Alcohol Use Disorder with Dr. Cummings

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Michael Cummings, M.D. and David Puder, M.D. do not have any conflicts of interest.

In this week's episode of the podcast, we interview Dr. Michael Cummings, a psychiatrist, researcher, and associate professor at Loma Linda University. This podcast is the first of a series on addiction and the focus of this week's episode is on alcohol use disorder. In this episode, Dr. Puder and Dr. Cummings dive into the history of alcohol use, vulnerabilities and mechanisms responsible for the development of alcohol use disorder and its related neurobiological circuits, and common pharmacological, psychotherapeutic, and behavioral interventions and treatments for alcohol use disorder.

This episode will count towards the CME requirements of the new DEA law. This is a one-time, 8 hour training requirement introduced by the Consolidated Appropriations Act of 2023 for all Drug Enforcement Administration (DEA)-registered practitioners. This training focuses on the treatment and management of patients with opioid or other substance use disorders. Here are some other episodes that meet the requirements:

- Episode 044: Marijuana and Mental Health (0.5 CME units)
- Episode 064: Does Cannabis Use Increase Schizophrenia and Psychosis? (0.75 CME units)
- Episode 066: Fentanyl: The Next Phase in the Opiate Epidemic (0.75 CME units)
- Episode 030: Ketamine and Psychedelics with Dr. Michael Cummings (0.75 CME units)

I hope this message finds you well. I am writing to inform you about the new one-time, eight-hour training requirement introduced by the Consolidated Appropriations Act of 2023 for all Drug Enforcement Administration (DEA)-registered practitioners. This training focuses on the treatment and management of patients with opioid or other substance use disorders.

In light of this new requirement, we are excited to announce that our podcast CME will offer/provide enough CME units to meet the new 8-hour CME requirement in the coming 4 months. Our course will provide you with the latest evidence-based information, best practices, and practical tools to enhance your knowledge and skills in addressing

addiction and supporting patients during the detoxification process and also in the midst of their addiction and recovery.

History of Alcohol Use and Modern Day Prevalence

Alcohol, also known as ethanol, was likely discovered before the beginnings of recorded history. It is made through a fermentation process involving microorganisms that chemically alter sugars, such as glucose and fructose, into ethanol and carbon dioxide. This fermentation process can be initiated by humans or can occur spontaneously in nature, such as in the ripe fruits of the marula tree in Africa.

Today, alcohol is the most widely consumed intoxicant, with approximately 55% of the United States population consuming it on a regular basis. Alcohol use disorder has been an ongoing issue for the field of medicine for decades and it is estimated that a cost of $249 billion is incurred annually between the cost of medical care and the cost of lost productivity. In addition to financial costs, alcohol addiction has a variety of deleterious health and wellness effects, including health deterioration, loss of family, and earlier mortality (Witkiewitz, Litten, Leggio, 2019).

Who is Vulnerable to Alcohol Use Disorder?

Alcohol is often the first mind-altering substance that individuals choose to experiment with; however, not all alcohol users develop series and chronic problems. It has been demonstrated in a variety of twin and linkage studies that approximately 50% of the risk of developing alcohol use disorder is related to genetics (Tawa, Hall, Lohoff, 2016; Gardner, 2011). In addition to genetics, physiological susceptibility to the effects of alcohol may influence addictive behavior. Specifically, individuals who are less responsive to the effects of alcohol often need larger quantities of alcohol to become intoxicated; subsequently, such less-responsive individuals are at the greatest risk of developing alcohol use disorder (Tawa, Hall, Lohoff, 2016). Finally, certain psychological predispositions may leave some individuals more vulnerable to the development of substance use disorders. In particular, individuals with a more anhedonic (pleasure-lacking) baseline are more likely to develop problems with substance use.

Often, these individuals self-report the initial consumption of such substances as the first time they felt “normal.”

Neurobiological Circuits of Substance Use Disorders

Several different neuroanatomical regions and circuits have been demonstrated to be implicated in the pathogenesis of substance use disorder. One such region is the ventral tegmentum, a component of the mesolimbic pathway involved in processes such as emotional regulation, reinforcement learning, and motivation (Gardner, 2011). The ventral tegmentum contains many dopamine releasing nuclei which impinge on the nucleus accumbens, an additional component of the reward circuit. Under normal conditions, dopamine, a neurotransmitter involved in pleasure sensation, is released in response to the pursuit phase and attainment of valued ends (Baik, 2013; Gardner, 2011). However, this dopamine-mediated reward circuit is also active in individuals with addiction, where the both pursuit and utilization of the related substances (or activities such as internet use, sex, etc.) also results in the release of dopamine, often in large amounts (Gardner, 2011).

Interestingly, it has been demonstrated in animal studies that ablation of the nucleus accumbens results in the development of complete resistance to addiction (Gardner, 2011). The nucleus accumbens has several subsequent projections to additional areas, including the prefrontal cortex, orbitofrontal cortex, cingulate gyrus, amygdala, and hippocampus. Each of the aforementioned projection sites may also be dysregulated in addiction. For example, the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC) can be implicated in the anticipation of the next administration of a substance (or behavior), thus strongly orientating people to environmental cues associated with their addiction. Moreover, previous studies have demonstrated that rats addicted to alcohol show greater amounts of neuronal firing when placed in the environment where they usually receive alcohol than when they are presented with alcohol itself. Similar findings have been demonstrated in humans, as well, where individuals suffering from addiction, when placed in a substance-related setting (such as a bar), have a chain of physiologic responses that mimic alcohol itself (Koob and Volkow, 2016). As such, environmental cues related to addiction may serve as significant risk factors for addicts.

While addiction used to be viewed as a character flaw, subsequent advances in medicine and psychiatry have helped to reorient our understanding of addiction as a

disease process in which certain individuals develop psychiatric illness due to vulnerabilities to addiction. This frameshift in understanding has been valuable in that it has prompted decreases in feelings of shame individuals may experience and has brought more comfort to the families of these individuals, as well. Importantly, the disease-model of addiction still gives agency to those suffering from addiction; even though they may not be responsible for having their addiction, they are still responsible for managing it.

The disease-model of addiction has resulted in several advances in the medications used to treat addiction. Currently, a variety of addiction medications exist with many unique mechanisms of action, each having unique values in terms of therapeutic indications and ideal patient populations. Below, a list of each medication is provided, along with their subsequent mechanism of actions, ideal patient populations, side effects, general notes, and clinical pearls.

Addiction Medications

Disulfaram

Mechanism of Action: Disulfaram inhibits an enzyme responsible for the metabolism of alcohol known as alcohol dehydrogenase. Inhibition of this enzyme subsequently results in a buildup of the intermediate acetaldehyde, a molecule associated with many of the negative hangover effects of alcohol use. The disulfaram-induced build-up of acetaldehyde results in many severely unpleasant effects for the patient (nausea, vomiting, dizziness), which can help to deter the patient from consuming alcohol. Disulfaram has an onset of action of 1-2 hours, and a half-life of approximately 1.5 days.

Ideal Patient Population: Disulfaram exhibits the greatest success when used to treat patients who have the desire to quit consuming alcohol, but are struggling to achieve the results they desire. Individuals who have no intention of quitting are less likely to benefit from disulfaram use.

Side Effects: Importantly, one should wait at least 24 hours after their last drink before beginning treatment with disulfaram in order to allow proper metabolism of residual alcohol in the body. Additionally, heavy drinking while on disulfaram can be lethal, and patients should be properly advised of this potentially fatal outcome.

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Naltrexone

Mechanism of Action: Naltrexone is an opioid antagonist that works by blocking the mu and delta opiate receptors in the nucleus accumbens, which are involved in the pathophysiology of addiction and reward. When these receptors are blocked, the addictive substances become less rewarding, thus decreasing the craving response.

Ideal Patient Population: Similar to disulfaram, naltrexone is also most useful in patients who desire to quit substance use; however, while disulfaram can only be used in treatment of alcohol use disorder, naltrexone has a wide range of applications and has been shown to reduce cravings for alcohol, amphetamines, and even behaviors such as kleptomania.

Side Effects: Naltrexone carries a slight risk of the development of post-dose nausea which can be avoided if consumed with food. Importantly, naltrexone may result in failure of adequate pain control when attempting to mediate pain response via opioid analgesics. Finally, naltrexone may result in reductions in experiences of pleasure along with an increased sensation of aches and pains, largely due to the endogenous enkephalin system, which is suppressed with naltrexone use.

Additional Notes: The typical oral dose of naltrexone ranges from 25 - 150 mg per day. Doses above 150 mg per day are not used because, at this dose, all opioid receptors are already blocked and any additional effectiveness is minimal. In addition to oral administration, naltrexone may also be prescribed as a once-monthly injection of 380 mg, which may be particularly useful for patients in environments in which temptation to relapse is increased or patients who may have adherence issues.

Acamprosate

Mechanism of Action: While the precise mechanism in the treatment of alcohol use disorder is not entirely known, it is believed that acamprosate modulates NMDA receptor activity and upregulates the activity of the nucleus accumbens, ultimately resulting in a blunting and reduction of the effects of alcohol and a reduction in craving.

Ideal Patient Population: Acamprosate requires 3 separate doses per day, thus increasing adherence issues. Therefore, acamprosate may best be avoided in patients who anticipate having trouble with medication adherence.

Side Effects: Anhedonia (decreased experience of pleasure) is a commonly reported side effect of acamprosate.

Additional Notes: Acamprosate requires the kidneys for clearance. Importantly, for patients with a GFR of less than 50mL/minute, the dose of acamprosate must be reduced by half.

Topiramate

Mechanism of Action: In regards to the treatment of alcohol use disorder, topiramate is a anti-epileptic drug that decreases appetite via manipulation of the feeding and satiety regions of the hypothalamus. In addition to feeding behavior, these centers are also involved in the craving of addictive substances; modulation of these centers via topiramate is effective for decreasing craving and impulsivity.

Ideal Patient Population: Topiramate is typically considered as an alternative for patients who have shown inadequate response or intolerance to the aforementioned medications.

Side Effects: Common side effects of topiramate may include cognitive difficulties, gastrointestinal symptoms, weight loss, mood changes, and fatigue.

Management of Acute Alcohol Withdrawal and Detox

Acute alcohol withdrawal can be a medical emergency. Alcohol is a central nervous system depressant and chronic use results in an upregulation of the nervous system in order to compensate for alcohol’s depressant effects. Cessation of alcohol use may result in unopposed upregulation of the adrenergic systems, with a series of deleterious effects as a result. Mild effects of alcohol withdrawal may include headaches, tremors, anxiety, sweating, and insomnia. Moderate effects encompass increases in heart rate, blood pressure, nausea, vomiting, and irritability. Finally, the most severe effects of alcohol withdrawal seizures, hyperthermia, cardiovascular instability, delirium tremens (confusion, hallucinations, life-threatening tremors), and even death.

The management of alcohol withdrawal is a multifaceted approach. Firstly, it is important that patients remain adequately hydrated, as dehydration is often a major issue with alcoholics. Additionally, alcoholics are often malnourished. In particular, thiamine deficiency can be a devastating effect of alcoholism, and may result in Wernicke's encephalopathy (symptoms include confusion and abnormal eye movements) if not adequately addressed. In alcohol withdrawal, it is encouraged to give an initial 100 mg dose of thiamine followed by additional maintenance doses 3 - 4 times daily. Importantly**,** dextrose may not be given before thiamine, as this can increase the metabolic burden and can precipitate or worsen Wernicke's encephalopathy.

In addition to management of fluids and nutrition, it is important to treat alcohols with cross-tolerant medications, such as benzodiazepines, to prevent serious negative side effects like delirium tremens or death. Benzodiazepines (such as lorazepam) and alcohol are both positive modulators of the GABA-A receptors. Therefore, treating alcohol withdrawal with benzodiazepines helps to prevent the overactivation of the nervous system and its subsequent damaging effects. Dr. Cummings notes that providers should be sure to give adequate amounts of these medications when treating alcohol withdrawal, as undertreatment may be devastating.

Addiction Treatment and the Integration of Medication, Therapy, and Support

While the use of medication interventions has a multiplicity of benefits, medications alone are inadequate for the treatment of addiction. In addition to medications, an appropriate approach to addiction treatment must also involve additional elements, such as an active participation in a treatment program, psychotherapy, and a supportive community. Lastly, it is important for both providers and patients to understand that substance use disorders are chronic, relapsing diseases. As such, relapses are often inevitable. Providers and patients alike must understand that in the face of a relapse, the appropriate response is not to give up, but simply to get things back under control. We hope that today's podcast has provided the listeners with valuable information and tools that may serve to facilitate management and treatment of alcohol addiction and its related disorders.

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