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Agmatine and Acetyl L Carnitine - A Novel Adjunctive Therapy for Management of Alcohol Withdrawal Syndrome

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Abstract: ***The majority of the rise in global alcohol consumption over the past few decades has been seen in developing nations. According to the ICMR Bulletin, there are 62 million alcoholics in India, which is equal to the size of France's population, and up to 50% of alcohol use disorder (AUD) patients experience alcohol withdrawal symptoms (AWS). The clinical appearance ranges from moderate to severe, and a small percentage of individuals have severe alcohol withdrawal symptoms, including delirium tremens that lead to the length of stay more than double for severe in AWS. Epileptic seizures and/or delirium tremens (DT), which can occur in up to 15% of AUD patients, are symptoms of severe AWS. When a chronic user abruptly discontinues drinking, the alcohol-mediated CNS inhibition is reduced, allowing glutamate-mediated CNS excitation unopposed, resulting in net CNS excitation. Benzodiazepines (BZDs) are currently the "gold standard" in the treatment of AWS. Available pharmacotherapy for alcohol withdrawal syndrome has various disadvantages including the fact that it only works on GABA. Agmatine is a polyamine that has been considered a potential central nervous system neurotransmitter or neuromodulator, it has a multi-model action on the other hand Acetyl l carnitine (ALCAR) is one of the most common carnitine metabolites discovered in humans and mammalian plasma and tissues, it enhancing brain energy metabolism, modulating neurotransmitters, and increasing neural plasticity. The synergistic effects of Agmatine and acetyl l carnitine can be used to manage delirium and other core symptoms of alcohol withdrawal. Hence, the aim of this review is to increase awareness of AWS and adjunctive use of Agmatine and acetyl l carnitine in the management of alcohol withdrawal syndrome and complications arising during alcohol withdrawal such as delirium, Fatigue, seizures, anxiety, cognitive impairment, melancholia (depression), agitation, and anhedonia.***

Keywords: Alcohol withdrawal symptoms, Delirium, Agmatine, acetyl l carnitine

1. Introduction

1.1 Medical Burden of Alcohol Abuse

The majority of the rise in global alcohol consumption over the past few decades has been seen in developing nations. Rises are more significant in nations where alcohol use is historically lower among the general population and where prevention, control, and treatment strategies are more difficult to access. According to the ICMR Bulletin, there are 62 million alcoholics in India, which is equal to the size of France's population. [(1)] Worldwide, an estimated 76.3 million people suffer from alcohol use disorders (AUDs), which are responsible for 1.8 million annual deaths. Up to 42% of patients are treated in general hospitals and one-third of patients admitted to hospital critical care units (ICU) are considered to have AUD. [(2)] Up to 50% of AUD patients experience withdrawal symptoms (AWS). [(3)] One of the most prevalent manifestations of Alcohol Dependence Syndrome is Alcohol Withdrawal Syndrome (AWS). AWS is a group of symptoms that occur in alcoholics following the cessation or reduction of excessive or extended alcohol usage. The clinical appearance ranges from moderate to severe, with symptoms often appearing a few hours after the last alcohol consumption. The clinical appearance ranges from moderate to severe, with symptoms often appearing a few hours after the last alcohol consumption. Tremors, fatigue, insomnia, hallucinations, paroxysmal sweats, tachycardia, fever, nausea, vomiting, seizures, depression, agitation, and anxiety are the most prevalent symptoms. A small percentage of individuals have severe alcohol withdrawal symptoms, including delirium tremens. These symptoms are triggered by disturbances in a number of neurotransmitter circuits that are involved in the alcohol pathway and indicate a homeostatic readjustment of the central nervous system. [(4) (5)] About 8% of hospitalized AUD inpatients experience alcohol withdrawal syndrome (AWS). The length of stay is more than doubled for severe in AWS,

which commonly requires ICU treatment. Epileptic seizures and/or delirium tremens (DT), which can occur in up to 15% of AUD patients, are symptoms of severe AWS. [6] Patients who are delirious have high rates of co-morbid conditions, and ultimately death at rates that are equivalent to those of patients with severe malignancy. However, the predicted mortality is in the region of 1% or less with early detection and appropriate treatment. [7]

The purpose of this review is to increase awareness of AWS and adjunctive use of Agmatine and acetyl l carnitine in alcohol withdrawal syndrome and manage the complications arising during alcohol withdrawal such asdelirium, Fatigue, seizures, anxiety, cognitive impairment, melancholia (depression), and agitation.

2. Pathophysiology

Alcohol acts as a central nervous system depressant, the excitatory (glutamate) and inhibitory (GABA) neurotransmitters are normally in a condition of equilibrium. (Figure 1a). Alcohol promotes GABA action, resulting in reduced CNS excitability (figure 1b). It induces a reduction in the number of GABA receptors through period (down regulation). As a result, gradually higher dosages of ethanol are required to provide the same euphoric effect, a condition called as tolerance. Alcohol acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, reducing excitatory tone in the CNS. To maintain CNS homeostasis, chronic alcohol consumption causes an increase in the number of NMDA receptors (up regulation) and the production of more glutamate (figure 1c). When a chronic user abruptly discontinues drinking, the alcohol-mediated CNS inhibition is reduced, allowing the glutamate-mediated CNS excitation unopposed, resulting in net CNS excitation (figure 1d) and neuropsychiatric complications such as delirium and seizures. [9] [10]

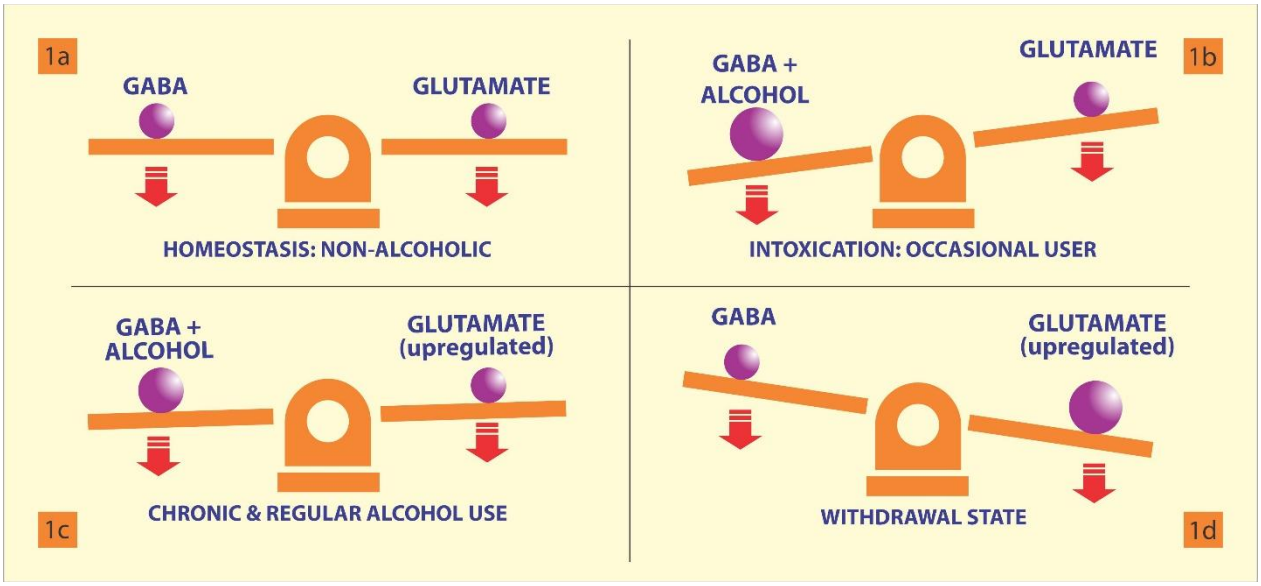

Figure 1: Pathophysiology of alcohol withdrawal syndrome

3. Alcohol Withdrawal Symptoms

The spectrum of withdrawal symptoms and the time it takes for these symptoms to manifest after cessation alcohol is listed in (table 1) In general, alcohol withdrawal symptoms are proportional to the amount of alcoholic intake and the duration of a patient's prior drinking habit. The majority of individuals have a similar set of symptoms with each episode of alcohol withdrawal.

Minor withdrawal symptoms can occur while the patient still has a measurable blood alcohol level. These symptoms may include insomnia, anxiety, tremulousness, fatigue. Patients with alcoholic hallucinosis experience visual, auditory, or tactile hallucinations but otherwise have a clear sensorium Patients who have a history of multiple detoxification episodes are more likely to experience withdrawal seizures. [11] If seizures are focal, there is no definite history of recent abstinence from drinking, seizures occur more than 48 hours after the patient's last drink, or the patient has a history of fever or trauma, causes other than alcohol withdrawal should be examined. [12]

In 1813, delirium tremens was identified as a disorder caused by excessive alcohol consumption. It is now well accepted that it can develop as early as 48 hours following abrupt cessation of alcohol intake in chronic alcoholics and can persist up to 5 days. Without effective treatment, it is anticipated to have a mortality rate of up to 37%. It is essential to recognize early indications of withdrawal as it may be fatal. [13]

Table 1: Symptoms of Alcohol Withdrawal Syndrome

Symptoms	Time of appearance
Minor withdrawal symptoms: insomnia, tremulousness, anxiety, fatigue gastrointestinal upset, headache, diaphoresis, palpitations, anorexia	6 to 12 hours
Alcoholic hallucinosis: visual, auditory, or tactile hallucinations	12 to 24 hours
Withdrawal seizures: tonic-clonic seizures	generalized 24 to 48 hours
Alcohol withdrawal delirium (delirium tremens): hallucinations (predominately visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis	48 to 72 hours

4. Agmatine Sulphate

Albrecht Kossel discovered Agmatine in 1910, a ubiquitous molecule biosynthesized from arginine by the enzyme arginine decarboxylase (ADC) (14) and therefore also known as decarboxylated arginine. The chemical structure of Agmatine is displayed in (figure no 2)

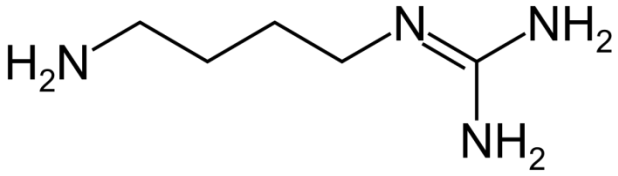

Figure 2: Chemical structure of Agmatine

However, due to a lack of understanding of the enzyme arginine decarboxylase (ADC), which may synthesize Agmatine from arginine, research on Agmatine limited progress during the 20th century. [15]

Reis and colleagues made the breakthrough in 1994 when they discovered Agmatine and ADC in the mammalian brain. [16] Numerous subsequent investigations concentrated on the physiological and pharmacological effects of Agmatine on animals. Agmatine has been shown to protect against a variety of organ diseases, including cardioprotection, nephroprotection, gastroprotection, neuroprotection, and glucoprotection. [17] Numerous research have been conducted over the last several decades to investigate the potential mechanisms of neurological diseases and the neuroprotective advantages of various drugs. However, the side effects of several medications constituted significant barriers to further clinical trials. Surprisingly, Agmatine was discovered to exist naturally in plants, and animals. [18]

Gilad et al studied the long-term safety of oral Agmatine therapy by taking a daily high dose of oral Agmatine for 4-5 years. During the follow-up period, all measures were within normal ranges, and no pain was reported. [19] Furthermore, substantial research has shown that Agmatine has a neuroprotective impact. The low incidence of side effects and extensive therapeutic efficacy has received a lot of attention. Several studies have demonstrated Agmatine's neuroprotection in stroke, traumatic brain injury, neurodegenerative diseases, neuropathic pain, addiction, epilepsy, and even psychiatric illness. The common processes involved in neuroprotective benefits include anti-oxidation, anti-apoptosis, anti-inflammation, brain blood barrier (BBB) protection, and cerebral edema reduction.

5. Acetyl L Carnitine: (ALCAR)

ALCAR is one of the most common carnitine metabolites discovered in humans and mammalian plasma and tissues. [20] Chemical structure is mentioned in (figure no 3). ALCAR has documented neuroprotective effects. [21] [22] including carnitine and an acyl moiety that may be utilized for energy. [23] As well as for acetylcholine production [24] amino acid neurotransmitters [23] and lipids. [25] ALCAR has been shown to have anti-inflammatory effects [21] to promote to membrane stabilization, serve as an antioxidant protecting against oxidative stress [25] and to increase the activity of nerve growth factor. Energy metabolism [23] and cholinergic responses are enhanced. [26] ALCAR treatment enhanced mitochondrial mass following spinal cord injury [27] and stimulated mitochondrial biogenesis in hypoxic rats. [28] Recent studies show that acetyl-L-carnitine treatment has antidepressant effects through enhancing brain energy metabolism, modulating neurotransmitters, and increasing neural plasticity. [29]

ALCAR is converted to acetyl-CoA, it has the ability to acetylate histones, which can alter gene expression, as well as proteins and enzymes, which can significantly alter activity. [30]

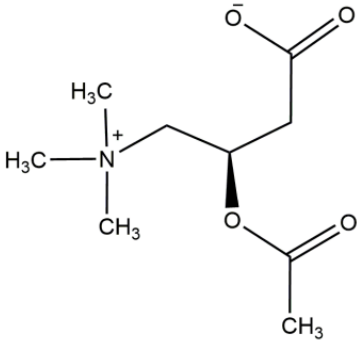

Figure 3: Chemical structure of acetyl l carnitine (ALCAR)

6. Goals of Treatment for Alcohol Withdrawal Syndrome

According to the American Society of Addiction Medicine, there are three immediate goals for alcohol and other substance detoxification: (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 compassionate and thus protects the patient's dignity"; and (3) "to prepare the patient for ongoing treatment of his or her dependence on alcohol or other drug. " [31]

6.1Treatment Setting

Depending on the intensity of the withdrawal, patients with AWS can be treated in an in-patient or outpatient environment. For individuals with mild to moderate AWS, an outpatient setting, as opposed to an inpatient setting can be more safe and effective, less expensive, and more acceptable owing to the reduced impact on the patient's personal life. [32] Atypical laboratory results, the absence of a support network, acute illness, a high risk of DTs, a history of withdrawal seizures, poorly controlled chronic medical conditions, serious psychiatric conditions such as suicidal ideation, severe alcohol withdrawal symptoms, or substance abuse are all contraindications to outpatient treatment. [33]

6.2 Pharmacological treatment for alcohol withdrawalsyndrome

6.2.1 Benzodiazepines

Benzodiazepines (BZDs) are currently the "gold standard" in the treatment of AWS. [34] Furthermore, BZDs are the only class of drugs that have been shown to be effective in preventing the development of advanced forms of AWS, with a reduction in the incidence of seizures (84%), DT, and the associated risk of risk of mortality. [35] BZDs' efficacy in the treatment of AWS appears to be mediated by their activation of GABAA receptors with alcohol mimicking effects. [36] No study has found any agent to be clearly superior to the others. There is greater evidence for long-acting agents (chlordiazepoxide and diazepam). [37] Given their ability to produce a smoother withdrawal. [38]

The medication (BZD) itself and its active metabolites generated by phase I liver oxidation mediate the therapeutic action. Following that, all products of oxidative metabolism are inactivated and eliminated via phase II liver glucuronidation. [39] Short-acting agents may be preferred in patients with impaired liver metabolism, such as the elderly or those with severe liver disease, to avoid excessive sedation and respiratory depression. [35] Treatment of DT necessitates the use of BZDs as primary drugs, with neuroleptics used as needed to reduce psychosis and dysperceptions. However, the use of BZDs is linked with an increased risk of excessive sedation, motor and cognitive impairments, and respiratory depression, with these effects being particularly prominent in patients with liver impairment. [34] Moreover the risk of abuse and dependence. [40]

6.2.2 Adjunctive Treatment

Agmatine:

Agmatine is a polyamine that has been considered as a potential central nervous system neurotransmitter or neuromodulator. Agmatine particularly inhibits NMDA glutamate receptor channels. [41] As well as NOS inhibition several studies have shown that exogenous Agmatine treatment protects cells against glutamate and NMDA-induced cellular damage. [42] Agmatine also reverses or prevents biological actions in the CNS that are dependent on glutamatergic pathways [43] α2-Adrenoceptor increases the GABA release in various brain regions. [44] The physiological interaction of α2-adrenoceptors and GABA receptors in the CNS is well established, and α 2-adrenoceptor expression is validated in GABAergic presynaptic nerve terminals. [45] Agmatine's functional interaction with 2-adrenoceptors has significant inhibitory effects on nicotine-induced behavioral sensitization and enhances morphine-induced conditioned location preference, analgesia, and anticonvulsant activity. [46] Figure 4 depicts a proposed mechanism of action of Agmatine against alcohol withdrawal syndrome.

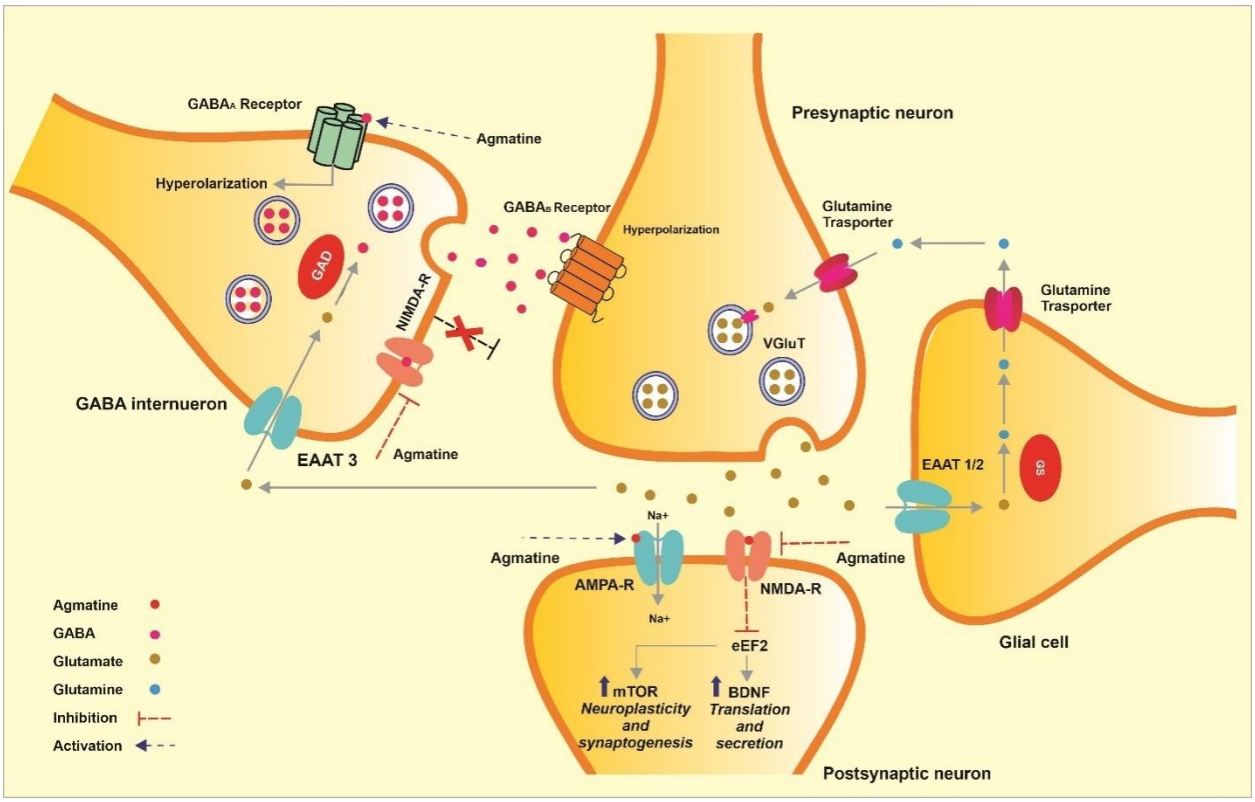

Figure 4: Agmatine's potential mechanism of action against alcohol withdrawal syndrome. Agmatine may inhibit the NMDA (N-methyl-D-aspartate) receptor, which is located on GABAergic interneurons. This disinhibits GABAergic interneurons and increases firing activity in pyramidal cells, causing glutamate release. As a result, extracellular glutamate rises and activates the AMPA receptor, stimulating the mTOR pathway. Agmatine may potentially blocks the NMDA receptor on glutamatergic neurons. This reduces eEF2 (eukaryotic elongation factor 2) phosphorylation, which inhibits BDNF translation. EAAT3 (excitatory amino acid transporter) transports glutamate to GABA interneurons and EAAT1/2 transporters to glial neurons. GABA is synthesized from glutamate by the enzyme GAD (glutamic acid decarboxylase) GS (glutamine synthetase) converts glutamine from glutamate. The GABA B receptor is activated by GABA binding, which promotes cell hyperpolarization and so limits glutamate release. Glial cells lower extracellular glutamate levels by converting into glutamine. Glutamine is stored until it is required and then transported into presynaptic neurons via the glutamine transporter. VGluT (vesicular glutamate transporters) then store glutamate into presynaptic neurons. Agmatine may bind to GABA as well, a receptor that causes receptor hyperpolarization

7. Managing Delirum

7.1.1 DELIRIUM and Acetyl L Carnitine, Agmatine

Acetylcholine, serotonin and gamma-aminobutyric acid (GABA) are among the common neurotransmitters believed to have a role in the pathophysiology of delirium. Acetylcholine (Ach) is a neurotransmitter that has been linked to attention, memory and perceptual disturbances. [47] [48] Normal aging causes physiological changes in the human body that result in a decrease in Ach-producing cells and a decrease in oxidative metabolism in the brain, which ultimately results in a decrease in Ach synthesis, putting geriatric people at greater risk of developing delirium. [47] Any dysfunctions in the interaction route between choline and acetyl coenzyme A (CoA) might decrease acetylcholine levels. [49]

7.1.2 Role of ALCAR in acetylcholine

ALCAR has numerous neuromodulator and neurotrophic actions, including promoting acetyl CoA uptake into mitochondria during fatty acid oxidation, increasing acetylcholine production, and stimulating protein and phospholipid synthesis, all of which are essential for membrane formation and integrity. [50] ALCAR treatment has been proven in a number of trials to maintain and/or raise acetylcholine levels in the brain. [24]

7.1.3 Role of Agmatine in GABA/glutamate imbalance:

Agmatine may inhibit the NMDA (N-methyl-D-aspartate) receptor, which is located on GABAergic interneurons. This disinhibits GABAergic interneurons and increases firing activity in pyramidal cells, causing glutamate release. As a result, extracellular glutamate rises and activates the AMPA receptor, stimulating the mTOR pathway. Agmatine may potentially block the NMDA receptor on glutamatergic neurons. This reduces eEF2 (eukaryotic elongation factor 2) phosphorylation, which inhibits BDNF translation. EAAT3 (excitatory amino acid transporter) transports glutamate to GABA interneurons and EAAT1/2 transporters to glial neurons. GABA is synthesized from glutamate by the enzyme GAD (glutamic acid decarboxylase) GS (glutamine synthetase) converts glutamine from glutamate. The GABA B receptor is activated by GABA binding, which promotes cell hyperpolarization and so limits glutamate release. Glial cells lower extracellular glutamate levels by converting into glutamine. Glutamine is stored until it is required and then transported into presynaptic neurons via the glutamine transporter. VGluT (vesicular glutamate transporters) then store glutamate into presynaptic neurons. Agmatine may bind to GABA as well. A receptor that causes receptor hyperpolarization. Agmatine's potential mechanism of action at the NMDA receptor may result in modulation of GABA and glutamate levels during withdrawal syndrome such as anxiety, irritability, agitation, compulsive behavior, mobility, and muscle strength have been substantially reduced by Agmatine. [51] Mentioned in (Figure no 4)

7.1.4 Role of Agmatinein increasing serotonin

Agmatine treatment also increases levels of noradrenaline and serotonin in the hippocampus (52). Agmatine works on serotonin neurotransmitter, Agmatinehas the potential to inhibit the serotonin reuptake transporter (SERT) found on presynaptic neurons. This leads to an increase in serotonin (5-HT) levels at the synaptic cleft, which causes a cellular response at the postsynaptic neuron (53). Mentioned in (Figure no 5)

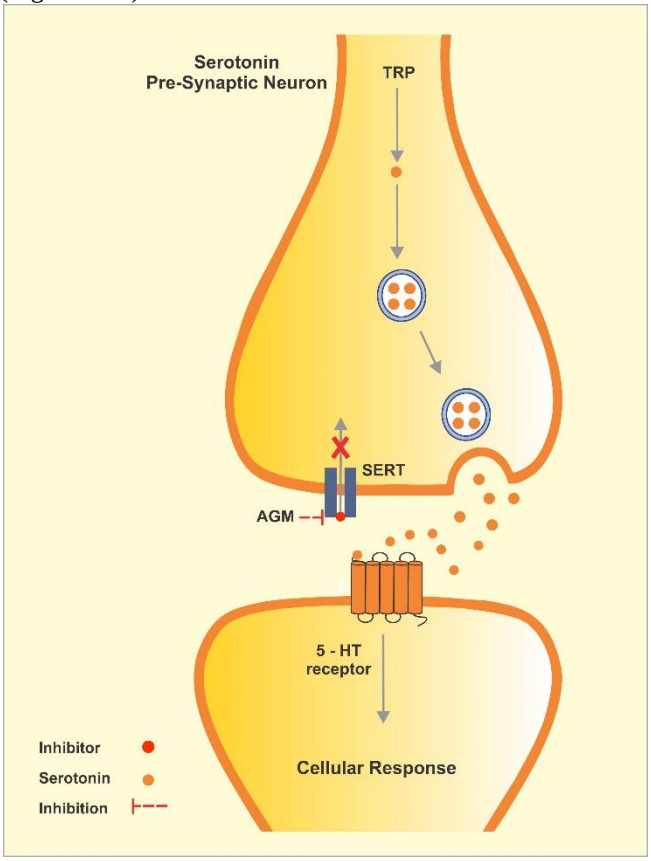

Figure 5: Potential mechanism of action of Agmatine

8. Managing other Core Symptoms of Alcohol Withdrawal Symptoms

8.1Seizures, anxiety and Agmatine:

Agmatine is an endogenous polyamine synthesized by arginine decarboxylase from L-Arg. Studies showed Agmatine is located in the brain and serves as a neurotransmitter or co-transmitter. [(14)]It has the ability to bind to 2-adrenoceptors, imidazoline, and glutamate NMDA receptors. Agmatine has been demonstrated to inhibit NOS isoenzymes in the central nervous system. Agmatine is considered to have antiepileptic action by inhibiting NO production and blocking glutamate NMDA receptors. [(54) (55)] Decreasing extracellular glutamate levelsand activation of α2-adrenoceptors. [(56)] Systemic administration of Agmatine was found to reduce acute seizures. Furthermore, Agmatine maintained GABA/glutamate balance by raising GABA levels while significantly decreasing glutamate concentration. [(57)] Hence minimizes seizures and reduces anxiety.

8.2Fatigue, Cognitive impairmentand acetyl l carnitine (ALCAR)

Acetyl-L-carnitine (Alcar) is an ester of the trimethylated amino acid, L-carnitine, and is a constituent of the inner mitochondrial membrane that comprises acetyl and carnitine moieties. It is synthesized in the human brain, liver, and kidneys by the enzyme Alcar transferase. [(58)] Previous studies shown that ALCAR easily crosses the blood-brain barrier, undergoes limited metabolism, and is eliminated in the urine via renal tubular reabsorption. [(59)] ALCAR is utilized clinically for age-related neurodegenerative conditions such as Alzheimer's dementia, fatigue, cognitive impairments, depression, and age-related disorders due to its various effects. [(60) (61) (62)] Previous studies concluded Acetyl l carnitine (ALCAR) is linked to significant increases in patient energy levels, physical function, and cognitive health. [(62) (63)]

ALCAR has numerous neuromodulator and neurotrophic actions, including promoting acetyl CoA uptake into mitochondria during fatty acid oxidation, increasing acetylcholine production, and stimulating protein and phospholipid synthesis, all of which are essential for membrane formation and integrity. [(50)] Animal studies have shown that chronic ALCAR treatment extends life, improves cognitive behavior in aged animals, and improves long-term memory performance; one of the proposed mechanisms of action of ALCAR is by improving mitochondrial bioenergetics, which allows neurons to produce the ATP required to maintain normal membrane potential. [(64) (65)]

ALCAR treatment has been proven in a number of trials to maintain and/or raise acetylcholine levels in the brain [(24) (66).] De Simone et al. [(66)] Discovered enhanced choline acetyltransferase activity and nerve growth factor (NGF) receptor expression in the striatum, as well as higher NGF protein levels in the hippocampus, after intracerebroventricular injection of ALCAR every other day from 0 to 21 days of life. Maintaining acetylcholine levels is important since this neurotransmitter is essential for learning and memory [(67) (68)]. Attention, learning, and memory need cholinergic pathways in the basal forebrain and hippocampus. [(69)] Acetylcholine stimulates hippocampal and cortical synaptic plasticity via astrocyte-neuron interactions. [(70)]

The carnitine shuttle is responsible for releasing acetyl-CoA groups for acetylcholine production (figure 6) and in buffering the level of free coenzyme A in the cytosol, which can inhibit acetylcholine production via choline acetyltransferase. [(24)] Acetyl group donor in the formation of Acetylcholine which helps in improve cognition. In addition ALCAR involved in the transport of fatty acids into the mitochondrial matrix for subsequent β-oxidation & thereby production of ATP (energy) and ameliorate mental as well as physical fatigue in alcohol withdrawal syndrome.

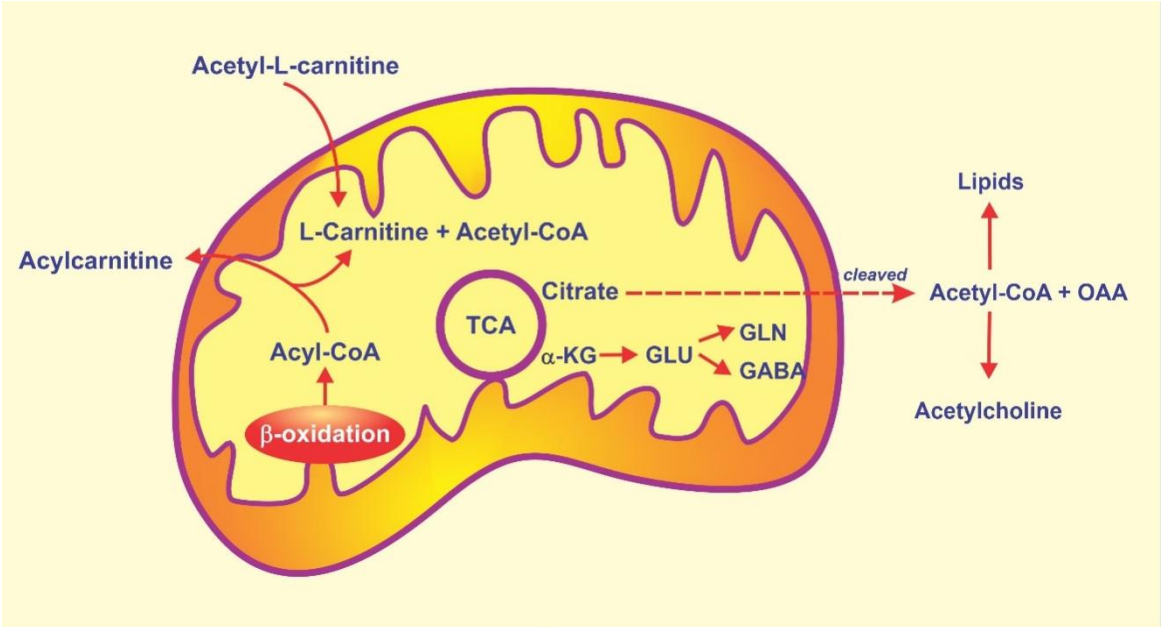

Figure 6: ALCAR metabolism in the brain

In the mitochondrial matrix, the permeable mitochondrial membrane acetyl-L-carnitine (ALCAR) is divided, generating acetyl-CoA and L-carnitine. Acetyl-CoA can be converted into glutamate, glutamine, or GABA or oxidized for energy via the tricarboxylic acid (TCA) cycle. Citrate, which is produced by the condensation of acetyl CoA and oxaloacetate (OAA), may also exit the mitochondria and, after cleavage by citrate lyase, produces cytosolic OAA and acetyl-CoA, which can be utilized for lipid synthesis or as a precursor for cholinergic. In settings when the amounts of these molecules are high, free L-carnitine in the mitochondrial matrix can be utilised to produce carnitine derivatives of acyl-CoA conjugates, reducing their toxicity.

8.3Alcohol withdrawal syndrome induce depression

Alcohol-dependent individuals experience psychiatric symptoms after alcohol detoxification (80% in one recent study). [71] Suicidal behavior is more likely to occur during intoxication (due to increased aggressiveness and reduced inhibitions) than during abstinence, while feelings of guilt, anxiety, and low mood typically emerge after alcohol withdrawal. [72]

8.3.1 Role of Agmatine:

The majority of polyamines in the brain are stored in astrocytes and synaptic vesicles, allowing them to play a role in glial and neuronal interactions. Polyamines, for instance, are generated in neurons, stored in synaptosomes, and released to influence neurotransmission via ionotropic glutamate receptors such as N-methyl-aspartate (NMDA) receptors and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors in the brain. [73] Many psychiatric disorders, including schizophrenia, have been linked to altered expression of polyamines and associated metabolic enzymes. [74] Mood disorders [75] Stress and anxiety [76] addiction [77] and suicidal behavior. [78] [79] Excitotoxic conditions cause an increase in extracellular glutamate to increase NMDA receptor activation, leading to an influx of Ca^{2+} and Na^{+}. By activating nitric oxide synthase, NMDA receptor stimulation also activates nitric oxide (NO) production pathways, resulting in NO, one of the main mediators of cellular death**.** [80] [81] NO synthesis inhibition may be beneficial in the treatment of brain disorders associated with its overproduction. Several studies have indicated that Agmatine's neuroprotective characteristics in many neurodegenerative disorders are related to its ability to antagonize NMDA receptors and limit NO production, as well as its ability to counteract the effects of oxidative stress. [82] In preclinical studies the first evidence of Agmatine's antidepressant effects was revealed in a study that investigated at its impact on depression-related behavioral tests (immobility time in the tail suspension test and forced swimming test) in mice. [83] Other studies have since confirmed Agmatine's antidepressant effectiveness in rodent behavioral tests. [84] [85]

A human clinical trial in 2010 demonstrated the safety of oral Agmatine. [18] In 2013, Shopsin et al provided the first evidence that Agmatine may be used to treat MDD, however, none of these Agmatine-treated patients relapsed with the addition of a serotonin-depleting drug, showing that the mechanism behind Agmatine's antidepressant activity is most likely independent to the serotonergic system. [86] In 2018, a gas chromatography-mass spectrometry study quantified Agmatine levels in the brains of post-mortem humans who died by suicide and found lower Agmatine levels in the suicide cortex regardless if these individuals previously met the criteria for MDD or the control group. [87] In summary, these findings suggest that Agmatine may have a role in the neurobiology of MDD and emphasize the potential advantages of Agmatine as an antidepressant therapy.

8.3.2 Role of acetyl l carnitine (ALCAR)

Studies have shown that neuroplasticity impairment may be a significant pathophysiological cause of depression. [88] Furthermore, research has shown that acetyl-L-carnitine (ALCAR) has a myriad of neuroplasticity-related functions and have significant antidepressant potential. ALC is a naturally occurring form of L-carnitine (LC). Carnitines, either free carnitine or as acylcarnitines such as ALC, are abundant in biological tissues and cells. [50] Acetyl l carnitine (ALCAR) has been shown to be useful in mood disorders in humans, particularly in the elderly, including major depressive disorder and dysthymia. [89] [90] ALCAR was recently studied in a multicentric, double-blind, randomized clinical trial (RCT) in an elderly population with dysthymic disorder. [91]

It is quite interesting considering that rapid effects have also been shown in preclinical models of depressive-like behavior. [92] A new meta-analysis evaluated the effect of ALCAR on depression symptoms in published randomized controlled trials. When compared to a placebo, ALCAR administration again demonstrated efficacy. Furthermore, ALCAR efficacy was equivalent to that of traditional antidepressants, but with significantly fewer adverse effects. [93] These findings are consistent with the findings of another meta-analysis that included 34 trials and 4769 patients with persistent depressive disorders. In that study, ALCAR treatment had the lowest incidence of adverse events and discontinuation of the any drug comparator. [94]

9. Synergistic Effect of Agmatine and Acetyl-L-Carnitine in Management of Alcohol Withdrawal Syndrome

Agmatine and acetyl L-carnitine (ALCAR) may be effective in the management of delirium and other core symptoms of alcohol withdrawal, in India Rejiyana® is available as adjunctive therapy; it contains Agmatine 250 mg and acetyl L-carnitine 500 mg, and can be given at a dose of BID per day, This drug is prescribed to manage alcohol withdrawal symptoms with standard treatment, Add on in patients showing poor response to ongoing benzodiazepine combinations, or as a co-prescription along with standard alcohol withdrawal treatment. Significant reduction in delirium; reduces alcohol cravings, anxiety, and fatigue-related symptoms. In addition, it minimizes seizures, reduces melancholia, and improves patient cognition. In addition, this drug is prescribed for depression, partial responder's non-responses, and treatment-resistant depression as adjunctive therapy with standard treatment. It is safe and effective, with minimal side effects compared to current

pharmacotherapy. The synergistic effect of Agmatine and acetyl l carnitine in the management of alcohol withdrawal syndrome is mentioned in (**Figure no 7)**

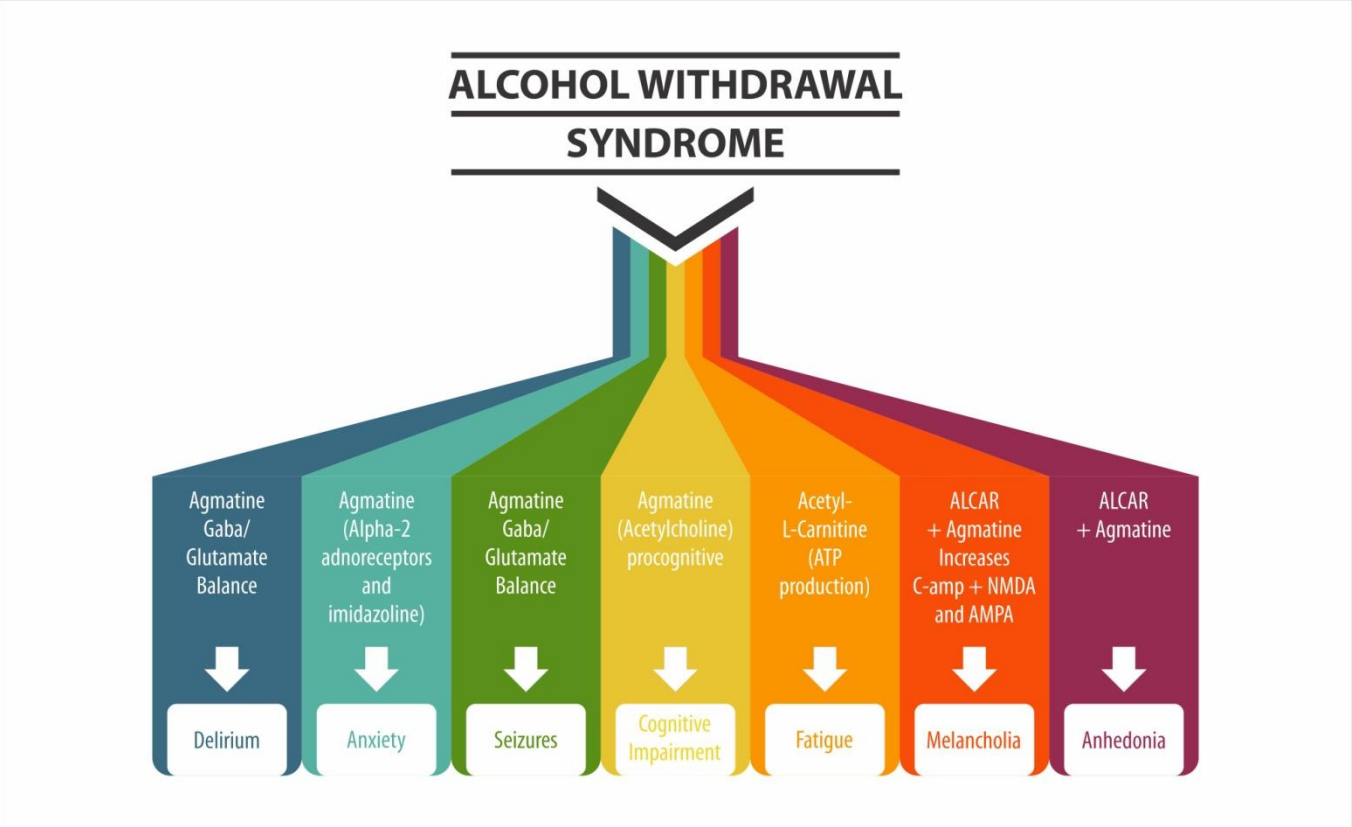

Figure 7: Synergistic effect of Agmatine and acetyl l carnitine in management of alcohol withdrawal syndrome

10. Conclusion

Agmatine and acetyl l carnitine (ALCAR) is an endogenous neuromodulators with substantial therapeutic potential for CNS diseases, according to extensive evidence. Notably, Agmatine has been shown to be effective in neurodegenerative disorders, TBI, SCI, pain-associated medical conditions, and neuropsychiatric disorders (particularly major depressive disorders) It mechanisms of action by modulating NMDA and imidazoline receptors, as well as oxidative stress, apoptosis, inflammation, and numerous intracellular signaling pathways. ALCAR has a wide spectrum of pharmacological effects on the nervous system. It has neuroprotective and neurotrophic effects. It influences the expression of many genes. Many of the neuronal responses may result not only from ALCAR acting via improved energy supply, and gene activity, but also by acting more directly to provide acetyl moieties to be used, for example in acetylcholine synthesis, or by providing activated acyl groups for the acylation of membrane phospholipids. Many studies suggest that the mode of action of ALCAR may involve, as well as synaptic function, an increase of cholinergic activity, acetylation of proteins, and neurotrophic effects stimulating NGF, as well as enhancing anterograde axonal transport. Both the drug molecule produces synergistic effect to manage delirium and alcohol withdrawal syndrome considering that currently, available pharmacotherapy for CNS disorders has various disadvantages. It is interesting to examine the therapeutic value of Agmatine and acetyl l carnitine for management of delirium and alcohol withdrawal syndrome. Although Agmatine and acetyl l carnitine administration has been demonstrated to be safe and effective.

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