International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 16, Issue 6, 2024

Review Article

ADVANCEMENTS IN UNDERSTANDING AND MANAGING ALCOHOL WITHDRAWAL SYNDROME: A COMPREHENSIVE REVIEW

AJEET PAL SINGH[1,2*], ASHISH KUMAR SHARMA[1], THAKUR GURJEET SINGH[3]

[1]NIMS Institute of Pharmacy, NIMS University, Jaipur-303121, Rajasthan, India and St. Soldier Institute of Pharmacy, Jalandhar-144011, Punjab, India. [2]NIMS Institute of Pharmacy, NIMS University, Jaipur-303121, Rajasthan, India. [3]Chitkara College of Pharmacy, Chitkara University, Punjab, 140401, India

*Corresponding author: Ajeet Pal Singh; *Email: ajeetakarpuria@gmail.com

Received: 05 Sep 2024, Revised and Accepted: 20 Oct 2024

ABSTRACT

Alcohol withdrawal syndrome (AWS) is a clinically significant condition that can arise upon abrupt cessation or reduction of alcohol consumption in individuals with alcohol dependence. This review article provides a comprehensive overview of AWS, encompassing its epidemiology, pathophysiology, clinical manifestations, assessment tools, and management strategies. We discuss the neurobiological mechanisms underlying AWS, including the role of neurotransmitter systems such as gamma-aminobutyric acid (GABA) and glutamate, as well as neuroadaptive changes that occur with chronic alcohol use. Furthermore, we explore the spectrum of clinical manifestations associated with AWS, ranging from mild withdrawal symptoms to severe complications such as delirium tremens and seizures. Diagnostic tools and scoring systems commonly used for assessing AWS severity are examined, along with evidence-based approaches for pharmacological and non-pharmacological management of AWS. Additionally, we highlight emerging research areas and future directions in the field of AWS, including novel treatment modalities and potential biomarkers for predicting withdrawal severity and treatment response. This comprehensive review aims to provide clinicians, researchers, and healthcare professionals with a thorough understanding of AWS to facilitate early recognition, appropriate management, and improved outcomes for individuals affected by this condition.

Keywords: Alcohol withdrawal syndrome, Alcohol dependence, Neurobiological mechanisms, Management strategies and Pharmacological treatment

DOI: https://dx.doi.org/10.22159/ijcpr.2024v16i6.5024 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Alcoholism is an obsession characterized by a chronic dependency on alcohol. Alcoholism is the reason behind family and work problems and can also cause serious health problems such as liver diseases [1]. Alcoholism is taking an increasing toll on the world's population [2]. Globally, harmful use of alcohol causes approximately 3.3 million deaths every year (5.9% of all deaths), and 5.1% of the global burden of disease is attributable to alcohol consumption. It causes more than 60 different disorders and is the third most important risk factor for the global burden of disease. Estimated number of alcohol users in India, in 2005 was 62.5 million, 17% of them being dependent users, accounting for 20%–30% of hospital admissions due to alcohol-related problems [3]. Due to overuse of alcohol arises Alcohol Dependence Syndrome (ADS). It is one of the most common psychiatric disorders, is associated with both physiological symptoms, such as tolerance and withdrawal and behavioural symptoms such as impaired control over drinking [4]. When an alcohol-dependent individual abruptly terminates or substantially reduces his or her alcohol consumption, a characteristic withdrawal syndrome ensues [5]. AWS (Alchol withdrawal Syndrome) show cluster of symptoms which occur in alcohol-dependent people after cessation or reduction in heavy or prolonged alcohol use [4]. AWS consists of symptoms and signs arising typically within few hours of consumption of their last drink and occur neurobiological changes [6].

The alcohol withdrawal syndrome

Withdrawal stands at the core of alcohol dependence. The alcohol withdrawal syndrome is a complex set of symptoms occurring in alcohol-dependent patients after alcohol cessation. It involves a wide range of brain neurotransmitters implicated in the development of alcohol tolerance and reflects a homeostatic readjustment of the CNS [7]. Signs and symptoms that typically develops in alcohol dependent people within 6–24 h of their last drink [8]. The common AWS noted in patients presenting to clinics are anxiety, tremors of body and hands, elevated blood pressure, tachycardia, insomnia, elevated body temperature, sweating, hallucinations, dilated pupils nausea, disorientation, irritability, headache and grand mal seizure [9].

The first consists of those of autonomic hyperactivity, which appears within hours of the last drink and usually peak within 24–48 h. The most common features are tremulousness, sweating, nausea, vomiting, anxiety, and agitation. The second set of symptoms is those of neuronal excitation, which include epileptic form seizures (usually grand mal) that usually occur within 12–48 h of abstinence.

The third set of symptoms comprises delirium tremens (or alcohol withdrawal delirium), which develops in a very few cases; it is characterised by auditory and visual hallucinations, confusion and disorientation, clouding of consciousness, impaired attention, and pronounced autonomic hyperactivity. If untreated, death may occur from respiratory and cardiovascular collapse [10].

Table 1: Common sign and symptoms of alcohol withdrawal syndrome

Time of appearance after cessation of alcohol use	Symptoms
Within 24 h	Tachycardia, sweating, tremor, hypertension, anxiety and agitation
24 to 48 h	Epileptic seizures
48 to 72 h	Auditory and visual hallucinations, confusion and disorientation. It can lead to death from respiratory and cardiovascular collapse.

Prevalence

The Global Information System on Alcohol and Health is an essential tool for assessing and monitoring the health situation and trends related to alcohol consumption, alcohol-related harm, and policy responses in countries [11].

The prevalence of alcohol withdrawal in the general population is low (5% in US adults in 1995), but is higher among those admitted for detoxification and rehabilitation for alcohol abuse (up to 86%).1 In a UK national survey conducted in 2002, 38% of male respondents and 23% of female respondents self-reported hazardous drinking (5 or more drinks for a man or 3 or more drinks for a woman) on a typical drinking day. However, in the setting of medical practice, this fig. is higher, with the prevalence of alcohol abuse or dependence reaching 20% of hospital inpatients and up to 40% of patients attending Accident and Emergency departments.4 The cost of alcoholism is a large burden on the UK economy and was estimated to cost the NHS £1.5 billion in 2000/2001, with 1 in every 26 hospital bed days being attributable to some degree of alcohol misuse. Despite this substantial problem, a survey of NHS general hospitals conducted in 2000 and 2003 indicated that only 12.8% had a dedicated alcohol worker. In addition, few guidelines exist promoting the initiation of clear and uniform AWS treatment protocols [6].

Clinical descriptions of alcohol withdrawal syndromes by severity [12]

AWS, or alcohol withdrawal syndrome, typically manifests a cluster of symptoms within 1 to 3 d after the last alcoholic drink. In some cases, these symptoms may appear even when the blood alcohol level is above 0.5‰ or higher.

Table 2: Different types of symptoms seen in patient with alcohol consumption

Autonomic symptoms	Motor symptoms	Awareness symptoms	Psychiatric symptoms
Tachycardia	Hand tremor	Insomnia	Illusions
Tachypnea	Tremulousness of body	Agitation	Delusions
Dilated pupils	Seizures	Irritability	Hallucinations
Elevated blood pressure	Ataxia	Delirium	Paranoid ideas
Elevated body temperature	Gait disturbances	Disorientation	Anxiety
Diaphoresis	Hyperreflexia	-	Affective instability
Nausea/vomiting	Dysarthria	-	Combativeness
Diarrhea	-	-	Disinhibition

Pathophysiology of alcohol withdrawal syndrome

Alcohol affects the way in which nerve cells communicate [13] and also show effects on multiple neurotransmitter systems in brain like:-amino butyric acid (GABA) which is major inhibitory neurotransmitter, glutamate is the major excitatory neurotransmitter and other are dopaminergic transmission and noradrenergic transmission [14] and these all neurotransmitters are effected due to prolonged alcohol intoxication, so pathophysiology of alcohol withdrawal is complex [14]. Alcohol/Ethanol act as a CNS depressant that produces euphoria and behavioral excitation at low blood concentrations due to increased glutamate binding to N-methyl-D-aspartate (NMDA) receptors; at higher concentrations, it leads to acute intoxication by potentiation of the gamma-aminobutyric acid (GABA) effects [15]. Due to Chronic excessive use of alcohol disrupts all the balance of activity of the neurotransmitters gamma-aminobutyric acid (GABA) and glutamate (Dana Bartlett). Because of the importance of these neurotransmitters to the pathophysiology of alcohol withdrawal, they are discussed here in detail [16].

GABA system

Gamma-aminobutyric acid (GABA) is one of the primary inhibitory neurotransmitter in the central nervous system [16] that helps to regulate brain function by rendering nerve cells less sensitive to further signalling [13]. The binding of GABA to GABA receptors increases the flow of chloride ions into the cell, hyperpolarizing the membrane and decreasing a cell's responsiveness to stimulation. Gamma-aminobutyric acid receptor complexes have binding sites for GABA but also for drugs such as barbiturates and benzodiazepines and possibly for alcohol, as well. The interaction between GABA, GABA receptors, and alcohol is not completely understood [16]. Single doses of alcohol facilitate the inhibitory function of the GABAA receptor, contributing to alcohol's intoxicating effects [17]. Acutely, alcohol increases the activity and transmission of GABA, enhancing its inhibitory effect and, decreasing central nervous system activity and causing the well-known effects of alcohol intoxication, such as decreased coordination and drowsiness. Chronic alcohol use decreases the sensitivity of GABA receptors to GABA, so more and more alcohol is required to achieve the same level of intoxication [18]. This results in the requirement of increasingly larger doses of ethanol to achieve the euphoric effect, a phenomenon known as tolerance [19]. In the absence of alcohol, the resulting decrease in inhibitory function may contribute to symptoms of nervous system hyperactivity associated with both acute and protracted AW [13].

Glutamate system

Glutamate is an excitatory neurotransmitter. The binding of glutamate to N-methyl-D-aspartate (NMDA) receptors increases the flow of calcium ions across cell membranes, causing depolarization and increasing the cell's responsiveness to stimulation. Acutely, alcohol inhibits the activity of glutamate, and chronic alcohol consumption increases the number of glutamate receptors, an effect that is often referred to as upregulation of receptors [16] and production of more glutamate to maintain CNS homeostasis [19].

When someone who chronically uses alcohol to excess suddenly stops drinking or precipitously reduces consumption of alcohol, there are two important effects:

1) The inhibitory effect of alcohol on the GABA system is removed, and

2) There is increased activity of the upregulated glutamate receptors [16].

Other mechanisms are also stimulated during alcohol withdrawal [14] (Wayne Hall).

Dopamine is another neurotransmitter involved in alcohol withdrawal states. During alcohol use and withdrawal the increase in CNS dopamine levels contribute to the clinical manifestations of autonomic hyperarousal and hallucinations [19]. Also increased noradrenergic transmission probably contributes to sympathetic hyperactivity and activation of the hypothalamic-pituitary-adrenal axis increases cortisol secretion [14].

Disturbances of mood, thought, and perception

Withdrawing alcoholics exhibit psychiatric difficulties that may be related to the process of withdrawal itself or to co-occurring conditions. The major psychiatric problems associated with acute and protracted withdrawal are anxiety, depression, and sleep disturbance. Less frequently, psychotic symptoms, including delusions and hallucinations, may be associated with withdrawal [13].

Complications in AWS

In a patient with AWS, the seizure threshold declines on cessation of drinking and seizures may occur, usually within 48 h of stopping

drinking. The diagnosis is made by way of a history of a seizure within a few hours to 2 d after discontinuation of prolonged, heavy drinking or reduction in consumption, often accompanied by symptoms and signs of AWS [6]. Seizures may occur in more than 5 percent of untreated patients in acute alcohol withdrawal. Another severe complication is delirium tremens (DT's), which is characterized by hallucinations, mental confusion, and disorientation. The mortality rate among patients exhibiting DT's is 5 to 25 percent [13]. These complications may include the following:

• Gastritis (i. e., an inflammation of the stomach lining, which often is associated with bleeding)

• Gastrointestinal bleeding (e. g., from the esophagus, stomach, or intestines)

• Liver disease

• Cardiomyopathy (i. e., any disorder of the heart muscle)

• Pancreatitis (i. e., an inflammation of the pancreas)

• Disturbances in the electrolyte balance (e. g., alcohol ketoacidosis-a metabolic derangement that results in too much acid in the bloodstream-and abnormally low levels of magnesium in the blood)

• Deficiency of the vitamin folate, which can cause lower-than-normal numbers of blood cells

• Deficiency of the vitamin thiamine, which can lead to serious neurological problems, such as Wernicke's encephalopathy (accordingly, thiamine should be administered to all patients undergoing AW to prevent the development of this syndrome)[17].

Detoxification

Detoxification is the process of weaning a person from a psychoactive substance in a safe and effective manner by gradually tapering the dependence-producing substance or by substituting it with a cross-tolerant pharmacological agent and tapering it. This process minimizes the withdrawal symptoms, prevents complications and hastens the process of abstinence from the substance in a more humane way [19].

Goals of detoxification

Three goals of drug and alcohol detoxification as described by the American Society of Addiction Medicine (ASAM) are as follows:

1. "To provide a safe withdrawal from the drug(s) of dependence and enable the patient to become drug-free".

2. "To provide a withdrawal that is humane and thus protects the patient's dignity".

3. "To prepare the patient for ongoing treatment of his or her dependence on alcohol or other drugs [9]."

Treatment for alcohol withdrawal syndrome

The substances abused must be determined early in treatment because there are substantial differences in severe complications and in the management of withdrawal from alcohol and sedatives, opiates, and stimulants. Although the initial symptoms of withdrawal example, dysphoria, insomnia, anxiety, irritability, nausea, agitation, tachycardia, and hypertension — are similar for all three classes of drugs, complications and, therefore, treatment can differ greatly. Pharmacologic treatment of drug withdrawal often involves substituting a long-acting agent for the abused drug and then gradually tapering its dosage [20]. Outpatient management of AWS is indicated where the patient is willing to participate, does not have significant co morbid medical, psychiatric, cognitive or polysubstance use problems, has transportation to/from the follow-up visits, and has support in the community. Pharmacological treatment is directed at treating the symptoms of AWS, including seizure prevention [6].

Synthetic drugs for AWS

Pharmacotherapy involves disease treatment with pharmaceuticals that act on a specific target, enzyme or receptor. The interest in pharmacotherapy is growing because of the identification of novel neurotransmitter systems that initiate and sustain alcohol drinking, synthesis of neurotransmitter analogues that may alter dependence, use of phyto-pharmacologic agents that reduce alcohol consumption, and medications that have improved the treatment of other addictive disorders, such as nicotine and opioid dependence. The following drugs are approved for managing the withdrawal symptoms [20].

Benzodiazepines

Benzodiazepines bind to the Gamma-amino-butyric acid (GABA) A receptors at a site distant from the GABA-binding site and enhance the GABA-induced chlorideinflux. Two commonly used benzodiazepines are chlordiazepoxide and diazepamthat, in addition to having anticonvulsant capabilities (diazepam>>chlordiazepoxide), also reduces everity of the withdrawal symptoms. However, its chronic use results in deterioration of cognitive functioning, physical dependence and tolerance. Thus, in benzodiazepine treated patients, the drug withdrawal may induce withdrawal symptoms that may be resistant to other drugs listed above.

Carbamazepine

Carbamazepine is a GABA receptor agonist and has potency to suppress seizures, neuropathic pain and manic-depressive illness. The drug has also been shown to be efficacious and can be chosen as an alternative to benzodiazepines in treatment of the withdrawal symptoms.

Chlormethiazole

This drug is a positive allosteric modulator at the barbiturate/picrotoxin site at the GABA A receptor. It effectively treats and/or prevents DTs in alcoholism patients, if given at an early stage.

Buspirone, a non-benzodiazepine anxiolytic

Buspirone may reduce anxiety with less side effects and addiction potential than benzodiazepines.

Baclofen

The advances in knowledge of neurobiology and neurochemistry have prompted the use of drugs in the treatment of alcohol withdrawal that act through "t GABA pathways", such as the Baclofen, which are GABA-B pathways (agonist). the efficacy of Baclofen in the treatment of uncomplicated AWS was comparable to that of the "gold standard" diazepam, with significantly decreased CIWA-Ar scores [9].

Adjuvant treatments

Adjuvants such as atenolol, propranolol and clonidine may be used in conjunction with benzodiazepines in patients with coexisting conditions such as coronary artery disease. Bromocriptine (a dopamine agonist) and chlormethiaxole (a CNS depressant) have also been used in supportive treatment of alcohol withdrawal. Acupuncture can also be used as an adjunctive treatment to the alcohol withdrawal symptoms in combination with other medication [20].

Herbal drugs for AWS

There have been promising results from different research groups studying the therapeutic effects of plant extracts on withdrawal symptoms.

• Passiflora incarnata Linneaus and a tri-substituted Benzoflavone moiety (BZF) isolated from the extract may counter the dependence produced by benzodiazepine or other addiction-prone substances like morphine, nicotine, and alcohol.

• Poyares, *et al.* showed that valerian, a naturally occurring root, decreased WASO (wake time after sleep onset) with the mild anxiolytic effect in patients experiencing withdrawal symptoms in response benzodiazepine withdrawal after receiving 2-week of treatment.

• The aqueous extract of kudzu root or purified puerarin, in addition to suppressing alcohol intake, also suppressed the severity of alcohol withdrawal symptoms. More clinical studies are warranted to identify the active ingredients and decipher the underlying mechanisms for the beneficial effects of herbal extracts in humans [20].

Table 3: Drugs used in the treatment of AWS

Drugs used for treatment of AWS	
Class	**Examples**
Benzodiazepines (preferably long-acting)*	✓ Chlordiazepoxide, ✓ Diazepam, ✓ Oxazepam, ✓ Lorazepam
Anticonvulsants	✓ Carbamazepine:
Sedative – Hypnotic	✓ Chlormethiazole:
Anxiolytic	✓ Buspirone
Skeletal Muscle Relaxants ✓ GABA mimetic	✓ Baclofen:
Adjunctive agents Beta-blockers	✓ Atenolol, ✓ Propranolol and ✓ Clonidine

Table 4: Ayurvedic medicines used for treatment of alcohol withdrawal syndrome

Ayurvedic medicine	**Key ingredients**	**Therapeutic benefits**	**Usage in AWS**
Ashwagandha (Withania somnifera)	Root extract	Reduces stress and anxiety, stabilizes mood	Helps in calming the nervous system, reducing anxiety, and improving mood swings during alcohol withdrawal.
Brahmi (Bacopa monnieri)	Whole plant extract	Cognitive enhancer reduces anxiety and stress	Enhances brain function, reduces anxiety, and improves memory, aiding in the cognitive symptoms of alcohol withdrawal.
Shankhapushpi (Convolvulus pluricaulis)	Whole plant extract	Nervine tonic, anti-anxiety	Provides relief from mental exhaustion, anxiety, and agitation often experienced during alcohol withdrawal.
Jatamansi (Nardostachys jatamansi)	Rhizome extract	Sedative, calming effects	Helps in reducing restlessness, insomnia, and irritability associated with alcohol withdrawal.
Guduchi (Tinospora cordifolia)	Stem extract	Immune booster, detoxifier	Supports liver detoxification, enhances immunity, and helps in restoring balance in the body during alcohol withdrawal.
Kumari (Aloe vera)	Leaf extract	Liver tonic, anti-inflammatory	Aids in liver protection and detoxification, supporting recovery from the damage caused by chronic alcohol use.
Yashtimadhu (Glycyrrhiza glabra)	Root extract	Anti-inflammatory, anti-stress	Reduces stress levels, calms the nervous system, and provides digestive support, often compromised in alcohol withdrawal patients.
Pippali (Piper longum)	Fruit extract	Liver stimulant, digestive aid	Stimulates liver function and aids in the digestion and detoxification process, helping to manage digestive issues in alcohol withdrawal.
Vacha (Acorus calamus)	Rhizome extract	Anti-depressant, calming effects	Helps reduce depression and anxiety, common symptoms during alcohol withdrawal, and improves mental clarity.
Chandraprabha Vati	Herbal compound (contains Triphala, Shilajit, and others)	Adaptogenic, anti-stress, detoxifier	Helps reduce anxiety and stress, improves overall mental well-being, and supports liver detoxification during alcohol withdrawal.

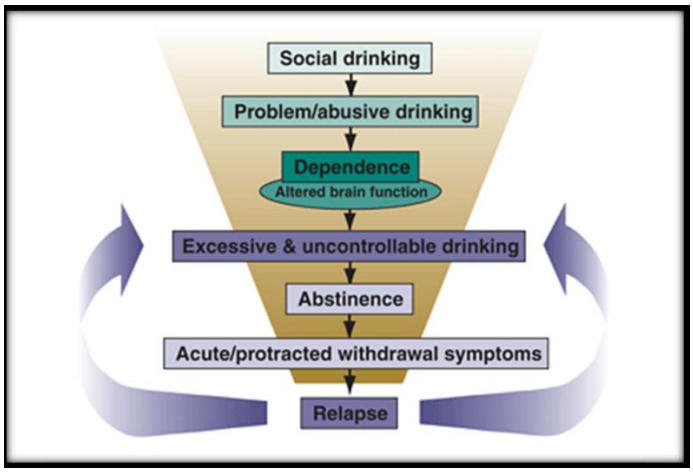

Fig. 1: Alcohol relapse behaviour

Alcohol relapse behavior

Relapse may be defined as the resumption of alcohol drinking following a prolonged period of abstinence. Clinically, vulnerability to relapse commonly is associated with an intense craving or desire to drink [22].

CONCLUSION

In conclusion, alcohol withdrawal syndrome (AWS) presents a complex and clinically significant challenge for individuals with alcohol dependence. This review has underscored the multifaceted nature of AWS, spanning its epidemiology, pathophysiology,

clinical manifestations, assessment tools, and management strategies.

Our exploration of AWS has shed light on the intricate neurobiological mechanisms at play, particularly the involvement of neurotransmitter systems like gamma-aminobutyric acid (GABA) and glutamate, alongside the neuroadaptive changes induced by chronic alcohol use. Moreover, we have elucidated the diverse spectrum of clinical manifestations associated with AWS, from mild withdrawal symptoms to severe complications such as delirium tremens and seizures.

Diagnostic tools and scoring systems for AWS severity have been discussed alongside evidence-based pharmacological and non-pharmacological management approaches. Importantly, this review has emphasized the need for early recognition and appropriate intervention to improve outcomes for individuals grappling with AWS.

Looking ahead, emerging research areas offer promising avenues for advancing our understanding and management of AWS. Novel treatment modalities and potential biomarkers hold the potential to enhance both the prediction of withdrawal severity and treatment response.

In essence, this comprehensive review aims to equip clinicians, researchers, and healthcare professionals with the insights necessary to navigate AWS effectively, fostering early recognition, tailored management, and, ultimately, better outcomes for those impacted by this condition.

ACKNOWLEDGMENT

It's our privilege to express the profound sense of gratitude and cordial thanks to our respected chairman Mr. Anil Chopra and Vice Chairperson Ms. Sangeeta Chopra, St. Soldier Educational Society, Jalandhar for providing the necessary facilities to complete this review.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors had contributed equally to the review work in various ways such as Conceptualization, Conducting comprehensive searches of relevant literature and Data Analysis.

CONFLICT OF INTERESTS

Declares none

REFERENCES

1. Rehm J. The risks associated with alcohol use and alcoholism. Alcohol Res Health. 2011;34(2):135-43. PMID 22330211.
2. Park SH, Kim DJ. Global and regional impacts of alcohol use on public health: emphasis on alcohol policies. Clin Mol Hepatol. 2020;26(4):652-61. doi: 10.3350/cmh.2020.0160, PMID 33053937.
3. Ramos Vera C, Serpa Barrientos A, Calizaya Milla YE, Carvajal Guillen C, Saintila J. Consumption of alcoholic beverages associated with physical health status in adults: secondary analysis of the health information national trends survey data. J Prim Care Community Health. 2022;13:21501319211066205. doi: 10.1177/21501319211066205, PMID 34991399.
4. Sachdeva A. Alcohol withdrawal syndrome: benzodiazepines and beyond. J Clin Diagn Res. 2015 Sep 1;9(9):VE01–VE07. doi: 10.7860/JCDR/2015/13407.6538, PMID 26500991.
5. Becker HC. Alcohol dependence withdrawal and relapse. Alcohol Res Health. 2008;31(4):348-61. PMID 23584009.
6. McKeon A, Frye MA, Delanty N. The alcohol withdrawal syndrome. J Neurol Neurosurg Psychiatry. 2008;79(8):854-62. doi: 10.1136/jnnp.2007.128322, PMID 17986499.
7. DE Witte P, Pinto E, Ansseau M, Verbanck P. Alcohol and withdrawal: from animal research to clinical issues. Neurosci Biobehav Rev. 2003;27(3):189-97. doi: 10.1016/S0149-7634(03)00030-7, PMID 12788332.
8. Stern RS. Psoriasis. Lancet. 1997;350(9074):349-53. doi: 10.1016/S0140-6736(97)05257-4, PMID 9251649.
9. Sachdeva A, Choudhary M, Chandra M. Alcohol withdrawal syndrome: benzodiazepines and beyond. J Clin Diagn Res. 2015;9(9):VE01-7. doi: 10.7860/JCDR/2015/13407.6538, PMID 26500991.
10. O CP. Drug addiction and drug abuse. In: Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. Vol. 1996, New York McGraw-Hill; 1996.
11. Hedaoo PA. Herbal remedies of alcohol addiction. World J Pharm Pharm Sci. 2019;8(6):491-510. doi: 10.20959/wjpps20196-13962.
12. Jesse S, Brathen G, Ferrara M, Keindl M, Ben Menachem E, Tanasescu R. Alcohol withdrawal syndrome: mechanisms manifestations and management. Acta Neurol Scand. 2017;135(1):4-16. doi: 10.1111/ane.12671, PMID 27586815.
13. Louis MD, Trevisan A, Nashaat Boutros MD, Petrakis IL, Krystal JH. Complications of alcohol withdrawal pathophysiological insights. Alcohol Heal Res World. 1998;22(1):61-6. PMCID PMC6761825.
14. Hall W, Zador D. The alcohol withdrawal syndrome. Lancet. 1997;349(9069):1897-900. doi: 10.1016/S0140-6736(97)04572-8, PMID 9217770.
15. Jesse S, Brathen G, Ferrara M, Keindl M, Ben Menachem E, Tanasescu R. Alcohol withdrawal syndrome: mechanisms manifestations and management. Acta Neurol Scand. 2017;135(1):4-16. doi: 10.1111/ane.12671, PMID 27586815.
16. Canver GA, BR, Newman RK. Alcohol withdrawal syndrome Treasure Isl. StatPearls Publ. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441882. [Last accessed on 24 Oct 2024].
17. Suzdak PD, Schwartz RD, Skolnick P, Paul SM. Ethanol stimulates gamma-aminobutyric acid receptor-mediated chloride transport in rat brain synaptoneurosomes. Proc Natl Acad Sci USA. 1986;83(11):4071-5. doi: 10.1073/pnas.83.11.4071, PMID 2424017.
18. Schuckit MA. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 19th ed. New York: McGraw-Hill. Alcohol and alcoholism; 2015.
19. Kattimani S, Bharadwaj B. Clinical management of alcohol withdrawal: a systematic review. Ind Psychiatry J. 2013;22(2):100-8. doi: 10.4103/0972-6748.132914, PMID 25013309.
20. Kosten TR, O Connor PG. Management of drug and alcohol withdrawal. N Engl J Med. 2003;348(18):1786-95. doi: 10.1056/NEJMra020617, PMID 12724485.
21. Madhavan J. Ayurvedic management of alcohol withdrawal syndrome a case report. MJCCS. 2018;2(6):000184. doi: 10.23880/MJCCS-16000184.
22. Howard C Becker. Alcohol dependence withdrawal and relapse. Alcohol Res Health. 2008;31(4):348-61. PMID 23584009.