A REVIEW ON ALCOHOL DEPENDENCE

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ABSTRACT

Alcohol use is widely prevalent in Indian society and results in loss of physical health outcomes like liver cirrhosis, diabetes, accidents, and various mental and behavioral problems. Abstinence from alcohol has been the prevailing treatment goal for individuals with alcohol dependence. Alcohol related liver damage can be divided into three categories fatty liver, alcoholic hepatitis and alcoholic cirrhosis. Many neurobiological and environmental factors influence motivation to drink. Genetics have an important and critical contribution in the development of alcohol abuse. Alcohol interacts with several neurotransmitter systems in the brain's reward and stress circuits. These interactions produce alcohol's acute reinforcing effects.

KEY WORDS: Alcohol dependence, Cirrhosis, Fatty liver, Alcoholic Hepatitis

INTRODUCTION

Excessive alcohol use results in 3.2 % deaths worldwide. Alcohol use is widely prevalent in Indian society and results in loss of physical health outcomes like liver cirrhosis, diabetes, accidents, and various mental and behavioral problems[1]. In United states alcohol use is the third leading and preventable cause of death[2]. Abstinence from alcohol has been the prevailing treatment goal for individuals with alcohol dependence (AD) within the context of specialty alcohol treatment. Most people who meet criteria for AD and could benefit from treatment never receive treatment. About half of these individuals do not seek treatment because they report a desire to continue drinking. To increase acceptability of treatment, reductions in alcohol consumption have been examined as alternative outcomes in treatment trials for AD[3]. Alcoholism is a chronic, relapsing disorder defined by compulsive alcohol seeking, loss of control over drinking and in a negative emotional state when not drinking. The major health issue that results from binge drinking is gut leakage and organ damage[4]. Alcohol dependence is a highly relevant disease in clinical medicine. Social, psychological, and biological factors influencing the etiogenesis of alcohol dependence are manifold and subject to intensive research worldwide. Alcohol dependence is a disease particularly characterized by frequent but very different comorbidities[5].

NEGATIVE EFFECTS OF ALCOHOL

Effect on liver

Liver is particularly susceptible to alcohol related injury because it is the primary site of alcohol metabolism. Alcohol related liver damage can be divided into three categories fatty liver, alcoholic hepatitis and alcoholic cirrhosis. Alcoholic liver disease and particularly cirrhosis is one of the most prevalent and devastating condition caused by alcohol consumption and leading cause of alcohol related death[6].

Effect on Brain

Alcohol interacts with several neurotransmitter systems in the brain's reward and stress circuits. These interactions produce alcohol's acute reinforcing effects. Following chronic exposure, these interactions result in changes in neuronal function that underlie the development of sensitization, tolerance, withdrawal, and dependence[7]. Alcohol use results in alterations in attention, verbal learning, memory, altered development of gray and white matter volumes, elevations in anxiety and neurogenesis[8].

Effect on Kidney

Alcohol affects kidneys by altering form and structure of kidneys. Alcohol promotes kidney dysfunction by increasing production of Reactive Oxygen Species which leads to an excessive amount of free radicals, which triggers tissue injury and increases inflammation. Alcoholic kidney injury may be associated with complex interaction of ethanol-induced oxidative stress and proinflammatory alterations[9].

Effect on Heart

Alcohol has complex effects on cardiovascular health. In healthy adults consuming low to moderate amount of alcohol each day impacts on hemodynamics or Blood Pressure (BP). Alcohol consumption is associated with transient increase in blood pressure that

ranges from 4-7 mmHg for systolic BP and 4-6 mmHg for diastolic BP. Prevalence of hypertension in persons consuming alcohol is twice as that of non-drinkers. Alcohol increases risk of diseases such as Coronary Heart Disease, Stroke, Peripheral Arterial Disease and Cardiomyopathy[10].

ALCOHOL DEPENDENCE (AD)

AD represents a chronic and relapsing disease affecting nearly 10 % of the general population both in the United States and in Europe, with a widespread burden of morbidity and mortality[11]. AD is a major mental health problem in India. About 5-7 % of Indian population has been estimated to abuse alcohol and 10-20 million people estimated to be in need of treatment for AD, with AD accounting for 1.2 % of total deaths in India[12]. The development of alcohol dependence is a complex and dynamic process. Many neurobiological and environmental factors influence motivation to drink[13].

Etiology

Genetics have an important and critical contribution in the development of alcohol abuse. There are two possible ways of transmission either there is genetic heterogeneity with two distinct subtypes or a mixed pattern of transmission including a dominant gene with multifactorial substrate[14]. However studies have shown that environmental factors may increase susceptibility for developing Alcohol Use Disorder (AUD)[15].

Symptoms

Alcohol related problems have been divided in to abuse symptoms and dependence symptoms

Abuse symptoms- associated adverse consequences, conduct problems.

Dependence symptoms- compulsive use behavior, craving, withdrawal, tolerance[16].

Neurobiology of Alcohol dependence

Behavioral control is not only a cognitive function but depends on dynamic and interconnected relations between reward, impulsive system and control inhibitory system[17]. Chronic alcohol abuse causes critical changes in neural reward motivational systems and simultaneously induces deficits in inhibitory control. These neurobiological adaptations account for compulsive alcohol use despite negative consequences and for emergence of negative emotional state when alcohol blood level decreases[18]. The progression of alcohol dependence consists of worsening dysfunction of interconnected reward and control circuits which becomes negatively imbalanced[19]. Short term alcohol consumption increases inhibitory transmission whereas after long term exposure excitatory transmission is enhanced.

GABA

Short-term alcohol consumption increases the $GABA_A$ receptor function, and therefore enhances inhibitory neurotransmission. Alcohol binds to the $GABA_A$ receptor in a specific binding site and induces chloride ion flux in an allosteric modulator manner[20]. $GABA_A$ receptors are composed of α, β, γ and δ subunits, subtypes containing δ and β3 sub-units seem to be more susceptible to alcohol[21]. Long-term exposure to alcohol, leads to a decrease in GABA neurotransmission, due to a neuroadaptation process called down-regulation. At the cellular level, a decrease in the number of $GABA_A$ receptors as well as changes in the protein composition of the receptor takes place. Decrease in $GABA_A$ receptor α1 subunit in the cortex, cerebellum and ventral tegmental area (VTA), decreases sensitivity to neurotransmission and counteracts the depressant effects of alcohol and helps restore equilibrium[22].

Glycine

Glycine plays a crucial role as an inhibitory neurotransmitter in the spinal cord and brain stem, but simultaneously, it may potentiate the action of glutamate (the major excitatory neuro-transmitter) via its co-agonist site on the N-methyl- D-asparate (NMDA) receptors. Glycine acts through strychnine-sensitive glycine receptors (GlyRs), which are pentameric ion channels producing their effects through chloride current. It seems that the main mediator of glycinergic inhibition is a subtype consisting of α1 and β subunits. It has been shown that alcohol modulates GlyRs with a greater affinity for α1-GlyRs, which may explain some of alcohol-induced behavioral effects[23]. The glycine levels in the synaptic cleft is under the control of glycine transporters (GlyTs), which belong to the Na+- and Cl-dependent neurotransmitter transporter family. Glycine reuptake inhibitors may reduce alcohol consumption by activating inhibitory transmission through GlyRs [21].

Adenosine

Adenosine modulates neurotransmission in the CNS by suppressing the release of other neurotransmitters. There are four classes of G protein-coupled adenosine receptors (A1, A2A, A2B, A3), but the A1 receptor, whose action is coupled with K+ channel activation and Ca2+ channel inhibition, is presumably the most significantly responsible for reducing neuronal excitability. Adenosine extracellular concentration is mainly controlled by nucleoside transporters, which regulate adenosine passage through the plasma membrane, and therefore modulate adenosine signaling[24]. Acute ethanol administration increases adenosine signaling. Adenosine uptake is suppressed through inhibition of nucleoside transporters, which leads to an increase in extracellular adenosine. Another possible mechanism may occur via metabolism of ethanol to acetate. Ethanol is incorporated into acetyl coenzyme A with the concomitant formation of AMP and its subsequent conversion to adenosine[25]. Ethanol may also affect adenosine receptors coupling[24]. Increased activation of the adenosine system, primarily through A1 receptors, results in the ataxic and sedative effects

of alcohol. In similar way to the GABAergic system, chronic alcohol exposure leads to a compensatory decrease in adenosine activity[26]. Because adenosine signaling has a particularly important influence on glutamatergic neurotransmission, adenosine is considered to be strongly involved in alcohol addiction[26].

Dopamine

Alcohol does cause increase in dopamine directly rather it appears that alcohol directly affects the GABA system and the endorphin system. Neurons from the GABA system extend into the reward pathway and when alcohol affects the GABA system these neurons release dopamine into the reward pathway[27]. Neurons extend from the endorphin system into the reward pathway and these also release dopamine into the reward pathway when alcohol directly stimulates the endorphin system. The dopamine in the reward pathway is involved in the phenomena of "wanting," "learning," and "reward," dopamine in the reward pathway may make person crave for drugs and it may also reinforce habitual drug use[28].

Treatment

The following drugs are used for the treatment of Alcohol Dependence

Table 1: Pharmacological treatment of Alcohol Dependence[29,30]

Drug	Dose	Side effects	Contraindications
Acamprosate	333-mg enteric coated tablets Adults ≥ 132 lbs (60 kg): two tablets three times per day Adults < 132 lbs: two tablets with the morning meal, one with the midday meal, and one with the evening meal.	Diarrhea, headache, flatulence, nausea, vomiting, dyspepsia.	Severe renal impairment (creatinine clearance < 30 mL per minute [0.5 mL per second])
Disulfiram	Begin with 250 mg once per day; increase to 500 mg once per day.	Disulfiram–alcohol interaction: palpitations, flushing, nausea, vomiting, headache.	Alcohol, metronidazole (Flagyl), or paraldehyde use psychosis; cardiovascular disease
Fluoxetine	Begin with 20 mg per day; may increase to 60 mg per day as needed.	Nausea, headache, sedation, anxiety, sexual dysfunction.	Use of an MAOI, mesoridazine (Serentil), or thioridazine (Mellaril)
Nalmefene	Available only in an injectable form to treat opiate overdose.	Nausea, tachycardia, vasodilation, dizziness, headache, chills, vomiting.	None
Naltrexone	50 mg once per day	Nausea, headache, anxiety, sedation.	Narcotic use, acute opioid withdrawal, acute hepatitis, liver failure
Ondansetron	4 mcg per kg twice per day.	Malaise, fatigue, headache, dizziness, anxiety.	None
Topiramate	Begin with 25 mg morning dose and increase to a total of 300 mg given twice a day in divided doses.	Recent FDA warning of metabolic acidosis, especially with renal or liver disease. Dizziness, somnolence, ataxia, impaired concentration, confusion, fatigue, paraesthesia's, speech difficulties, diplopia, nausea.	None
Baclofen	Begin with 5 mg PO TID may increase by 15 mg/day for every three days	CNS depression, respiratory depression, ataxia, seizures.	Hypersensitivity
Gabapentin	300 mg twice per day or once daily dosages up to 18000 mg at bed time	Dizziness, somnolence, fatigue, peripheral edema, hostility, diarrhoea,	None

	Could begin with 300 mg per day on the first day, then 300 mg twice per day on the second day and 300 mg three times per day on the third day; may increase to maximum dosage of 1,800 mg per day	asthenia, infection, dry mouth, nystagmus, constipation, nausea, vomiting, ataxia, fever, amblyopia	
Sertraline	Begin with 50 mg per day; may increase to 200 mg per day	Ejaculatory dysfunction, Dry mouth, sweating, somnolence, fatigue, tremor, anorexia, dizziness, headache.	Use of an MAOI such as mesoridazine, thioridazine, or linezolid

Patient Counselling

- Overcoming an addiction to alcohol can be a long and bumpy road. At times, it may even feel impossible. But it's not. If patient is ready to stop drinking and willing to get the support patient need, he *can* recover from alcoholism and alcohol abuse—no matter how bad the addiction or how powerless he feels.
- Recovery starts with admitting that person has a problem with alcohol. There are many things person can do to help himself to stop drinking and achieve lasting recovery.
- Most people with alcohol problems do not decide to make a big change out of the blue or transform their drinking habits overnight. Recovery is usually a more gradual process.
- In the early stages of change, denial is a huge obstacle.

Get rid of temptations. Remove all alcohol, barware, and other drinking reminders from home and office.

Announce goal. Let friends, family members, and co-workers know that patient is trying to stop drinking. If they drink, ask them to support his recovery by not doing so in front of him

Avoid bad influences. Patient should distance himself from people who don't support his efforts to stop drinking or respect the limits he've set. This may mean giving up certain friends and social connections.

When someone drinks heavily and frequently, his body becomes physically dependent on alcohol and goes through withdrawal if he suddenly stops drinking. The symptoms of alcohol withdrawal range from mild to severe, and include:
Alcohol withdrawal symptoms usually start within hours after he stops drinking, peak in a day or two, and improve within five days. But in some alcoholics, withdrawal is not just unpleasant—it can be life threatening.
Practice saying "no" to alcohol in social situations.

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