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The Effect Of Alcohol On The Brain: A Review

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ABSTRACT

Alcohol use has a profound effect on brain structure and function, especially with chronic or heavy use. It influences neurotransmitter systems, such as gamma-aminobutyric acid (GABA) and glutamate, resulting in changed mood, behavior, and cognitive functioning. Chronic alcohol use can lead to structural changes in the brain, such as decreased gray and white matter volume, particularly in areas involved in memory, decision-making, and impulse control. In teens and young adults, whose brains are in development, alcohol will have more robust and potentially permanent effects. Having an understanding of the neurobiological effects of alcohol is paramount in the construction of successful prevention and treatment methodologies for alcohol-use disorders.

INTRODUCTION

Alcohol and its first metabolite acetaldehyde are neurotoxins, which implies that they are toxic to neurons, the predominant form of brain cell. Alcohol readily diffuses from the blood through the blood-brain-barrier into all the structures within the brain such as the cerebral cortex (which is involved in higher-order thinking), the cerebellum (balance and coordination), and the brainstem (which is in charge of breathing, being awake, etc.)

Alcohol is crafted by Ethanol and water is the primary constituents of the majority of alcoholic.

The ethanol levels. Ethanol exists in alcoholic drinks as an end result of fermentation of carbohydrates by yeast. It can also be produced from ethylene derived from cracked petroleum hydrocarbons. The alcoholic drink industry has largely been unwilling to employ synthetic ethanol produced from ethylene for the purpose of the manufacture of alcoholic drinks, since it contains impurities. In the identification of whether or not synthetic ethanol has been used to enhance products, the fact that synthetic ethanol contains less of the low 14C level compared to fermentation ethanol made from carbohydrates.

There are three primary forms of alcohol related brain damage; Wernicke's encephalopathy, Korsakoff's syndrome and alcoholic dementia. Both Wernicke's and Korsakoff's may be present individually or together when it is referred to as Wernicke-Korsakoff syndrome.

Wernicke's encephalopathy tends to come on suddenly and is marked by movement and balance disturbances, loss of coordination, confusion, disorientation and abnormal eye movement.

Korsakoff's syndrome develops more slowly and the symptoms are typically issues with attention and concentration, memory gaps which are typically filled in incorrectly (confabulation) and an inability to learn new facts.

Alcoholic dementia is also distinguished by declining function in planning, decision making and risk assessment. There is generally a shift in personality, decrease in impulse and emotional control and this may generate conflict and behavior that is not socially appropriate. There are, in addition, difficulties with attention, concentration and memory.

Degree of alcohol intake in a population is the overall alcohol per capita consumption (APC), being the recorded and unrecorded alcohol intake per capita in individuals aged 15 years and older in a given calendar year, typically reported as liters of pure alcohol, and tourist consumption-adjusted (World Health Organization 2018). Recorded alcohol consumption refers to data obtained from social statistics and consists of the commercially and taxed alcoholic drinks (World Health Organization 2018), which can be quantified through sales and taxation or through production, export, and importation. Unrecorded consumption comprises that from a wide variety of sources, e.g., legally homemade alcoholic drinks, tourist imports, illegally manufactured or smuggled liquor, and surrogate alcohol; World Health Organization 2018). APC is occasionally reported for existing drinkers only. APC is converted to grams of pure alcohol per day for certain uses (World Health Organization 2018)

Several factors influence APC and account for differences between countries or world regions and trends over time within countries or regions. Economic wealth is the first such factor. Here is an association between affluence and alcohol consumption when comparing countries or regions cross-sectionally; the higher the per capita purchasing power, the higher the APC and the lower the proportion of male abstainers, World Health Organization 2018). Additionally, the share of unrecorded APC is lowest in HICs (11%) and much higher in LMICs (approximately 40%) (World Health Organization 2018). Although these findings may indicate the relevance of economic circumstances for drinking, more compelling evidence comes from time-series analyses of within-country changes. Accounts for Sweden and Thailand present strong correlations between purchasing power and the intensity of alcohol use, i.e., APC is increased in economic boom times. Consequently, numerous instances of consumption reductions due to economic crises are there, although empirical evidence regarding the effects of economic crises on alcohol consumption is inconsistent.

STATISTICS

According to current Statistics, fifteen million Americans today are alcoholics. Scientists know that alcohol interferes with the functioning of our brain by harming our frontal lobe, which is the memory, problem-solving, and motor control part of our brain (2010-2023).

What scientists are still trying to figure out is how specifically alcohol harms the frontal lobe, how teenagers are more susceptible to Alcohol Use Disorder (AUD) than adults, and how other illnesses are connected to alcohol.

STRUCTURAL CHANGES IN THE BRAIN

Symptoms are: vomiting, seizures, drowsiness, trouble staying awake, fainting, low body temperature, low gagging reflex, which can increase the risk of choking if a person vomits, clammy skin.

An untreated alcohol overdose will kill you. High-level alcohol overdoses can lead to permanent brain damage even if the individual lives.

The greater a person's blood alcohol level, the more susceptible they are to alcohol overdoses.

The excessive drinking of high-alcohol beverages is more likely to lead to alcohol poisoning. Individuals with smaller body sizes, less frequent alcohol use, or with liver disease histories are also more susceptible to alcohol poisoning

Long-term effects;

Eventually, alcohol abuse may lead to permanent brain damage.

- Wernicke-Korsakoff syndrome;

One of the alcohol-related brain damages is Korsakoff syndrome. Korsakoff syndrome tends to occur following an attack of Wernicke's encephalopathy, which is acute alcohol-related brain impairment.

The two disorders, collectively referred to as Wernicke-Korsakoff syndrome, occur in individuals who are thiamine (vitamin B-1)-deficient to a severe degree. Alcohol misuse interferes with the body's ability to utilize this nutrient, but other conditions, including extreme eating disorders, cancer, AIDS, and diseases affecting the body's capacity for nutrient absorption, can lead to Wernicke-

Korsakoff syndrome. Some of the symptoms of Wernicke's encephalopathy are; Confusion and disorientation that persist long after the duration of drunkenness, malnourishment that can lead to severe weight loss, difficulty in moving the eyes or bizarre and jerky eye movements, poor balance

After Wernicke's encephalopathy, the individual develops symptoms of Korsakoff syndrome.

This condition is a form of dementia.

Symptoms are; memory impairment, specifically trouble making new memories, poor judgment, reduced planning and organizational abilities, changes in mood and personality, hallucinations increasingly worsening cognitive impairment that can impact all aspects of functioning, such as speech, vision, and bowel and bladder control. Vitamin supplements and total alcohol abstinence can reverse Wernicke-Korsakoff syndrome symptoms within the first 2 years of alcohol abstinence.

- Fetal alcohol syndrome;

Fetal alcohol spectrum disorders, commonly known as fetal alcohol syndrome, occur when a developing fetus is exposed to alcohol during pregnancy. Fetal alcohol syndrome impacts various areas of functioning, and it can lead to brain damage. Intellectual disability, hyperactivity, poor memory, difficulty concentrating, poor coordination, vision and hearing problems.

Physicians have not yet determined a safe amount of alcohol to drink during pregnancy, so the most effective way to avoid fetal alcohol syndrome is to completely avoid alcohol during this period. If a pregnant woman cannot avoid alcohol, she should try to limit her alcohol use as much as possible.

- Head injuries;

Alcohol is an exacerbating factor of traumatic brain injuries (TBI) caused by falls, motor vehicle accidents, fights, and other head trauma. 35–81% of those who seek treatment for a TBI are alcohol-impaired.

In the short term, a head injury can lead to confusion and disorientation. It can also cause harmful brain swelling. Serious head injuries can even be fatal because they impair the brain's capacity to regulate vital functions, like breathing and blood pressure.

The long-term consequences of head injury; symptoms of dementia, e.g., trouble creating new memories, mood or behavior changes, greater likelihood of getting Alzheimer's disease and Parkinson's disease, alteration of the pattern of blood flow within the brain

- Psychological impact

The most typical psychological results of alcohol consumption involve difficulty concentrating, mood alterations, and depression.

Alcohol produces many different psychological consequences, such as; alterations in personality and mood, alterations in impulse, difficulty concentrating, and depression.

One of the most serious psychological consequences, though, is addiction. After a period of time, individuals who drink high amounts of alcohol become tolerant of the drug. They also become addicted. The addiction is such that their brains are accustomed to the drug, and they get withdrawal when they do not consume alcohol. Addiction causes an individual to keep on consuming alcohol even when it kills them. Those with serious alcohol use disorder can develop a life-threatening withdrawal state known as delirium tremens (DT). DT starts with mental symptoms that consist of; anxiety, insomnia, severe cravings for alcohol, paranoia, hallucinations or delusions.

Unrecognized and untreated, DT can prove fatal in greater than one-third of individuals upon whom it comes. Individuals experiencing DT can become prone to convulsions, hazardous alterations of blood pressure, and profuse vomiting and diarrhea, which will lead to lack of nutrients.

- Physiological effects

Alcohol serves to do much more than negatively impact the brain. Both severe intoxication and long-term abuse can disable virtually every system within the body. High blood pressure, heart disease, irregular heart rhythms, blood vessel damage, liver disease, kidney disease, pancreatitis, inflammation of the pancreas, a weakened immune system, and a higher risk of developing specific cancers, such as esophageal, breast, liver, and colon cancer.

Risk Factor:

The following categories of individuals appear to be in greater danger of

Developing alcohol;

Individuals who have been drinking in a harmful manner for 5 or more years.

Individuals drinking 28 or more drinks per week regularly.

Individuals who have regular 'memory blackouts' when they are drinking.

Individuals aged over 35.

Individuals with alcohol-related damage to the liver.

Individuals who have had extensive withdrawals or decodes.

Individuals who drink regularly to the point of bingeing.

Individuals who fail to consume sufficient food while drinking.

Individuals who have been hospitalized as a result of their alcohol consumption.

The effects of alcoholism on the brain are varied and determined by an extensive array of variables.

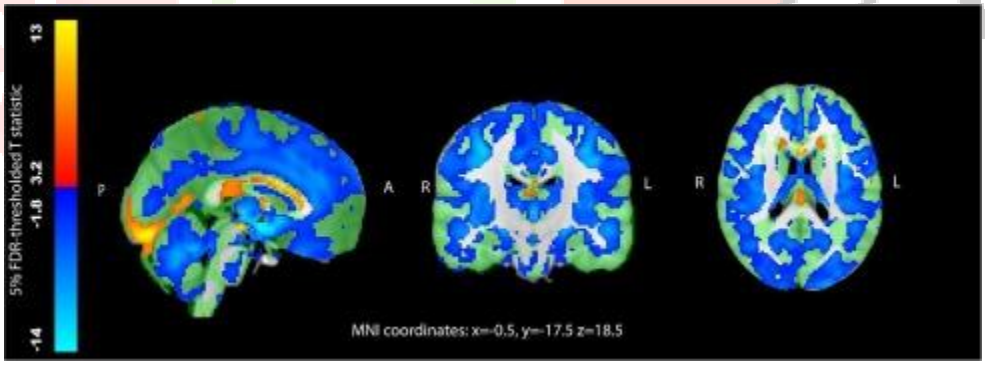
They comprise the quantity of alcohol taken, age at drinking initiation, and period of drinking; the age of the patient, educational level, gender, genetic history, and alcoholism family history; and neuropsychiatric risk factors such as exposure to alcohol in utero and overall health status. Overall physical and mental wellbeing is also a significant consideration since co morbid medical, neurological, and psychiatric illness may interact to enhance the impact of alcoholism on brain and behavior. Some examples of frequent co morbid illnesses include: Medical illnesses like malnutrition and cardiovascular and liver diseases.

Neurological disorders like head trauma, brain inflammation (i.e., encephalopathy), and fetal alcohol syndrome (or fetal alcohol effects)

Psychiatric disorders like depression, anxiety, post-traumatic stress disorder, schizophrenia, and use of other drugs.

Imaging Studies:

MRI (Magnetic Resonance Imaging): MRI scans can be employed to identify structural changes in the brain, like shrinking of particular areas of the brain (e.g., the frontal lobes, which tend to be affected by long-term use of alcohol).



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CT scan {Computed Tomography}: A CT scan may be useful to exclude other etiologies of brain damage, although it is not as sensitive as MRI to detect subtle changes associated with alcohol dependence. {PET scan {Positron Emission Tomography-PET scan}}: PET scans can help determine brain metabolism and point out places with reduced activity, which may be a reflection of alcohol damage.

NEUROLOGICAL DISRUPTIONS

- Neuropsychological Testing

Cognitive Tests: These tests assess different cognitive functions, including memory, attention, problem-solving, and executive functions, to determine the degree of impairment.

Behavioral Assessments: These tests assist in assessing changes in behavior and personality, which can be associated with alcohol-induced brain damage.

- Laboratory Tests:

Blood Tests: While they are not specifically used to diagnose brain injury, blood tests can measure liver function and other alcohol-related health indicators. Chronic alcohol dependency tends to affect liver function, which indirectly might have an effect on brain health. In case of suspected damage to the brain through alcohol consumption, diagnosis and intervention need to come quickly. Treatment is usually ceasing alcohol, nutritional supplementation (including thiamine), and rehabilitation to handle cognitive and behavioral symptoms. Professional consultation with a healthcare provider is needed for extensive assessment and a tailored treatment protocol.

COGNITIVE IMPAIREMENTS

The intention of this critical systematic review was to address available scientific evidence for applications of non-invasive (rTMS and tDCS) and invasive (DBS) neurostimulation. We sought to more clearly understand and treat alcohol use disorders (AUD) and determine certain areas to enhance the quality of studies on this topic in the future. A number of large-scope reviews have before spoken to and addressed applications of brain stimulation methods in substance use disorders (SUD), such as for tobacco (nicotine), alcohol, stimulants and opiates. However, to our knowledge, this review is the first to specifically address the application of non-invasive and invasive brain neuromodulation to study and treat AUD.

As demonstrated by a number of case reports in patients who have received DBS for the treatment of severe types of substance dependence, a considerable decrease of alcohol craving and sustained alcohol abstinence (8 years) have been obtained after bilateral stimulation of the NAc, a key part of the reward circuit.

However, although with established clinical efficacy in AUD, NAc stimulation is still an invasive and expensive neurosurgical intervention, potentially linked to short-term surgical complications (e.g. brain hemorrhage) and serious long-term side effects (e.g. surgical wound infection, seizures and stimulation-induced psychiatric disturbances). In addition, AUD patients often have compromised liver function and deranged prothrombin and thrombocytopenia, thus at risk of intracranial hemorrhage, which overwhelmingly outbalances the advantages of DBS. As such, DBS is usually reserved for the most life-threatening severe cases of AUD that are refractory to pharmacotherapy. Research into the impact of tDCS on alcohol dependence included targeting the DLPFC with low-intensity (2 mA) anodal tDCS and produced quite variable findings on alcohol craving.

More specifically, results varied, ranging from significantly attenuated cue-induced alcohol craving by active tDCS to non-significant differences of the latter vs. sham tDCS. With regards to stimulation parameters, multi-session protocols proved more effective compared to single-sessions for decreasing alcohol craving and consumption. Despite these constraints, tDCS devices are fairly low-cost, easy to use in double-blind controlled trials and safe and easy to implement in conjunction with behavioral tasks in clinical contexts. As such, their effectiveness in decreasing alcohol craving and consumption in AUD needs more research.

Research that has studied the effect of TMS in alcohol-dependent individuals has taken alcohol-related craving as the primary outcome measure. It has then been theorized that the use of a neuromodulatory strategy may reverse these changes, thereby counteracting the allostatic load of hedonic dysregulation. Based on this observation, the authors proposed that dorsolateral prefrontal cortex stimulation with rTMS may yield a "craving downregulated" therapeutic window, within which phenomena of compulsivity (hypohedonia-driven craving) do not disrupt rehabilitation program advancement.

Moreover, poorly designed sham-controlled studies and blinding approaches (or absence thereof) restrict the clinical utility of rTMS research conducted thus far in AUD. Finally, psychiatric disorders (i.e. moodiness, depression, anxiety and schizophrenia) which co-occur with AUD can affect the effectiveness of brain stimulation regimens. Therefore, additional research is needed to identify the differential impact of brain stimulation in co-occurring disorders. In conclusion, the lack of information regarding AUD severity, the fact that more than one questionnaire has been used for craving assessment and the absence of long follow-up periods after the cessation of neurostimulation limit the scope of the research published in the field of AUD. In this context, further advance will only be achieved if other controlled and randomized double-blind clinical trial in large patient cohorts (if possible multicentric) examining long term abstinence are performed.

MEDICATIONS

Alcohol use disorder encompasses repeated alcohol consumption that results in tolerance, alcohol withdrawal syndrome, physical and psychological dependence as well as compulsive and uncontrolled intake of alcoholic drinks. The most significant reason for the treatment of alcohol use disorder is focused on minimizing alcohol withdrawal syndrome and enhancing alcohol drinking behavior. The herbal medicines used to treat alcohol use disorder in China have been available for various centuries. Kudzu (Pueraria lobata), discussed above, may be employed for the treatment of alcohol use disorders, and puerarin from kudzu may alleviate the anxiogenic actions of alcohol withdrawal. Dihydromyricetin, a flavonoid isolated from Hovenia dulcis may be another drug candidate for alcohol use disorder. Hypericum perforatum and Salvia miltiorrhiza may be good natural products to treat alcohol use disorder and will be discussed below, whereas Scutellaria baicalensis plays a significant role in the treatment of liver disease.

1.Hypericum perforatum

The Hypericum perforatum extract (HPE) is commonly employed for the treatment of affective disorders. It may decrease voluntary alcohol consumption in the food consumption was reduced marginally, whilst no alteration in body weight, was noted versus the control. The entire treatment was devoid of tolerance development. These findings support that HPE may have some positive effects on alcohol withdrawal syndrome among individuals. Correlation of hyperforin content of Hypericum perforatum extracts with their effects on alcohol drinking in C57BL/6J mice: A preliminary study. J. Psychopharmacol. 2003

2. Salvia Miltiorrhiza

Danshen, the dried roots of Salvia miltiorrhiza, is a traditional herb with more than 1000 years of clinical use.

It possesses numerous biological and pharmaceutical activities including antioxidant, anti-inflammatory and anti-apoptotic activities. Salvia miltiorrhiza extracts may decrease voluntary alcohol consumption and maintenance of alcohol drinking behavior in Sardinian alcohol-preferring (sP) rats. There are two kinds of main bioactive compounds contained in Salvia miltiorrhiza, which are linked to its functions, such as water-soluble phenolic acids and lipophilic diterpenoid quinines.

3. Scutellaria Baicalensis

It's a shock for some to discover that there are medications available that are approved to treat AUD. The newer forms of these medications are designed to counteract changes in the brain due to AUD.

In the end, deciding to seek treatment might be more crucial than the method employed as long as the method does not involve heavy confrontation and includes empathy, motivational support, and a focus on altering drinking behavior.

What Medications Are Used to Treat Alcohol Use Disorder?

There are specific medications that have been demonstrated to effectively assist individuals in quitting or avoiding drinking and preventing relapse to drinking.

Current Medications

There are currently three approved drugs for AUD in the United States, and they are a useful and effective adjunct in treating individuals with this disorder. Naltrexone can be taken as a tablet or injection and lessens the desire to drink.

Acamprosate is a tablet that reduces the aversive symptoms that are occasionally experienced during alcohol abstinence, facilitating easier maintenance of abstinence.

Disulfiram is a tablet that deters drinking by inducing unpleasant effects when alcohol is taken.

Because of the multiple biological processes underlying AUD, novel medications are necessary to offer a wider range of treatment options.

As with any other disease, individuals with substance use disorders should have a variety of treatment options accessible to them. Researchers are striving to create a greater menu of drug therapies that may be personalized to individual requirements.

In the ideal scenario, health care professionals will be able to determine what AUD treatment works best for each individual someday. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is funding research aimed at finding genes, behaviors, and other characteristics that can anticipate how well a person will react to a given treatment. Such advances have the potential to make treatment decisions even better in the future.

Use of Drugs in the form of Medication for Brain:

We found four therapies (acamprosate, disulfiram, naltrexone, and nalmefene) that are registered for use in the treatment of alcohol dependence, four therapies (baclofen, topiramate, varenicline, and gabapentin) that are not yet registered, and two (psylocybin and MDMA/Ecstasy) future potential therapies.

- Acamprozate

Acamprosate is among the FDA and EMA-approved drugs to be used to treat alcohol dependence. It is a good-tolerated and fairly safe drug that has been on the market for alcohol dependence syndrome treatment since 1989. Accidental injury, anxiety and depression, asthenia, pain, anorexia, nausea, stomach upset, dizziness, dry mouth, insomnia, itching, and sweating are the most frequent side effects of this drug. It is a medication that can be administered safely in patients with hepatic insufficiency since it is excreted unchanged primarily via the kidneys. The literature suggests that acamprosate acts on glutamatergic transmission by influencing N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate-5 receptors, which is the likely mechanism of action of acamprosate. This compound may also indirectly influence GABA receptor transmission.

- Nalmefene

Nalmefene is the first drug approved by the EMA for the treatment of alcohol dependence syndrome in adults. Mechanism of action of nalmefene lies in the fact that it is a selective modulator of opioid receptors; it functions primarily as an antagonist of μ- and δ-receptors and a κ-receptor partial agonist .Its action on μ-receptors suppresses the experience of pleasure when alcohol is consumed, while its action on κ-receptors decreases the dysphoria related to alcohol withdrawal .The most frequently observed side effects of nalmefene are dizziness, nausea, fatigue, headache, pharyngitis, sleep disturbances and insomnia, vomiting, hyperhidrosis, increased appetite, tachycardia .In clinical trials with addicted patients, nalmefene appears to be a good-tolerated, effective drug for treating alcohol dependence syndrome under clinical conditions .In addicted patients with psychiatric disorders, nalmefene, when taken as needed, has been found to decrease alcohol craving both in study groups . Clinical moderators of response to nalmefene in a randomized-controlled trial for alcohol dependence: An exploratory analysis. Drug Alcohol Depend. 2022.

- Disulfiram

The likely mechanism of action of disulfiram is its blockade of the aldehyde dehydrogenase enzyme, leading to an accumulation of plasma acetaldehyde. Increased plasma acetaldehyde concentration causes aversive feelings upon alcohol intake, i.e., tachycardia, shortness of breath, tachypnea, and feelings of heat, anxiety, panic, headache, nausea, vomiting. By contrast, efficacy of disulfiram in the clinical trials is uncertain, because results of clinical trials on curbing alcohol craving are inconsistent partially, since the patients find it hard to conform to the drug's compliance.

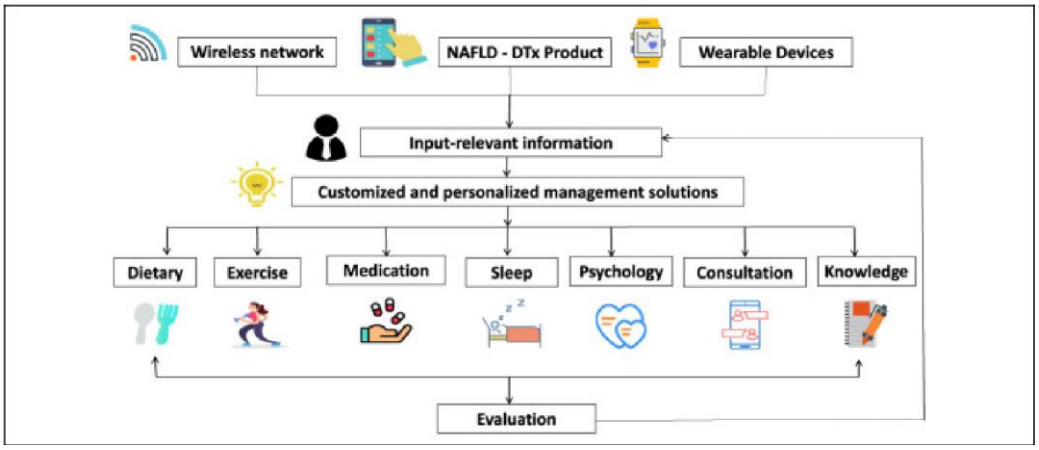
- Naltrexone

Naltrexone is an opioid competitive antagonist with a specific affinity for μ-receptors, and therefore the decrease in alcohol intake with simultaneous use of this drug is connected with the suppression of the reward system and the decrease in pleasure felt after drinking alcohol products. Naltrexone has been approved by the FDA since 1984 for medication-assisted treatment of alcoholism, including in extended-release form, and since 1994 for opioid dependence.

A systematic review comparing the efficacy of oral naltrexone and extended-release naltrexone in alcohol-dependent HIV-positive patients revealed that drug therapy decreased alcohol use and enhanced viral suppression without major side effects In a clinical trial of 32 alcohol-dependent subjects, extended-release naltrexone was determined to be linked with extended abstinence as a result of better patient compliance and thus could be used as first-line therapy in individuals with the issue of alcohol abuse. Treatment outcomes of long-acting inject capable naltrexone vs oral naltrexone in alcohol use disorder in veterans. Ment. Health Clin. 2019.

FUTURE TREATEMENT

Both non-invasive (rTMS and tDCS) and Invasive (DBS) brain stimulation methods acting on respectively basal ganglia systems or prefrontal cortical areas are safe and well tolerated and hold promise in the clinical treatment of alcohol drinking and craving. Invasive DBS must continue to be the treatment of last resort in extremely severe life-threatening AUDs, while non-invasive brain stimulation methods may serve as treatment options for less severe AUDs. However, a successful strategy to utilize optimally brain stimulation methods in the treatment of AUD addictions must be capable of applying in future researches and clinical trials a number of enhancements.



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- First, a thorough characterization of patient populations in clinical terms like consumption and craving severity levels is essential to enable valid comparability between studies.
- Second, accurate primary and secondary outcome measures and pre-hoc selection of evaluation criteria must be clearly specified to justify transposable data. To this end, alcohol craving must continue to be the primary criteria to measure efficacy. Third, a good and stable measurement of craving at baseline and after treatment is essential to be able to compare between studies. To this end, we would highly advise the use of ecological cue- or sensory driven approaches which have been found to be highly correlated with short-term relapse. Feasibility study of a computerized carbohydrate estimation system by using Thai food images compared with dietitian's estimation. Front Nutr 2021. Fourth and finally, a good choice of proper targets (e.g. left, right or bilateral DLPFC, NAc, STN, dorsal striatum, lateral habenula, mPFC or hypothalamus is still among the most significant challenges of neuromodulation research.

Numerous treatments are currently available for AUD, but treating it is still not accessible to everyone. While AUD is extremely prevalent, with 5.9% of global deaths linked to alcohol use, only about 22% of patients are being treated for this destructive condition. In the US, only 1 of every 6 adults had ever had their drinking habits evaluated by a health care provider, and in 2015, only 8.3% of individuals were treated in a specialty facility out of the 15.8 million adults who indicated a need for treatment due to alcohol consumption. Although with a high rate of AUD prevalence, the stigma of addiction and a lack of systematic screening in primary care remain as they are obstacles to treatment seeking and access. Furthermore, treatment in the U.S. is only accessible to those with the time to seek it and to those with the finances to do so. Epidemiology of DSM-5 alcohol use disorder is the outcome of the national epidemiologic survey on alcohol and related conditions III. JAMA Psychiatry 2015.

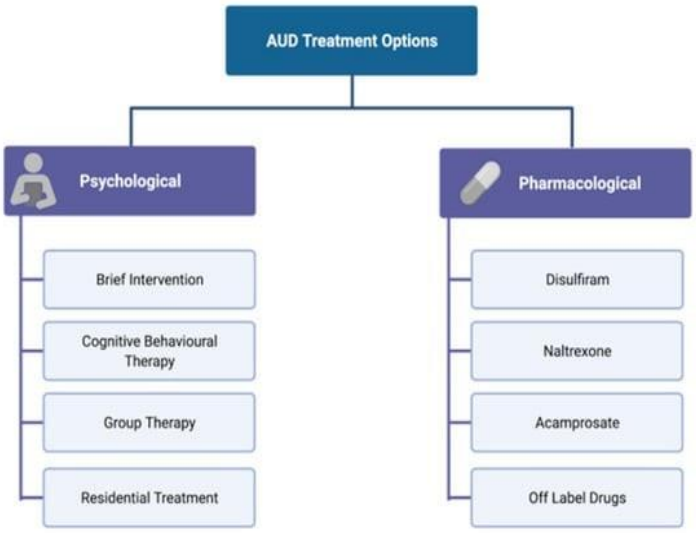
Treatment of AUD consists of both non-pharmacological treatment like motivational interviewing, cognitive behaviors therapy (CBT), group therapies, and support groups like Alcoholic Anonymous (AA) as well as pharmacological treatments, including medications directed against some of the alcohol affected neurotransmitter systems.

In mild AUD, it is advisable to initiate one or more non-pharmacological strategies prior to initiating pharmacological treatment, while in severe cases, the combination of nonpharmacological and pharmacological therapy is advised.

Psychological and Non-Pharmacological Therapies for AUD

Non-pharmacological treatment for AUD varies from one-on-one interventions to comprehensive in-patient residential treatment and from more conventional methods like counselling to the utilization of contemporary technology. Most psychological treatments have short-term targets for abstinence or reduction in drug or alcohol use, with health professionals encouraging compliance and treatment involvement, in addition to serving as a source of constructive encouragement and reinforcement. Long-term objectives are to sustain abstinence, or consequence-free consumption of small quantities of alcohol, and to assist the patient in overcoming the mental illness and social issues resulting from AUD.

Psychiatry 2 There are twelve TLRs found in mice, with TLR4 being the most extensively studied subtype for alcohol action. Other TLRs in brain are also involved in alcohol's neuroimmune effect. For instance, TLR2 KO mice have decreased ethanol intake. Furthermore, TLR2 can be involved in mediating ethanol-evoked neuroinflammatory consequences and anxiety-like behavior following ethanol withdrawal.



Conclusion and Future Directions:

Currently, there is considerable evidence that AUDs are linked with substantial alterations in the adult human brain, including significant decreases in WM (e.g., Monnig et al., 2013). Although there is excitement and interest regarding how drinking may affect the human adolescent brain, empirical research is still limited. Our aim in this systematic review was to provide one of the earliest syntheses of the human data in this new field to ascertain how active alcohol use affects the developing human adolescent brain.

With regard to this question, we identified only 21 studies that met our criteria for empirically assessing differences in structural and functional brain development in AU adolescents. Although key design issues deserve serious attention, we think that available data assessed in this systematic review enable us to make the following tentative conclusions regarding the association between active adolescent alcohol use (AU) and human brain development.

- First, whereas other good-quality reviews of adolescent AU and brain development have had a much more extensive range of inclusion criteria (e.g., family alcohol use history, genetic vulnerability, other drug abuse; we used a more constrained set of criteria to assess the effect of AU on the emerging brain. In line with the overall greater body of literature in the field, despite this tightly focused set of studies, the message remains clear: alcohol is a special cause of structural and functional changes in the human adolescent brain.

- Second, this systematic review illuminates where those brain differences lie.

In line with the wider literature in this field, within the present systematic review, we found volumetric and connectivity contrasts for Au vs. non-Au youth in prefrontal regions of central importance, such as but not limited to, the MFG, superior frontal gyrus, left frontal cortex, frontal pole, and IFG. These regions are crucially engaged in the capacity and command of executive control. Of concern to risk for future drinking, executive control includes response inhibition, which in everyday social interactions, reflects youths' capacity to avoid being tempted to do risky, but rewarding and thrilling things (e.g., drinking with peers). We also found structural and functional differences between AU versus non-AU youth throughout the meso-corticolimbic reward system, which is a dopamine-dependent brain circuit that comprises the dorsal striatum (caudate/putamen), thalamus, anterior cingulate, internal capsule and IFG.

Involvement of this system overlaps with human adult alcohol addiction studies, and perhaps is central to the interplay between incentive salience ('wanting' vs. 'liking') a substance, control, and reward in drinking decision-making regarding whether and how much to consume.

Rodent models indicate that early and repeated exposure to alcohol in adolescence tips the balance towards more 'wanting' (incentive salience), increases the rewarding characteristics of alcohol (e.g., more positive experience of alcohol use, more rewarding experience of intoxication), but at the same time decreases the aversive and punishing components of drinking (e.g., alcohol's sedative effects, experiencing hangovers). The third of these conclusions from this systematic review is that, in line with available human, adolescent AU females are potentially at increased risk for structural and functional changes in brain.

This is important since gender differences have been observed in MRI scans of normal brain development, with peak GM volume in the frontal and parietal lobes occurring later in boys compared to girls during late childhood/early adolescence.

The higher deviation from normal developmental paths indicates a more harmful effect of alcohol on young female brain development.

For that reason, it has been suggested by some that AU disrupts intact NMDA-mediated synaptic pruning. As it relates to global psychosocial effect, females' differential neurodevelopmental impact of AU bears particular importance when considering increased alcohol-related outcomes documented for females within epidemiologic analyses. However, the nature of this pattern - whether it is a premorbid risk constellation, a correlate, or an effect of adolescent AU - remains far from clear. The possible involvement of sex hormones in this equation opens up a space for future research. Fourth, we had evidence for an association between amount of alcohol consumed and adolescent brain structure and function. Specifically, higher AU consumption was associated with reduced brain volume in a number of areas, reduced WM integrity and reduced levels of BOLD response. Our fifth conclusion pertains to what these data imply regarding clinical prevention and intervention implications.

Overall, these aggregate data imply that there is a distinct pattern of brain structure and function for AU compared to non-AU youth.

Specifically, such brain-based distinctions are germane because they have been shown to put adolescents at higher risk for future binge drinking and prolonged AUDs deep into adulthood Although there is concern about how this development would continue unabated, there is also hope.

The larger human adolescent addiction literature indicates that differences observed revert to normal when AU is terminated. Therefore, the human adolescent brain can perhaps catch up once adolescents can cut down or

abstain from AU. One potential clinical route could be to strengthen and enhance prefrontal/executive control abilities, in order to enable AU youth to make better decisions towards minimizing AU. In a similar way, strategies that re-direct AU youth towards the interaction between incentive salience, control and reward could be especially helpful.

Potential interventions are motivational interviewing (which increases substrates of self-reflection and introspection among adolescents; mindfulness (which enables youth to decouple the relationship between desire to use and actual use; Bowen et al., 2014), and contingency management (which could help increase the rewarding effects of reduced use/abstinence; Stanger.

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