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Alcohol Related Cognitive Impairments: an Overview for Clinical Practitioners

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Abstract

The harmful effects of chronic alcohol use have become increasingly evident in recent years. Studies have linked chronic alcohol use to an array of pathology affecting all organ systems, especially the central nervous system. The neurocognitive effects of alcohol may become irreversible with the persistent consumption. Repeated offensives can ultimately cause neurotransmitter dysregulation and direct and indirect neurotoxicity, subsequently resulting in various clinical syndromes. This article reviews literature relevant to cognitive impairments and treatment options associated with alcohol use for practitioners so that they may provide appropriate treatment and educate patients and their families.

Introduction

The harmful effects of chronic alcohol use have become increasingly evident in recent years. Studies have linked chronic alcohol use to an array of pathology affecting all organ systems including the Central Nervous System (CNS). The cognitive effects of alcohol are often dose dependent and may become irreversible with persistent consumption. Repeated offenses can ultimately result in cerebral deficits that range from neurotransmitter dysregulation to direct and indirect neurotoxicity [1].

The DSM-5 defines alcohol induced major or mild neurocognitive disorder as one of substance/medication-induced conditions characterized by significant decline in one's cognitive function that persist even after alcohol use has ceased [2]. Unfortunately, 17% of adolescents and 9% of adults suffer from alcohol dependence in the United States. It's estimated that alcohol related offenses costs the public roughly $223.5 billion dollars annually in legal, traffic, and medical expenditures. Furthermore, drinking is responsible for more than 100,000 deaths and 5% of the total mortalities in the United States annually [1].

Although there are studies showing that moderate alcohol consumption protects against dementia in individuals older than 75 [3], this effect has been interpreted with caution in a systematic review of meta-analysis published in 2011 studying individuals older than 65 [4]. According to a longitudinal prospective study which studied cognitive function in more than 7000 individuals over a 10 year time period, excessive alcohol consumption in midlife is associated with faster cognitive decline in all cognitive domains later in life in men. The decline was less in females and was only seen in executive functions [5]. Studies have shown that alcohol-related dementia accounts for up to 24% of dementias seen in nursing home residents [6]. Also, it has been reported that prevalence of alcohol related dementia is 10% of all dementia cases [3]. Unfortunately, elderly Americans are seldom screened and treated for alcohol use disorders. It is currently estimated that 60% of adults over the age of fifty used alcohol within the last year. Furthermore, nearly 5% of this older aged population suffers from alcoholism. If prolonged, cognitive impairments in the elderly can lead to irreversible deficits that can have a dramatic impact on their quality of life. In order to prevent the adverse effects of alcohol dependence, it's imperative that elderly patients receive proper screening and treatment for substance abuse disorder [7]. This paper will discuss commonly seen cognitive deficits caused by alcohol abuse and their various treatment options.

Acute effects of Alcohol Intoxication

Alcohol intoxication can cause a broad spectrum of CNS acute and chronic manifestations. Acute alcohol intoxication presents with poor attention span, difficulties with abstract thinking, problem solving, anterograde amnesia, and reduces visuospatial abilities. These manifestations are often precipitated from temporary disruption of neurotransmitter activity within the brain. When used acute, these changes are mostly reversible. A few of the neurochemical systems altered during times of acute alcohol intoxication are the gamma-aminobutyric acid (GABA), opiate, dopamine, and glutamine pathways. Changes in the GABA and glutamate pathways are associated with intoxication and sedation while dopamine and opiate pathways are responsible for pleasure and addiction [8].

Once absorbed systemically, ethanol up-regulates dopaminergic neurons in an area of the brain known as the ventral tegmentum. Upon stimulation, these nerves release dopamine into the nucleus accumbens. This region of the brain is known as the "reward center" and is responsible for pleasure and addiction associated with alcohol use. Although alcohol stimulates dopamine directly, it is hypothesized that the neurotransmitter GABA is mainly responsible for the dopaminergic surge. GABA is inhibitory neurotransmitter that helps regulate the release of dopamine. However, ethanol is unique in that it inhibits GABA release. This ultimately results in the disinhibition of neurons in the ventral tegmentum and aids in the dopaminergic surge seen during alcohol intoxication. In cases of chronic alcoholism, molecular modification occurs that results in an increased number of GABA channels to compensate for decreased activity due to continuous alcohol exposure. Once these chronic changes occur, withdrawal will be seen with decreased blood alcohol

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levels due to hyper excitation of GABA neurons and a subsequent hypo excitation of dopaminergic activity [8].

Acute alcohol exposure is further modified by the production of endogenous opioids. Once ingested into the body, alcohol modulates the release of enkephalins and beta-endorphin. These endogenous opioids contribute to further disinhibition of dopaminergic activity in the reward centers of the brain and helps perpetuate the potential for addiction [9].

Cognitive Disorders caused by Chronic Alcohol Abuse

Historically, there has been controversy regarding alcohol's potential to cause lasting cognitive impairment. This is due to the complex nature of the disease and the lack of primary literature surrounding the issue. Because of the vast number of unanswered questions regarding alcohol related dementia, physicians are left guessing whether direct neurotoxicity or secondary effects of alcohol exposure lead to dementia. Diagnosing alcohol induced neurocognitive impairments further complicated by the wide range of symptoms seen in chronic alcoholics. However, over the last decade alcohol induced neurocognitive impairment has gained global attention by the research community [10]. As mentioned earlier, the DSM-5 defines alcohol induced neurocognitive impairment as a decline in cognitive function that persists even after alcohol has ceased. Furthermore, the DSM classification breaks the diagnosis down into major and minor criteria. Minor criteria are defined as a decrease in cognitive function that doesn't interfere with daily living but requires increased effort to accomplish normal activities. Likewise, major criteria are defined as a decline in cognition that affects most aspects of one's daily activities. However, before considering alcohol induced neurocognitive disorder patients must undergo a thorough evaluation by a trained clinician. Suspected individuals should be screened for nutritional, psychiatric, hepatic, traumatic and acute illnesses before the diagnosis can be made [1].

It is estimated that 78% of alcoholics will demonstrate some level of cerebral pathology on autopsy. Still there is much debate over how much alcohol consumption will lead to alcohol-related dementia. In 1998, a researcher by the name of Oslin set out to determine the correlation between the level of alcohol consumption and the development of lasting cognitive impairment. According to Oslin et al. a diagnosis of probable alcohol-related dementia is indicated when clinical symptoms of dementia are observed in the context of a significant history of alcohol use. His guidelines included a minimum average of 35 drinks per week for men and 28 drinks per week for women for a five year period. Additionally, his guidelines state that symptoms must persist for 60 days after cessation of alcohol use. This guideline has been recognized in the clinical arena and was one of the pioneer studies that identified the correlation between dementia and chronic alcohol abuse [12].

Studies have identified a variety of mechanisms through which alcohol impairs cognition. Perhaps the most significant implications are the direct effects alcohol has on the neurotransmitter levels in the brain. This is commonly referred to as the "neurotoxicity hypothesis". This hypothesis recognizes degenerative neuropathology from glutamate induced excitotoxicity secondary to up regulated NMDA receptors. Generally speaking, NMDA receptors when stimulated by glutamate excite the nervous tissue. Naturally ethanol exhibits an inhibitory effect on these glutamate receptors in the central nervous system. In cases of chronic ethanol exposure, NMDA receptors are unregulated as part of a compensatory mechanism. With repeated withdrawal, glutamate release excites the overwhelming number of new NMDA receptors which leads to permanent neuronal loss and ultimately dementia [13].

There are also a number of neurocognitive disorders seen in alcoholics secondary to nutritional deficiencies. The two most common alcohol induced amnestic disorders include pellagra and Wernicke-Korsakoff syndrome. Pellagra is a nutritional disorder caused by niacin deficiencies. In cases of pellagra, niacin absorption is altered with chronic alcohol intake which can lead to lethal if untreated so proper screening and recognition of alcohol abuse is essential in improving the prognosis of those at risk [1].

The more serious amnestic disorder seen in alcoholics is Wernicke-Korsakoff syndrome. Wernicke's encephalopathy results from prolonged thiamine deficiency. Alcohol alters the absorption and metabolism of thiamine leading to severe losses with chronic exposure. Thiamine is a cofactor for essential biochemical pathways such as glucose metabolism and regulation. Thiamine deficiencies left untreated can ultimately lead to atrophy and infarct of cerebral tissue most notable the mammalian bodies and thalamus. Clinically, Wernicke's encephalitis is diagnosed by the classical triad of ophthalmoplegia, ataxia, and dementia. Prolonged Wernicke's encephalitis can lead to severe memory impairment known as Korsakoff syndrome. Often these two syndromes manifest from the same etiology and is referred to as Wernicke-Korsakoff Syndrome (WKS). Recognizing and diagnosing WKS is imperative in preventing the life threatening complications often seen in undiagnosed individuals [14].

Another alcohol related disorder with cognitive impairment is Marchiafava-Bignami Disease (MBD). This fatal condition is much less common than above mentioned conditions but is associated with interesting psycho-neurological findings on history, examination, and brain imaging. Although MBD is very rare, it is almost always diagnosed in alcoholics [1]. It can cause a variety of psychiatric consequences like mania, depression, paranoia, and dementia. It has poor prognosis and often leads to death in a few months [15]. MBD causes progressive demyelination and necrosis of corpus callosum that is identifiable in brain MRI. In addition to its psychiatric consequences it can also result in seizures, paresis, ataxia, limb hypertonia, dysarthria, and signs of interhemispheric disconnection. However the etiology is not fully understood [16].

Neuropathology of Alcohol Specific Brain Damage

According to brain weight studies by Kubota et al. a group of uncomplicated alcoholics (drinking more than 418 g of ethanol per day) had a significantly reduced brain weight compared with controls [17]. There is pathological evidence suggesting that alcohol causes damage to both gray matter and white matter. White matter damage is predominant and results in a reduction in brain volume. A component of the white matter loss appears to be reversible in some cases, given a significant period of evidence [1].

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Assessment of Cognitive Impairment due to Alcohol

Open communication and a good rapport with the patient are key factors in identifying and treating alcohol abuse disorders. The physician should find a way to screen and treat without alienating the patient or appearing judgmental. Screening starts with an excellent history and physical examination. It is recommended by the National Institute o Alcohol Abuse and Alcoholism (NIAAA) that all adults should receive screening annually for alcohol abuse. There are many different screening tools such as the Alcohol Use Disorders Identification Test (AUDIT) questionnaire that can be helpful when trying to identify substance abuse [18]. Additionally, the physical examination may offer clues such as signs of liver disease, including gynecomastia, jaundice, ascites, or signs of confusion and personality changes. Imaging is also useful when evaluating a patient with a longstanding history of alcohol abuse. Cerebral atrophy is well documented with alcoholism. In such instances, CT imaging will often identify global cerebral atrophy, enlarged ventricles, and larger than normal sulci. Functional imaging will show lower frontal lobe glucose utilization and decreased cerebral blood flow [1].

All geriatric patients presenting with cognitive deficits should be screened for alcohol abuse. Based on their clinical examination, a laboratory analysis may be warranted. Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with the pathognomonic ration of 2:1 and an elevated gamma-glutamyltransferase (GGT) may provide objective data. Carbohydrate deficient transferrin (CDT) is a more sensitive and specific marker for recent heavy alcohol consumption. There is some evidence that cognitive impairment related to alcohol is reversible and so once these patients are identified, prompt action should be taken [19].

These patients are more likely to present with medical complaints such as abdominal pain, pancreatitis, gastritis, malnutrition/weight loss or physical injuries related to disinhibited behavior. They may also present with psychiatric concerns such as depression, anxiety and memory loss. After careful physical examination and history taking, a complete blood count with differential, electrolyte and liver panel, folate and vitamin B_{12} should be assessed, and a head CT may be helpful if cognitive impairment is severe enough to warrant head imaging. Early detection, education, counseling and close follow up with appropriate referrals are key. It is also important for physicians to practice introspection. Like the general public, we may find ourselves fostering stereotypes and biases about alcoholism. This may hinder our diagnostic practices. Most clinicians will agree that screening all patients, thought it may take a few minutes can be valuable and may have a lasting impact on not just the health care system, but also encouraging sobriety and promoting the general health and wellbeing of our patients.

Screening

Screening for alcohol abuse is the mainstay for the prevention of alcohol related diseases. In order to prevent the lasting cognitive deficits seen with chronic alcohol use, high risk individuals must be appropriately screened and treated early on. According to a study published by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), only fourteen percent of alcoholics receive proper treatment [20]. Furthermore, of those receiving treatment only a small percentage were detected through screening. Treatment for alcohol abuse is typically indicated when a maximum of four drinks for men, and there drinks for women are consumed on a daily basis [20]. There are a variety of screening modalities physicians can use when screening for alcoholism. The CAGE questionnaire is a popular screening technique used by many primary care doctors. The "C" in the acronym prompts the physician to ask the patient if they have ever felt they should cut down on drinking. Likewise, the "A" should prompt the physician to ask if the patient is ever annoyed when people criticize them for their drinking habits. The "G" represents if the patient feels guilty for drinking whereas the "E" questions their desire to drink first thing in the morning [20]. Each question is worth one point and a teat should be considered positive when a patient scores two points or higher. Another questionnaire commonly used is the Alcohol Disorders Indentification Test (AUDIT). Research shows that the AUDIT questionnaire is especially effective for detection of alcohol abuse in adolescents, women, and minorities [21]. These are just a few of the many screening options physicians have at their disposal when trying to identify alcohol abuse.

Behavioral Therapies

Although medications are commonly used to help combat alcohol addiction, studies have shown that long-term recovery is most successful when using a combination of both medical and behavioral therapies [20]. Perhaps the most important part of initiating therapy is the ability of the physician to properly engage and demonstrate concern about the patient's addiction. In fact, studies have shown that two or more doctor's visits, and a follow-up phone call by the physician, significantly increase a patient's recovery rate over a four year period. Still there are many strategies physicians have at their disposal to help promote abstinence. A few examples of commonly used therapies include cognitive behavioral therapy, motivational, and family therapy [20]. Cognitive behavioral therapy involves the patient being counseled one-on-one with a physician. Here, a patient-doctor relationship is strengthened in order to help identify situations that promote alcohol use. By helping one understand what triggers their desire to drink, patients are better equipped to recognize and avoid high-risk situations. Motivational therapy is imperative for helping patients build the confidence necessary to begin the healing process. However, perhaps the most important intervention for promoting abstinence is family therapy. This form of therapy is directed at helping the patient develop a stronger support system at home. By optimizing ones social support they are more likely to cope with stressful situations by turning to loved ones instead of alcohol [20].

Medications

As mentioned earlier, alcohol-abuse disorder is best treated with a combination of behavioral and medical therapies [21]. However, medical therapies are generally discussed in the context of acute alcohol withdraw and those used to maintain sobriety. When considering medical therapy for acute withdrawal, it's imperative to understand that symptoms can become life threatening if not treated appropriately. In management of acute alcohol withdrawal, the goal is to prevent the patient from developing alcohol withdrawal delirium, also known as delirium tremens (DTs), the most severe form of alcohol withdrawal syndrome. DTs generally develop 3-5

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days after alcohol cessation and are characterized by severe agitation, hallucinations, hypertension, and tachycardia [22]. If the patient has a history of extended alcohol use or prior DTs, it's recommended that he or she be monitored through the inpatient setting. Patients with DTs are screened for metabolic and electrolyte abnormalities and started on a daily regimen of thiamine. Patients are monitored hourly for signs and symptoms of alcohol withdrawal or agitation using the Clinical Institute of Withdrawal Assessment for Alcohol (CIWA) scoring system. Depending on the patient's symptoms and their CIWA score, these individuals are placed on benzodiazepine regimen. Depending on the physician and the patient's symptoms both short acting and long acting benzodiazepines use in alcohol withdrawal suggests that there is no superior benzodiazepine when selecting one treatment regimen [22].

There are also a variety of medications that are marketed to help patients maintain sobriety. As discussed throughout the paper, these medications are often used in combination with behavioral therapies in order to reach their highest potential. Currently, the U.S. Food and Drug Administration (FDA) has approved three medications for the treatment of alcohol dependence. These three medications consist of naltrexone, disulfiram, and acamprosate with different mechanisms of action [23]. In order to choose any of these three medications their side effect profile needs to be taken into consideration. Naltrexone is a commonly prescribes medication that has been proven by many studies to reduce the relapse rate in patients suffering from alcohol dependence. Naltrexone works as an opioid receptor antagonist and reduces the reinforcing effects of alcohol, which ultimately results in fewer cravings. Disulfiram is an acetaldehyde dehydrogenase inhibitor that has fallen out of favor due to mixed studies showing no reduction in relapse rate for those using the medication. Finally, acamprosate is thought to block certain glutamate receptors, which ultimately decreases the debilitating withdrawal seen with chronic alcohol abuse. Nearly fifteen studies have been done on acamprosate verifying its effectiveness in improving sobriety in those suffering from alcoholism [23].

As it was briefly mentioned above, managing acute alcohol withdrawal symptoms is very important in preventing long-lasting cognitive disorders due to alcohol use. Following steps need to be considered in management of alcohol related dementia: 1) Evaluating nutritional and drinking history. 2) Immediate treatment of patients with parenteral thiamine. The oral thiamine is not effective because it does not reach an adequate plasma concentration. The recommended dose, frequency, route, and the length of thiamine treatment for patients suspicious for Wernicke-Korsakoff should be 200 mg three times daily intravenously until improvement in the symptoms is evidenced. 3) Cognitive functions in the patient with alcohol related dementia need to be evaluated continuously. 4) Diagnosing alcohol related dementia versus neurodegenerative disorder is critical. There are features associated only with alcohol related dementia including improvement with abstinence, impairment of executive, memory, and visuospatial functions but intact language functions, and presence of neurological finding like ataxia [24].

Although medications like memantine or donepezil might be useful in other types of dementia, especially Alzheimer's dementia, data is limited on their benefit in alcohol related dementia. There are very few studies showing cognitive improvement in alcohol related dementia with memantine [25]. Also, based on a case report in 2004, donepezil has been successfully used to improve cognitive function in alcohol related dementia [26].

Mutual-Help Groups

Despite the increasing number of medical therapies available to help patients overcome alcohol addiction, Mutual-Help Groups (MHGs) remain the most sought after treatment for combating alcoholism. MHGs are defined as a group consisting of two or more people who come together to help one another to overcome a debilitating addiction [20]. These groups are often anonymous and utilize a Twelve-Step Facilitation (TSF) therapy to help their members maintain sobriety. MHGs have grown in popularity due to a variety of factors. Most importantly, these groups are a convenient and inexpensive way for alcoholics to combat their disease. Additionally, these groups allow people to come together and build a support network with individuals suffering from a similar illness. A sixteen-year study was done showing the effectiveness of alcoholics being formally treated with medications and those simply attending MHGs. The study showed that individuals attending MMHGs and treated medically had the highest rate of success over an eight-year period then the groups being treated with a single form of therapy [27].

Conclusion

There is no question that alcohol related dementia has caused a heavy burden on the patients and families. In order to reduce the prevalence of this disease it is imperative that health care professionals, in particular, primary care providers, become efficient at screening for alcohol abuse, recognizing the disease, and planning management. Moving forward, we as a society must also become better at educating the public on the risk dos long-term alcohol abuse and its various neurocognitive effects. Only through proper screening and education, we can prevent the devastating impact of this ever growing epidemic.

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