatum, potentially due to enhanced uptake.[41,42,43] This persistent hypodopaminergic state is linked to negative affect, dysphoria, and increased relapse risk.[44,45] Although dopamine antagonists may reduce craving, side effects limit their use.[46] Partial agonists have shown some efficacy,[47,48] possibly by stabilizing dopamine function during withdrawal and relapse.[49] Severe withdrawal symptoms such as delirium tremens may involve altered cortical dopamine activity.[50,51]

4. SEROTONIN

Serotonin, mainly synthesized in the raphe nuclei of the brainstem, projects extensively throughout the brain and regulates key functions such as mood, emotion, sleep, aggression, and appetite via multiple receptor subtypes. Although it does not directly mediate the physical symptoms of alcohol withdrawal, its role in emotional processing suggests it contributes to withdrawal-related dysphoria and alcohol-related motivation. Chronic alcohol use has been shown to lower serotonin levels in several brain areas, and this reduction is strongly linked with higher alcohol consumption.[52,53] Interestingly, alcohol reintroduction after withdrawal reverses serotonin deficits in the nucleus accumbens.[54]

5. NORADRENERGIC SYSTEM

The noradrenergic system, primarily mediated by neurons in the locus coeruleus, plays a significant role in the autonomic and behavioral manifestations of alcohol withdrawal syndrome (AWS). During chronic alcohol consumption, alcohol inhibits the firing of noradrenergic neurons, leading to compensatory upregulation of norepinephrine (NE) receptors and increased NE synthesis to maintain homeostasis.[55] However, upon abrupt cessation of alcohol intake, this adaptive balance

is disrupted, resulting in a rebound hyperactivity of the noradrenergic system. This overactivation leads to many of the characteristic symptoms of AWS, including tachycardia, hypertension, depression, tremors, anxiety, insomnia, and agitation.[56] Moreover, heightened noradrenergic activity stimulates the hypothalamic-pituitary-adrenal (HPA) axis, further exacerbating stress and anxiety-related behaviors during withdrawal.[57] The interaction between NE and other neurotransmitter systems, particularly glutamate and corticotropin-releasing factor (CRF), amplifies the hyperexcitable neural state seen during AWS.[58] Therefore, understanding the role of the noradrenergic system in AWS not only enhances our comprehension of withdrawal pathophysiology but also provides crucial insights into targeted pharmacotherapy aimed at improving clinical outcomes.

6. ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS), comprising endogenous ligands such as anandamide and 2-arachidonoylglycerol (2-AG), along with CB1 and CB2 receptors, plays a vital role in regulating synaptic plasticity, emotional behavior, and stress responses. Chronic alcohol exposure has been shown to disrupt ECS signaling, particularly through downregulation of CB1 receptors in the prefrontal cortex and limbic areas, which contributes to increased anxiety and dysphoria during withdrawal.[59] Moreover, alcohol withdrawal is associated with reduced endocannabinoid tone, leading to increased glutamatergic activity and stress sensitivity.[60] Preclinical studies suggest that enhancing endocannabinoid signaling, for instance through inhibition of fatty acid amide hydrolase (FAAH), can attenuate withdrawal-induced anxiety and reduce relapse-like behavior in animal models.[61]

7. OPIOID SYSTEM

The opioid system, which includes endogenous peptides such as endorphins, enkephalins, and dynorphins acting on μ-, δ-, and κ-opioid receptors, is intricately involved in alcohol's rewarding and reinforcing effects. Chronic alcohol consumption induces neuroadaptive changes in opioid receptor expression, particularly upregulation of dynorphin and κ-opioid receptor activity, which has been associated with negative affect and stress during withdrawal.[62] Dysregulation of the opioid system during withdrawal contributes to dysphoria, craving, and increasedf relapse vulnerability. Moreover, recent evidence suggests that selective κ-opioid receptor antagonists may alleviate withdrawal-related mood disturbances and are under investigation as novel treatments for alcohol use disorder.[63]

SUMMARY OF NEUROTRANSMITTER CHANGES DURING ALCOHOL WITHDRAWAL

Table 1: Summary of neurotransmitter changes in alcohol withdrawal.

Neurotransmitter System	Change During Withdrawal	Mechanism / Effect	Associated Symptoms	References
GABA (γ-Aminobutyric Acid)	↓ GABAergic tone	Downregulation of GABAA receptors; reduced α1, increased α4 subunits	Anxiety, seizures, insomnia, tremors	[16,17]
Glutamate (NMDA, AMPA)	↑ Glutamatergic activity	NMDA/AMPA receptor upregulation; GluN2B phosphorylation; increased excitatory tone	Seizures, excitotoxicity, agitation	[20,25,27]
Dopamine (DA)	↓ Mesolimbic DA activity	Reduced VTA firing; decreased NAc dopamine; hypodopaminergic tone	Dysphoria, anhedonia, depression	[41,45,43]
Norepinephrine (NE)	↑ NE release	Locus coeruleus hyperactivity; increased NE synthesis and receptor sensitivity	Hypertension, tachycardia, anxiety, sweating	[56,57]
Serotonin (5-HT)	↓ 5-HT transmission	Decreased 5-HT levels and receptor function; reversed by alcohol reintroduction	Irritability, depression, mood instability	[52,54]
Corticotropin-Releasing Factor (CRF)	↑ CRF levels	HPA axis dysregulation; increased stress and relapse risk	Anxiety, irritability, stress-related behavior	[71,58]
Endocannabinoids	↓ CB1 receptor activity	Downregulated CB1 in PFC/amygdala; reduced endocannabinoid tone	Mood instability, altered stress response	[59,61]
Endogenous Opioids	↓ β-endorphin and enkephalins	Blunted reward signaling; upregulation of dynorphin/κ receptors	Dysphoria, craving, reduced pain tolerance	[62,63]
Acetylcholine (ACh)	↑ ACh release (in cortex/ hippocampus)	Dysregulated cholinergic tone; related to delirium tremens	Delirium, confusion	[51]

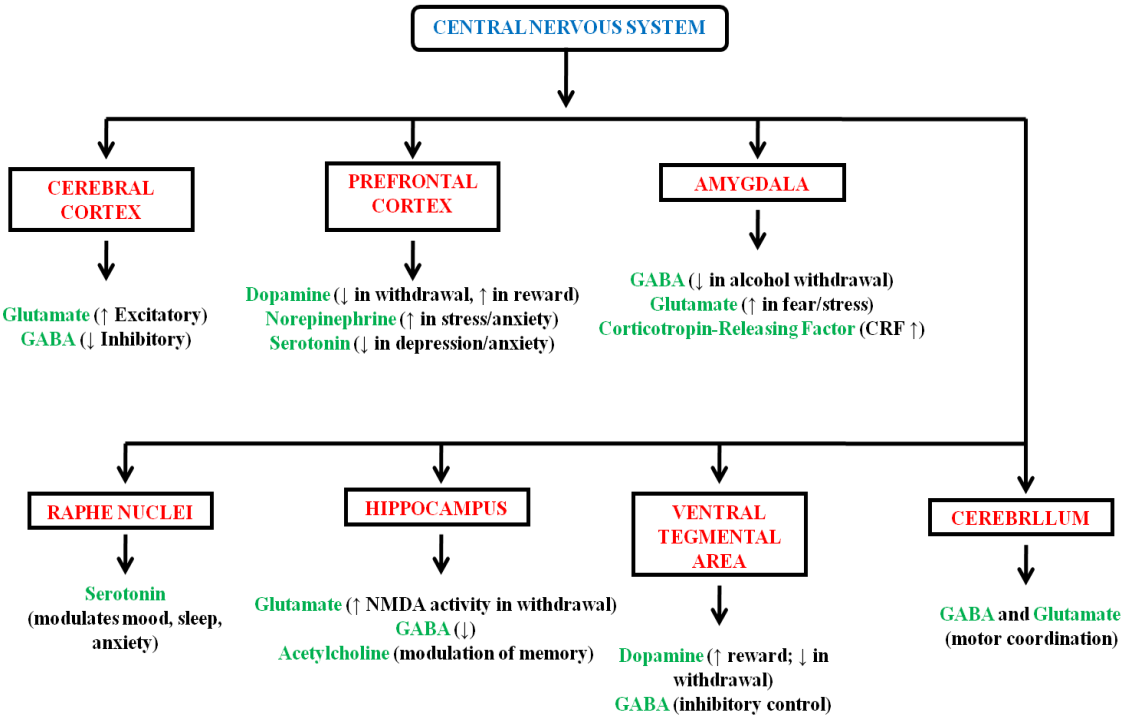

Figure 2: Schematic representation for CNS regions and affected neurotransmitters.

THERAPEUTIC AGENTS TARGETING SPECIFIC NEUROTRANSMITTER SYSTEMS

Table 2: Therapeutic agents targeting specific neurotransmitter systems.

Neurotransmitter System	Therapeutic Agent(s)	Mechanism of Action	Clinical Purpose / Effect	References
GABA (γ-Aminobutyric Acid)	Benzodiazepines (e.g., diazepam, lorazepam)	Positive allosteric modulators of $GABA_A$ receptors	Anxiolytic, anticonvulsant, sedation, prevent seizures	[50]
	Gabapentin, Pregabalin	Modulate GABA release and voltage-gated calcium channels	Reduce withdrawal severity, anxiety, insomnia	[33]
	Phenobarbital	Enhances GABAergic activity (barbiturate)	Anticonvulsant, used in severe withdrawal	[50]
Glutamate (NMDA)	Acamprosate	NMDA receptor antagonist; modulates glutamate-GABA balance	Maintains abstinence, reduces craving	[77]
	Memantine (experimental)	NMDA receptor antagonist	Potential to reduce excitotoxicity	[18]
Dopamine	Bupropion (off-label)	Norepinephrine and dopamine reuptake inhibitor (NDRI)	Manages dysphoria, may reduce craving	[53]
	Antipsychotics (e.g., haloperidol)	D2 receptor antagonism	Used in agitation or hallucinations	[51]
Norepinephrine (NE)	Clonidine, Dexmedetomidine	α2-adrenergic agonists; reduce sympathetic outflow	Reduce autonomic hyperactivity (BP, HR, sweating)	[70]
	Propranolol	Non-selective β-blocker	Controls tremor, tachycardia, anxiety	81]
Serotonin (5-HT)	SSRIs (e.g., fluoxetine, sertraline)	Increase synaptic 5-HT levels	Used for comorbid depression/anxiety (not for acute withdrawal)	[82]
CRF	CRF1 antagonists	Block CRF signaling	Potential to reduce	[71]

(Corticotropin-Releasing Factor)	(investigational)		stress-induced relapse	
Endocannabinoid	Cannabidiol (CBD) (investigational)	Modulates CB1 and CB2 receptors	May reduce anxiety, craving, and inflammation	[80]
Opioid System	Naltrexone	μ-opioid receptor antagonist	Reduces alcohol reward and relapse risk	[83]
Acetylcholine	Physostigmine (rare use)	Acetylcholinesterase inhibitor	May be used in managing delirium (rare, caution advised)	[51]

DISCUSSION

The neurochemical complexity of alcohol withdrawal syndrome (AWS) is best understood through the lens of translational research, particularly from well-validated animal models. Rodents exposed to chronic intermittent alcohol (CIE) via vapor inhalation or alcohol-containing liquid diets exhibit neurochemical and behavioral profiles that closely parallel human AWS, including heightened anxiety, seizures, and autonomic dysregulation.[64] These models not only replicate acute withdrawal features but also enable exploration of long-term neuroadaptations through protracted abstinence phases. Importantly, transgenic and knockout models targeting GABAA, NMDA, and CRF receptor systems have proven instrumental in dissecting the roles of individual neurotransmitters in both withdrawal and relapse.[65]

Behaviorally, these neurochemical changes manifest in predictable ways. The abrupt cessation of alcohol disrupts the homeostatic balance between inhibitory and excitatory neurotransmission. Chronic alcohol exposure enhances GABAergic tone and suppresses glutamatergic signaling; thus, withdrawal reverses this balance, leading to decreased GABA activity and unmasked glutamatergic hyperactivity both central drivers of withdrawal-related anxiety, seizures, and agitation.[66,67] Concurrent suppression of mesolimbic dopamine and serotonergic activity contributes to the dysphoric and depressive symptoms seen during withdrawal, which often persist into long-term abstinence.[68,69] Additionally, noradrenergic overdrive and elevated CRF levels in the hypothalamus and amygdala amplify stress responses, creating a neural environment primed for relapse.[70,71]

The impact of AWS on neurotransmitter systems is dynamic and evolves across temporal phases. During the acute phase (typically the first 72 hours post-cessation), the rapid dysregulation of GABA and glutamate systems results in life-threatening symptoms such as seizures and delirium tremens. In contrast, the protracted withdrawal phase, which can last for weeks or months, is characterized by lingering neurochemical imbalances that manifest as mood disorders, sleep disturbances, and persistent cravings.[72,73] Notably, even after outward symptoms subside, alterations in GABAA receptor expression, NMDA receptor function, and dopaminergic tone persist, highlighting the chronic neurobiological underpinnings of alcohol dependence.[74,75,76]

These findings support a growing consensus that treatment for AWS should extend beyond symptom suppression during acute detoxification. Conventional benzodiazepine therapy, while effective in preventing seizures, does not address long-term neurochemical recovery. Emerging pharmacotherapies that target specific neurotransmitter systems are therefore gaining attention. For instance, NMDA receptor antagonists such as acamprosate have shown efficacy in maintaining abstinence by stabilizing glutamatergic tone.[77] Similarly, GABA analogs like gabapentin and pregabalin offer benefits in managing protracted symptoms such as anxiety and insomnia, without the abuse potential associated with benzodiazepines.[78] Beyond these, CRF1 antagonists, kappa-opioid receptor blockers, and cannabidiol (CBD) are under investigation for their ability to modulate stress, reward, and mood-related circuits implicated in relapse.[79,80]

Overall, the persistence of neurotransmitter dysregulation after alcohol withdrawal underscores the importance of sustained, system-specific interventions. Predicted therapies for Alcohol Withdrawal Syndrome (AWS) now extend beyond conventional drugs to include plant-based extracts with neuroprotective and anxiolytic properties. Herbs like Ashwagandha**,** Bacopa monnieri**,** Passionflower**,** St. John's Wort, and Valerian show promise by modulating GABAergic, serotonergic, and glutamatergic systems involved in withdrawal symptoms. These plants may reduce anxiety, support mood, and restore neurotransmitter balance. Additionally, emerging agents such as GLP-1 agonists and epigenetic modulators (e.g., HDAC inhibitors) offer novel mechanisms to reduce cravings and relapse, suggesting a future for multi-targeted, holistic AWS treatment strategies. Continued integration of animal model findings with clinical research will be critical in refining our pharmacological strategies for AWS and long-term alcohol use disorder recovery.

CONCLUSION

Alcohol withdrawal syndrome (AWS) is a complex neuroadaptive response that results from the abrupt cessation or reduction of chronic alcohol intake. The syndrome is underpinned by profound alterations in central nervous system neurotransmission, particularly involving an imbalance between the inhibitory

GABAergic and excitatory glutamatergic systems. During prolonged alcohol exposure, the brain compensates for increased GABA activity and suppressed glutamate signaling by downregulating GABA receptors and upregulating glutamate receptors. Upon withdrawal, this adaptation leads to a relative deficiency in inhibitory signaling and an excess of excitatory neurotransmission—resulting in a hyperexcitable state associated with symptoms ranging from tremors and irritability to seizures and delirium tremens.

Beyond the GABA and glutamate systems, alcohol dependence also induces long-term neurochemical changes in dopaminergic and serotonergic circuits, both of which are essential to mood regulation, motivation, reinforcement, and relapse behavior. These changes not only contribute to the emotional and psychological symptoms experienced during withdrawal, such as anxiety and dysphoria, but also perpetuate the cycle of addiction by enhancing susceptibility to relapse.

Pharmacological interventions, including benzodiazepines, anticonvulsants, SSRIs, and newer agents targeting NMDA, AMPA, mGluR, and GABA receptor subtypes, offer varying degrees of effectiveness. However, individual variability in treatment response attributed to genetic polymorphisms, presence of co-occurring psychiatric disorders, and the severity of alcohol use disorder (AUD) poses significant challenges to standardized care. Additionally, the kindling phenomenon, whereby repeated withdrawals increase the severity of future episodes, underscores the importance of early intervention and prevention of recurrent detoxification cycles.

Imaging and neurochemical studies in both animals and humans have provided valuable insights into the brain regions and receptor systems affected by chronic alcohol exposure and withdrawal. These include the prefrontal cortex, nucleus accumbens, amygdala, hippocampus, and striatum regions implicated in decision-making, reward processing, memory, and emotional regulation. Understanding the region- and receptor-specific adaptations in these circuits may aid in the development of more targeted and effective treatments.

In conclusion, AWS is a dynamic and multifactorial condition that involves intricate neurobiological mechanisms affecting multiple neurotransmitter systems. The interplay between these systems contributes to both the acute withdrawal symptomatology and the long-term risk of relapse. Future research must continue to explore neurochemical pathways, genetic vulnerabilities, and personalized pharmacotherapeutic strategies to improve the treatment and prognosis of individuals with alcohol dependence. A holistic approach combining pharmacological, behavioral, and psychosocial interventions remains essential for successful management and recovery.

REFERENCES

1. Canver BR, Newman RK, Gomez AE. Alcohol Withdrawal Syndrome. [Updated 2024 Feb 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441882/
2. *Fever during alcohol withdrawal syndrome, Otero-Antón, E et al., European Journal of Internal Medicine, 10(2): 112 – 116.*
3. Johnson, B. A., Ait-Daoud, N., Akhtar, F. Z., & Ma, J.Z. Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. *Archives of general psychiatry*, 2004; *61*(9): 905–912. https://doi.org/10.1001/archpsyc.61.9.905
4. Jesse S, Bråthen G, Ferrara M, Keindl M, Ben-Menachem E, Tanasescu R, Brodtkorb E, Hillbom M, Leone MA, Ludolph AC. Alcohol withdrawal syndrome: mechanisms, manifestations, and management. Acta Neurol Scand, Jan. 2017; 135(1): 4-16. doi: 10.1111/ane.12671. Epub 2016 Sep 1. PMID: 27586815; PMCID: PMC6084325.
5. Airagnes G, Ducoutumany G, Laffy-Beaufils B, Le Faou AL, Limosin F. Alcohol withdrawal syndrome management: Is there anything new? Rev Med Interne, Jun. 2019; 40(6): 373-379. doi: 10.1016/j.revmed.2019.02.001. Epub 2019 Mar 7. PMID: 30853380.
6. Klenowski PM, Tapper AR. Molecular, Neuronal, and Behavioral Effects of Ethanol and Nicotine Interactions. Handb Exp Pharmacol, 2018; 248: 187-212. doi: 10.1007/164_2017_89. PMID: 29423839.
7. Das SC, Althobaiti YS, Alshehri FS, Sari Y. Binge ethanol withdrawal: Effects on post-withdrawal ethanol intake, glutamate-glutamine cycle and monoamine tissue content in P rat model. Behav Brain Res., Apr. 15, 2016; 303: 120-5. doi: 10.1016/j.bbr.2016.01.052. Epub 2016 Jan 25. PMID: 26821293; PMCID: PMC4779422.
8. C.L Faingold, P N'Gouemo, A Riaz, Ethanol and neurotransmitter interactions—from molecular to integrative effects, Progress in Neurobiology, 1998; 55(5): 509-535, ISSN 0301-0082, https://doi.org/10.1016/S0301-0082(98)00027-6. (https://www.sciencedirect.com/science/article/pii/S0301008298000276)
9. Zaleski, M., Morato, G. S., Silva, V. A. D., & Lemos, T. Neuropharmacological aspects of chronic alcohol use and withdrawal syndrome. *Brazilian Journal of Psychiatry*, 2004; *26:* 40-42.
10. Brailowsky S, García O. Ethanol, GABA and epilepsy. Arch Med Res., Jan-Feb, 1999; 30(1): 3-9. doi: 10.1016/s0188-0128(98)00013-x. PMID: 10071417.
11. Dahchour A, Ward RJ. Changes in Brain Dopamine Extracellular Concentration after Ethanol Administration; Rat Microdialysis Studies. Alcohol Alcohol, Mar. 12, 2022; 57(2): 165-175. doi: 10.1093/alcalc/agab072. PMID: 34693981.

12. Egervari G, Siciliano CA, Whiteley EL, Ron D. Alcohol and the brain: from genes to circuits. Trends Neurosci, Dec. 2021; 44(12): 1004-1015. [PMC free article] [PubMed]
13. Cohen SM, Alexander RS, Holt SR. The Spectrum of Alcohol Use: Epidemiology, Diagnosis, and Treatment. Med Clin North Am., Jan. 2022; 106(1): 43-60. [PubMed]
14. The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. J Addict Med., May/Jun., 2020; 14(3S,1): 1-72. [PubMed]
15. Ballenger JC, Post RM. Kindling as a model for alcohol withdrawal syndromes. Br J Psychiatry, Jul. 1978; 133: 1-14. [PubMed]
16. Olsen, R. W., & Liang, J. Role of GABA A receptors in alcohol use disorders suggested by chronic intermittent ethanol (CIE) rodent model. *Molecular brain*, 2017; *10:* 1-20.
17. Follesa, P., Biggio, F., Talani, G., Murru, L., Serra, M., Sanna, E., & Biggio, G. Neurosteroids, GABA A receptors, and ethanol dependence. *Psychopharmacology*, 2006; *186:* 267-280.
18. Shi, Q., Guo, L., Patterson, T. A., Dial, S., Li, Q., Sadovova, N., Zhang, X., Hanig, J. P., Paule, M. G., Slikker, W., Jr, & Wang, C. Gene expression profiling in the developing rat brain exposed to ketamine. *Neuroscience*, 2010; *166*(3): 852–863. https://doi.org/10.1016/j.neuroscience.2010.01.007
19. Henriques, J. F., Portugal, C. C., Canedo, T., Relvas, J. B., Summavielle, T., & Socodato, R. Microglia and alcohol meet at the crossroads: Microglia as critical modulators of alcohol neurotoxicity. *Toxicology letters*, 2018; *283:* 21–31. https://doi.org/10.1016/j.toxlet.2017.11.002
20. Gass, J. T., & Olive, M. F. Glutamatergic substrates of drug addiction and alcoholism. *Biochemical Pharmacology*, 2008; 75(1): 218–265.
21. Mulholland, P. J., & Chandler, L. J. The thorny side of addiction: Adaptive plasticity and dendritic spines. *ScientificWorldJournal*, 2007; 7: 9–21.
22. Miyakawa, T., Leiter, L. M., Gerber, D. J., Gainetdinov, R. R., Sotnikova, T. D., Zeng, H., Caron, M. G., & Tonegawa, S. Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, 2003; *100*(15): 8987–8992. https://doi.org/10.1073/pnas.1432926100
23. Yaka, R., Thornton, C., Vagts, A. J., Phamluong, K., Bonci, A., & Ron, D. NMDA receptor function is regulated by the inhibitory scaffolding protein, RACK1. *Proceedings of the National Academy of Sciences of the United States of America*, 2002; *99*(8): 5710–5715. https://doi.org/10.1073/pnas.062046299
24. Läck, A. K., Christian, D. T., Diaz, M. R., & McCool, B. A. Chronic ethanol and withdrawal effects on kainate receptor-mediated excitatory neurotransmission in the rat basolateral amygdala. *Alcohol (Fayetteville, N.Y.)*, 2009; *43*(1): 25–33. https://doi.org/10.1016/j.alcohol.2008.11.002.
25. Wang, J., Lanfranco, M. F., Gibb, S. L., Yowell, Q. V., Carnicella, S., & Ron, D. Long-lasting adaptations of the NR2B-containing NMDA receptors in the dorsomedial striatum play a crucial role in alcohol consumption and relapse. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, 2010; *30*(30): 10187–10198. https://doi.org/10.1523/JNEUROSCI.2268-10.2010
26. Gazdzinski, S., Durazzo, T. C., Yeh, P. H., Hardin, D., Banys, P., & Meyerhoff, D. J. Chronic cigarette smoking modulates injury and short-term recovery of the medial temporal lobe in alcoholics. *Psychiatry research*, 2008; *162*(2): 133–145. https://doi.org/10.1016/j.pscychresns.2007.04.003
27. Hermann, D., Weber-Fahr, W., Sartorius, A., Frischknecht, U., Hoerst, M., Tunc-Skarka, N., ... & Mann, K. Translational magnetic resonance spectroscopy reveals excessive central glutamate levels during alcohol withdrawal in humans and rats. *Biological Psychiatry*, 2012; 71(11): 1015–1021.
28. Zahr, N. M., Mayer, D., Rohlfing, T., Hasak, M., Hsu, O., Vinco, S., ... & Sullivan, E. V. Brain injury and recovery following binge ethanol: Evidence from in vivo MR spectroscopy. *Biological Psychiatry*, 2009; 67(9): 846–854.
29. Kapasova, Z., & Szumlinski, K. K. Rapid kindling of behavioral and neurochemical signs of alcohol dependence in mice. *Neuropsychopharmacology*, 2008; 33(2): 421–434.
30. Sidhpura, N., Weiss, F., & Martin-Fardon, R. Effects of the mGlu2/3 agonist LY379268 and the mGlu5 antagonist MTEP on ethanol seeking and reinforcement are differentially altered in rats with a history of ethanol dependence. *Biological psychiatry*, 2010; *67*(9): 804–811. https://doi.org/10.1016/j.biopsych.2010.01.005
31. Meinhardt, M. W., Hansson, A. C., Perreau-Lenz, S., Bauder-Wenz, C., Stählin, O., Heilig, M., ... & Spanagel, R. Rescue of infralimbic mGluR2 deficit restores control over drug-seeking behavior in alcohol dependence. *Journal of Neuroscience*, 2013; 33(7): 2794–2806.
32. Mann, K., Kiefer, F., Spanagel, R., & Littleton, J. Acamprosate: recent findings and future research directions. *Alcoholism, clinical and experimental research*, 2008; *32*(7): 1105–1110. https://doi.org/10.1111/j.1530-0277.2008.00690.x
33. Mason, B. J., Quello, S., Goodell, V., Shadan, F., Kyle, M., & Begovic, A. Gabapentin treatment for alcohol dependence: A randomized clinical trial. *JAMA Internal Medicine*, 2014; 174(1): 70–77.
34. Gonzales, R. A., Job, M. O., & Doyon, W. M. The role of mesolimbic dopamine in the development and maintenance of ethanol reinforcement. *Pharmacology & Therapeutics*, 2004; 103(2): 121–146.

35. Spanagel, R. Alcoholism: A systems approach from molecular physiology to addictive behavior. *Physiological Reviews*, 2009; 89(2): 649–705.
36. Samantha G. Malone, Jakob D. Shaykin, Dustin J. Stairs, Michael T. Bardo, Neurobehavioral effects of environmental enrichment and drug abuse vulnerability: An updated review, Pharmacology Biochemistry and Behavior, 2022; 221: 173471, ISSN 0091-3057, https://doi.org/10.1016/j.pbb.2022.173471.
37. Ary, A. W., Cozzoli, D. K., Finn, D. A., Crabbe, J. C., Dehoff, M. H., Worley, P. F., & Szumlinski, K. K. Ethanol up-regulates nucleus accumbens neuronal activity dependent pentraxin (Narp): implications for alcohol-induced behavioral plasticity. *Alcohol (Fayetteville, N.Y.)*, 2012; *46*(4): 377–387. https://doi.org/10.1016/j.alcohol.2011.10.003
38. Thielen, R. J., Engleman, E. A., Rodd-Henricks, Z. A., Lumeng, L., Li, T. K., & McBride, W. J. Ethanol drinking and deprivation alter dopaminergic and serotonergic function in the nucleus accumbens of alcohol-preferring rats. *Journal of Pharmacology and Experimental Therapeutics*, 2004; 309(3): 216–225.
39. Liu, X., & Weiss, F. Additive effect of stress and drug cues on reinstatement of ethanol seeking: Exacerbation by history of dependence and role of concurrent activation of corticotropin-releasing factor and opioid mechanisms. *Journal of Neuroscience*, 2002; 22(18): 7856–7861.
40. Zald D. H. The influence of dopamine autoreceptors on temperament and addiction risk. *Neuroscience and biobehavioral reviews*, 2023; *155:* 105456. https://doi.org/10.1016/j.neubiorev.2023.105456
41. Diana, M., Pistis, M., Carboni, S., Gessa, G. L., & Rossetti, Z. L. Profound decrement of mesolimbic dopaminergic neuronal activity during ethanol withdrawal syndrome in rats: electrophysiological and biochemical evidence. *Proceedings of the National Academy of Sciences of the United States of America*, 1993; *90*(17): 7966–7969. https://doi.org/10.1073/pnas.90.17.7966
42. Budygin, E. A., Oleson, E. B., Mathews, T. A., Läck, A. K., Diaz, M. R., McCool, B. A., & Jones, S. R. Effects of chronic alcohol exposure on dopamine uptake in rat nucleus accumbens and caudate putamen. *Psychopharmacology*, 2007; *193*(4): 495–501. https://doi.org/10.1007/s00213-007-0812-1
43. Barak, S., Carnicella, S., Yowell, Q. V., & Ron, D. Glial cell line-derived neurotrophic factor reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: Implications for alcohol reward and seeking. *Journal of Neuroscience*, 2011; 31(27): 9885–9894.
44. Diana, M. The dopamine hypothesis of drug addiction and its potential therapeutic value. *Frontiers in Psychiatry*, 2011; 2: 64.
45. Weiss, F., & Porrino, L. J. Behavioral neurobiology of alcohol addiction: recent advances and challenges. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, 2002; *22*(9): 3332–3337. https://doi.org/10.1523/JNEUROSCI.22-09-03332.2002
46. Swift R. M. Medications and alcohol craving. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*, 1999; *23*(3): 207–213.
47. Anton, R. F., Kranzler, H., Breder, C., Marcus, R. N., Carson, W. H., & Han, J. A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. *Journal of Clinical Psychopharmacology*, 2008a; 28(1): 5–12.
48. Kranzler, H. R., Armeli, S., Tennen, H., Covault, J., Feinn, R., Arias, A. J., & Oncken, C. A double-blind, randomized placebo-controlled trial of aripiprazole for the treatment of alcohol dependence. *Journal of Clinical Psychopharmacology*, 2008; 28(5): 531–536.
49. Myrick, H., Li, X., Randall, P. K., Henderson, S., Voronin, K., & Anton, R. F. The effect of aripiprazole on cue-induced brain activation and drinking parameters in alcoholics. *Journal of clinical psychopharmacology*, 2010; *30*(4): 365–372. https://doi.org/10.1097/JCP.0b013e3181e75cff.
50. Mayo-Smith, M. F. Pharmacological management of alcohol withdrawal: A meta-analysis and evidence-based practice guideline. *JAMA*, 1997; 278(2): 144–151.
51. Mainerova, B., Prasko, J., Latalova, K., Axmann, K., Cerna, M., Horacek, R., & Bradacova, R. Alcohol withdrawal delirium - diagnosis, course and treatment. *Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia*, 2015; *159*(1): 44–52. https://doi.org/10.5507/bp.2013.089
52. Murphy, J. M., Stewart, R. B., Bell, R. L., Badia-Elder, N. E., Carr, L. G., & McBride, W. J. Phenotypic and genotypic characterization of P rats and HAD rats. *Alcoholism: Clinical and Experimental Research*, 2002; 26(12): 1913–1922.
53. Donato, S., & Ray, L. A. Neurobiology and the Treatment of Alcohol Use Disorder: A Review of the Evidence Base. *Substance abuse and rehabilitation*, 2023; *14:* 157–166. https://doi.org/10.2147/SAR.S409943.
54. Weiss, F., Parsons, L. H., Schulteis, G., Hyytiä, P., Lorang, M. T., Bloom, F. E., & Koob, G. F. Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. *Journal of Neuroscience*, 1996; 16(10): 3474–3485.
55. Kushner, M. G., Abrams, K., & Borchardt, C. The relationship between anxiety disorders and alcohol use disorders: A review of major perspectives and

findings. *Clinical Psychology Review*, 2000; 20(2): 149–171. https://doi.org/10.1016/S0272-7358(99)00027-6
56. Becker, H. C. Alcohol dependence, withdrawal, and relapse. *Alcohol Research & Health*, 2008; 31(4): 348–361.
57. Valdez, G. R., & Koob, G. F. Allostasis and dysregulation of corticotropin-releasing factor and neuropeptide Y systems: Implications for the development of alcoholism. *Pharmacology Biochemistry and Behavior*, 2004; 79(4): 671–689. https://doi.org/10.1016/j.pbb.2004.09.027
58. Koob, G. F., & Volkow, N. D. Neurocircuitry of addiction. *Neuropsychopharmacology*, 2010; 35(1): 217–238. https://doi.org/10.1038/npp.2009.110
59. Pava, M. J., & Woodward, J. J. A review of the interactions between alcohol and the endocannabinoid system: Implications for alcohol dependence and future directions for research. *Alcohol*, 2012; 46(3): 185–204. https://doi.org/10.1016/j.alcohol.2012.01.002
60. Parsons, L. H., & Hurd, Y. L. Endocannabinoid signaling in reward and addiction. *Nature Reviews Neuroscience*, 2015; 16(10): 579–594. https://doi.org/10.1038/nrn4004
61. Stopponi, S., Fotio, Y., Domi, A., Borruto, A. M., Natividad, L., Roberto, M., Ciccocioppo, R., & Cannella, N. Inhibition of fatty acid amide hydrolase in the central amygdala alleviates co-morbid expression of innate anxiety and excessive alcohol intake. *Addiction biology*, 2018; *23*(6): 1223–1232. https://doi.org/10.1111/adb.12573
62. Walker, B. M., Zorrilla, E. P., & Koob, G. F. Systemic κ-opioid receptor antagonism by nor-binaltorphimine reduces dependence-induced excessive alcohol self-administration in rats. *Addiction biology*, 2011; *16*(1): 116–119. https://doi.org/10.1111/j.1369-1600.2010.00226.x
63. Chavkin, C., & Koob, G. F. Dynorphin, Dysphoria, and Dependence: the Stress of Addiction. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*, 2016; *41*(1): 373–374. https://doi.org/10.1038/npp.2015.258
64. Heilig, M., Egli, M., Crabbe, J. C., & Becker, H. C. Acute withdrawal, protracted abstinence and negative affect in alcoholism: Are they linked? *Addiction Biology*, 2010; 15(2): 169–184. https://doi.org/10.1111/j.1369-1600.2009.00194.x
65. Koob, G. F., & Volkow, N. D. Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry*, 2016; 3(8): 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8
66. Littleton, J. Neurochemical mechanisms underlying alcohol withdrawal. *Alcohol Health and Research World*, 1998; 22(1): 13–24.
67. Crews, F. T., & Nixon, K. Mechanisms of neurodegeneration and regeneration in alcoholism. *Alcohol and Alcoholism*, 2009; 44(2): 115–127. https://doi.org/10.1093/alcalc/agn079
68. Diana, M., Pistis, M., Carboni, S., Gessa, G. L., & Rossetti, Z. L. Profound decrement of mesolimbic dopaminergic neuronal activity during ethanol withdrawal syndrome in rats: Electrophysiological and biochemical evidence. *PNAS*, 1993; 90(19): 7966–7969. https://doi.org/10.1073/pnas.90.19.7966
69. LeMarquand, D. G., Pihl, R. O., & Benkelfat, C. Serotonin and alcohol intake, abuse, and dependence: Clinical evidence. *Biological Psychiatry*, 1994; 36(5): 326–337. https://doi.org/10.1016/0006-3223(94)90617-3
70. Mark S. Gold, Kenneth Blum, Abdalla Bowirrat, Albert Pinhasov, Debasis Bagchi, Catherine A. Dennen, Panayotis K. Thanos, Colin Hanna, Kai-Uwe Lewandrowski, Alireza Sharafshah, Igor Elman, Rajendra D. Badgaiyan. A historical perspective on clonidine as an alpha-2A receptor agonist in the treatment of addictive behaviors: Focus on opioid dependence. *INNOSC Theranostics and Pharmacological Sciences*, 2024; 7(3): 1918. https://doi.org/10.36922/itps.1918
71. Valdez, G. R., Roberts, A. J., Chan, K., Davis, H., Brennan, M., & Zorrilla, E. P. Increased ethanol self-administration and anxiety-like behavior during acute withdrawal and protracted abstinence: Regulation by corticotropin-releasing factor. *Alcoholism: Clinical and Experimental Research*, 2002; 26(10): 1494–1501. https://doi.org/10.1097/00000374-200210000-00007
72. Koob, G. F. Alcoholism: Allostasis and beyond. *Alcoholism: Clinical and Experimental Research*, 2003; 27(2): 232–243. https://doi.org/10.1097/01.ALC.0000057122.36127.C2
73. Sinha, R. Chronic stress, drug use, and vulnerability to addiction. *Annals of the New York Academy of Sciences*, 2008; 1141(1): 105–130. https://doi.org/10.1196/annals.1441.030
74. Charlton, M. E., Sweetnam, P. M., & Fitzgerald, L. W. Chronic ethanol administration regulates GABAA and NMDA receptor subunit mRNA expression in rat brain. *Alcoholism: Clinical and Experimental Research*, 1997; 21(8): 1506–1512. https://doi.org/10.1111/j.1530-0277.1997.tb04201.x
75. Floyd, R. A., & Carney, J. M. Free radical damage to protein and DNA: mechanisms involved and relevant observations on brain undergoing oxidative stress. *Annals of neurology*, 1992; *32:* S22–S27. https://doi.org/10.1002/ana.410320706
76. Melis, M., Camarini, R., Ungless, M. A., & Bonci, A. Long-lasting potentiation of GABAergic synapses in dopamine neurons after a single in vivo ethanol exposure. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 2002; *22*(6): 2074–2082. https://doi.org/10.1523/JNEUROSCI.22-06-02074.2002
77. Mason, B. J., Goodman, A. M., Chabac, S., & Lehert, P. Effect of oral acamprosate on abstinence

in patients with alcohol dependence in a double-blind, placebo-controlled trial. *JAMA*, 2006; 296(5): 633–641. https://doi.org/10.1001/jama.296.5.633

78. Myrick, H., Anton, R., Voronin, K., Wang, W., & Henderson, S. A double-blind evaluation of gabapentin on alcohol effects and drinking in a clinical laboratory paradigm. *Alcoholism, clinical and experimental research*, 2007; *31*(2): 221–227. https://doi.org/10.1111/j.1530-0277.2006.00299.x
79. Zorrilla, E. P., Valdez, G. R., & Weiss, F. Changes in levels of regional CRF-like-immunoreactivity and plasma corticosterone during protracted drug withdrawal in dependent rats. *Psychopharmacology*, 2001; *158*(4): 374–381. https://doi.org/10.1007/s002130100773
80. Turner, S. E., Williams, C. M., Iversen, L., & Whalley, B. J. Molecular Pharmacology of Phytocannabinoids. *Progress in the chemistry of organic natural products*, 2017; *103:* 61–101. https://doi.org/10.1007/978-3-319-45541-9_3
81. Petrakis, I. L., Desai, N., Gueorguieva, R., Arias, A., O'Brien, E., Jane, J. S., Sevarino, K., Southwick, S., & Ralevski, E. Prazosin for Veterans with Posttraumatic Stress Disorder and Comorbid Alcohol Dependence: A Clinical Trial. *Alcoholism, clinical and experimental research*, 2016; *40*(1): 178–186. https://doi.org/10.1111/acer.12926
82. Pettinati, H. M., Oslin, D. W., Kampman, K. M., Dundon, W. D., Xie, H., Gallis, T. L., & O'Brien, C. P. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *American Journal of Psychiatry*, 2010; 167(6): 668–675.
83. Johnson, B. A., & Ait-Daoud, N. Neuropharmacological treatments for alcoholism: Scientific basis and clinical findings. *Psychopharmacology*, 2000; 149(4): 327–344.