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Management of Alcohol Use Disorder

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Synopsis

This monograph is a review article on the spectrum of alcohol use disorders.We discuss the pharmacological properties of ethanol along with its metabolism. The historical, physical and laboratory elements that may assist in diagnosis of an alcohol use disorder are examined. The concepts of motivational interviewing and stages of change are mentioned, along with the ASAM patient placement criteria to determine the best level of treatment when the subject is ready to take action. Various therapeutic management options are reviewed including psychologic, pharmacologic, and complementary/alternative choices. The purpose of this article is to give the clinician a basic understanding of the tools available to diagnose and treat this "Cunning and baffling" brain and multisystem disease.

Keywords: Alcoholism; Alcohol Abuse; Alcohol Dependence; Alcohol use Disorder Addiction Treatment; Detoxification; Recovery; Rehabilitation

Definition

The idea of drinking alcoholic beverages to alter mood is not new. In the ninth chapter of the biblical book of Genesis, there is a story of Noah, the most righteous man on earth getting drunk [1]. Although techniques to brew, ferment, and distill alcoholic beverages have changed somewhat over the years, the basic essence has not. Alcohol is consumed worldwide by people of many different cultural and ethnic backgrounds. The attempt to legislate abstinence in the United States, "The noble experiment" of prohibition started in 1919 and failed in 1933. Each group has some sense of boundary, over which further drinking is considered excessive. Because these boundaries vary with society, it is difficult to come up with universally acceptable definitions of alcohol misuse and abuse. There is even variation on the size of a standard "Drink", though most would consider this to be about 14 grams of absolute (95%) ethyl alcohol [2,3]. Many organizations have developed definitions of alcohol misuse, abuse, dependency, and alcoholism. Alcohol misuse generally implies one or more episodes of overuse or incorrect use. To ingest alcohol through the eye (an "Eye-shot") instead of by mouth might be an example of incorrect use. An example of misuse might be a mild/moderate alcohol user with no previous consequences getting a DUI after drinking more heavily at a wedding or graduation party. The definitions of abuse vary slightly, but most involve the 3 C's: craving, compulsion, and continued use despite negative consequences. The definitions of alcohol dependence and alcoholism usually include the physiologic phenomena of tolerance and/or withdrawal symptoms. The Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR) had distinct divisions between the diagnoses of alcohol abuse and dependence [4]. The DSM 5no longer uses this "Either/Or" paradigm, but has combined both diagnoses into an Alcohol Use Disorder (AUD) category, with 2-3 of 11 fulfilled criteria being considered mild severity of disease, 4-5 as moderate, and 6or more classified as severe disease. The new definition is as follows: "A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.

5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following:

a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.

b. A markedly diminished effect with continued use of the same amount of alcohol.

11. Withdrawal, as manifested by either of the following:

a. The characteristic withdrawal syndrome for alcohol (refer to Criteria A and B of the criteria set for alcohol withdrawal, pp. 499-500).

b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms." [5]

Prevalence

Large studies such as the National Survey on Drug Use and Health (NSDUH), National Longitudinal Alcohol Epidemiologic Survey (NLAES) and National Epidemiologic Survey on Alcohol Related Conditions (NESARC) estimate the overall prevalence of alcohol use disorders at 6.8%-8.5% in the United States [6-8]. The NSDUH2014 study demonstrates that the incidence of alcohol abuse and use disorders highest in people whose first alcohol use was before the age of 14, with decreasing incidence as the age of first drink increases. The lowest incidence in this study occurs with first use after the age of 21 years. Alcohol is the most common substance use disorder in the United States. The societal costs of alcohol use disorder when considering lost earnings, medical& legal consequences, property destruction, and treatment, is estimated to be over 240 billiondollars [7,9].

The terms "Alcoholic" and "Alcoholism" refer to severe alcohol use disorder. They were popularized in the 1930s with the publication of "The Big Book" of Alcoholics Anonymous (AA). Today these terms are sometimes felt to be insulting or stigmatizing. The natural history of severe alcohol use disorder can be separated into 2 phenotypes, which often vary by age of onset and personality traits [10,11]. The first type 1 (or type A) is noted in about 75% of men with severe alcohol use disorder. Drinking patterns are usually similar to peers until the early to mid-20s when alcohol use escalates. The first major alcohol related life problems emerge between the late 20s and early 40s. Consequences of the disorder mount during the 50s, with attempts to control drinking, exacerbations and remissions. Often treatment or recovery support is sought during this phase of illness. Traits include a low degree of novelty seeking, fighting, and a high degree of guilt, harm avoidance and reward dependence. Type 2 (or type B) is a much smaller subset that begins alcohol use during pre-or early teenage years, with a rapidly escalating course. There is a high degree of novelty seeking and often other drug use. There is a low degree of guilt, fear, and harm avoidance. Medical, legal, and social consequences often escalate by the late teens or early 20s. Research such as the Collaborative Study on the Genetics of Alcoholism (COGA) sought to determine whether certain genetic patterns could be identified in families with alcohol dependent members. The study showed susceptibility genes in DNA regions in individuals with alcohol use disorder on chromosomes 1, 2, and 7 at a level that warrants further study [12-14]. Another large, multicenter study, the Adverse Childhood Experiences (ACEs), has documented links between adverse experiences in childhood and a range of adverse health outcomes in adulthood including increased alcohol and substance abuse. There is a linear correlation between the number of adverse childhood experiences and the risk of developing an alcohol use disorder. Genetic studies have not yet demonstrated this close correlation [15,16].

Taking the History

Alcohol use disorder is a diagnosis made by obtaining a thorough, honest history. The history should include:

1. Age of first use, first intoxication, and first regular use
2. Use patterns of parents, grandparents, siblings, spouse and friends
3. Consequences of use including blackouts, arguments, lost work, health, and legal issues
4. Heaviest use, current pattern of use, longest abstinence, and number of quit attempts

There are several reliable screening tools ranging from simple to complex, which can help the interviewer incorporate and standardize this part of the history. A commonly used screening tool is the CAGE questionnaire. If two questions are answered positively, there is a reported 60%-90% sensitivity and 40%-95% specificity [17]. One problem is that the questionnaire can miss binge drinkers. The CAGE is not copyrighted and represents 4 questions asked during the history:

- Have you ever felt you should **Cut** down on your drinking?
- Have people **Annoyed** you by criticizing your drinking?

- Have you ever felt bad or **Guilty** about your drinking?
- Have you ever taken a drink first thing in the morning (**Eye-opener**) to steady your nerves or get rid of a hangover?

Another screening tool is the Alcohol Use Disorder Identification Test (AUDIT). It is a 10-item questionnaire with each item scoring 0-4 points (maximum score = 40) with a score of 8 or more indicating potential problems. The AUDIT has a sensitivity of 57%-95% and specificity of 78%-96% for hazardous or harmful drinking and a sensitivity of 61%-96% and specificity of 85-96% for alcohol abuse or dependence [18]. The AUDIT is copyrighted by the World Health Organization, with the test and module available for free. The AUDIT-Consumption (AUDIT-C) is a shorter version asking 3 questions. It is used as the screening test in VA medical centers across the United States and has been shown to have good reliability [19,20]. The Michigan Alcohol Screening Test (MAST) is a 25-question test that can either be self-administered or given by interview. It is a reliable, widely used screen that is useful in assessing alcohol related problems longitudinally [21]. The Brief (BMAST) [22], Short (SMAST) [23], and Malmo Modifications (MmMAST) [24] are shorter versions that retain good sensitivity and specificity. Screening tests for specific populations include the Geriatric MAST [25] and the Problem, Oriented Screening Instrument for Teenagers (POSIT). These tests are not copyrighted and there is no fee for their use.

Unfortunately, the addictive illness (which sometimes accompanies alcohol use disorder), often involves elements of denial, rationalization, and lack of complete candor. For these reasons, it is important to use biological confirmation through physical and laboratory examination to confirm the history when possible. The physical exam can give many clues to alcohol abuse, but the findings are often non-specific. The odor of "Alcohol" on breath can be helpful, but is not necessarily a reliable indicator of ethanol consumption.

A partial list of body systems potentially affected by alcohol abuse includes: [26]

1. Central nervous system (CNS)- "Great mimicker" of psychiatric disorders; causes decreased sleep latency, blackouts, peripheral neuropathy, Wernicke-Korsakoff syndrome, cerebellar degeneration, Marchiafava-Bignami disease (corpus callosum demyelination/necrosis), and dementia.
2. Gastrointestinal-causes esophagitis, gastritis, enteritis, increased gastric acid production, decreased LES tone; promotes absorption of iron; interferes with absorption of some B vitamins; toxic to pancreas; associated with esophageal, gastric, pancreatic, hepatocellular, and colon cancer; leads to fatty liver and cirrhosis.
3. Hematopoietic-causes pancytopenia, toxic granulocytosis, elevated MCV.
4. Cardiovascular- increases HDL; 1 to 2 drinks per day may decrease the risk of cardiac death; decreases myocardial contractility; causes peripheral vasodilatation and decreases BP in low dose but increases BP long term in high doses; causes cardiomyopathy, arrhythmias, "Holiday heart".
5. Genitourinary- modest doses increase sex drive but decrease erectile capacity; leads to testicular atrophy with shrinkage of the seminiferous tubules; causes amenorrhea, decreased ovarian size, infertility and spontaneous abortions.
6. Other-causes fetal alcohol syndrome, alcoholic myopathy, osteonecrosis with increased fractures and avascular necrosis of the femoral heads, modest reversible decreases in T3 and T4.

Laboratory analysis can also provide clues of heavy alcohol consumption. Elevations in Mean Corpuscular Volume (MCV), Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), alkaline phosphatase, Gamma Glutamyl Transpeptidase (GGT), AST/ ALT ratio of greater or equal to 2-to-1, iron saturation, ferritin, and carbohydrate deficient transferring (CDT) may be noted. Specificity can be increased by combining markers such as GGT, MCV, and CDT, but many of these lab values can be elevated due to liver disease from other causes. They should not be mistaken for proof of alcohol use. Neither should a positive urine drug screen for alcohol be considered proof of alcohol use. There are reports of sugar in the urine of diabetics being fermented into alcohol by yeast contaminating the sample.

Ethanol Pharmacology

To understand how lab analysis can be a benefit in diagnosing an alcohol use disorder, it is important to briefly review ethanol metabolism. Ethanol (C_2H_5OH) is a colorless, volatile, flammable, water soluble liquid that can be produced by naturally by the fermentation of certain carbohydrates, or synthetically by the hydration of ethylene. Described as tasteless with a burning sensation when ingested, alcohol is rapidly absorbed into the blood stream from the mucous membranes (including the mouth), stomach, small intestine, and colon. Absorption could be impaired or delayed by the presence of food in the stomach. Because of its high-water solubility, alcohol can distribute from the bloodstream into all tissues.

Alcohol acts on a variety of brain receptors that facilitate or inhibit the permeability of ions (Cl^-, Na^+, K^+ or Ca^{++}) through their respective channels. Alcohol is a γ-aminobutyric acid (GABA) and serotonin agonist which has been attributed to alcohol-induced behaviors such as intoxication, tolerance, dependence, or craving. Ethanol facilitates passage of chloride through the GABA "A" channel ($GABA_A$), the same receptor enhanced by benzodiazepines and barbiturates. It potentiates the serotonin "3" (5-HT3) receptor by facilitating passage of sodium through the channel [10]. It

has been noted that variations in the serotonin transporter-linked polymorphic region (5-HTTLPR) are associated with susceptibility to alcohol intoxication and alcohol dependence [27]. Subjects with homozygous long allele (L) in this transporter region, versus short allele (S,) have been associated with reduced intoxication and a higher risk of developing alcohol dependence [28].

Alcohol is also a glutamate antagonist, inhibiting passage of sodium and calcium through N-methyl D-aspartate (NMDA) and non-NMDA channels. These actions lead to stimulation of dopamine production in the ventral tegmental area and nucleus accumbens producing a pleasurable "Brain reward" [29,30]. There is also evidence that alcohol may act on opioid receptors, further stimulating the dopamine reward system, enhancing itsself-reinforcing properties. There is some evidence that the effect of alcohol on the μ-opioid receptor is variable, [31] and that genetic differences in the μ-opioid receptor (OPRM1 118G vs 118A) may result in a more pronounced reward [32,33]. Subjects with the Asp40 allele of OPRM1 in which asparagine has been replaced by aspartate demonstrate greater euphoric response to alcohol consumption possibly due to the receptor's increased affinity for beta endorphins. In addition to its ability to produce a brain reward, alcohol may also act as a stress reliever [34]. The role of alcohol as an inhibitor of the stress related neuropeptide Corticotropin-Releasing Factor (CRF) has also been explored [35]. It is widely believed that while people initially drink due to the activation of the brain's reward system, the perpetuation and maintenance of addictive behaviors and severe alcohol use disorder is due to reward deficit and stress surfeit. Subjects eventually drink to relieve stress and prevent the dysphoria related to abstinence. In short, they drink in an attempt to feel "Normal" [36].

Alcohol is metabolized at a rate of around120mg/kg/hr (linear zero order kinetics) in naïve users, but this can be higher in regular heavy drinkers. Metabolism is by gastric and (primarily) hepatic alcohol dehydrogenases, along with microsomal ethanol oxidizing systems (MEOS- CYP2E1). The major metabolic pathway accounts for between 90%-98% of alcohol metabolism. There are 3 genes that encode hepatic alcohol dehydrogenase, with alpha, beta, and gamma subunits with the sigma subunit primarily found in gastric mucosa [37]. There are differences in alcohol metabolism between men and women due to lower weight, total body water content, and fluctuations in gonadal hormone levels [38]. An Italian study in 1990 demonstrated decreased gastric alcohol dehydrogenase activity and first-pass metabolism in women, potentially leading to higher blood alcohol levels per unit weight than in men [39]. The remainder of ingested alcohol is either excreted, or processed through minor metabolic pathways. These pathways include conjugation with glucuronic acid and sulfate to form Ethyl Glucuronide (EtG) or Ethyl Sulfate (EtS) [40]. Both metabolites can be found in serum, urine and hair sample analysis.

After drinking ethanol, these metabolites are excreted in the urine for longer periods of time than alcohol itself, leading to a broader detection window. EtG and EtS are direct measures of alcohol consumption, not an indirect marker of potential use. Ethyl glucuronide unlike Ethyl sulfate can be produced "*In vitro*" post specimen collection or be hydrolyzed by urinary bacteria potentially causing false positives or negatives [41]. Another direct biomarker (only formed in the presence of ethanol), is phosphatidylethanol, a membrane phospholipid found in the erythrocyte fraction of blood [42,43]. These direct biomarkers have been demonstrated to correlate well with blood alcohol concentrations in subjects with alcohol abuse related consequences [44].

Determining level of treatment

Diagnosing alcohol use disorders, particularly moderate or severe forms, may be important for many reasons. Prior to its classification as "A chronic brain disease" by the National Institute for Drug Abuse (NIDA), addiction was considered a biopsychosocial-spiritual illness. The cumbersome aspects of the definition were accepted because it implies that addiction affects all areas of a person's life. As health care professionals, we are often most concerned about the well-being of our patients rather than the legal, social, or moral implications of the diagnosis. Confirmatory physical findings and laboratory result can help break through the denial, rationalization, and lack of candor that frequently accompany addiction.

Years ago, "Treatment" of an alcohol or other substance use disorder implied the subject might be whisked away to a distant 28-day recovery program to undergo rigorous lessons in submission and humility. Twenty-eight-day treatment centers have been popularized, and spoofed in literature and movies. Use of the 28-day residential program for all levels of severity, and all substance use disorders was based on rationale, but not necessarily evidence. There is certainly a place for the 28-day treatment program in the treatment of substance use disorders today, but this level of care is now more frequently selected on the basis of established criteria determining need.

Currently treatment options are evaluated and considered based on severity of illness, presence (or absence) of co-occurring disorders, social support, and willingness of the subject to engage. Many care providers, insurance companies, and societies that have formulated criteria, but those published by the American Society of Addiction Medicine (ASAM) are considered to be the standard. Included in the ASAM Criteria (now 3rd edition) are care recommendations for adults and adolescents [45]. For the purposes of this article, we will focus on the adult table. The ASAM Patient Placement Criteria uses a numerical system to differentiate levels of care with **Level 4**, which indicates hospital admission to either a medical or psychiatric unit, as the highest level (Figure 1). In Level 4patients are medically managed in an environment where nursing care and medical services are available 24 hour a day. The cost of hospital services can be thousands to tens of thousands of dollars per day depending on level of care, tests, and procedures performed.

Criteria Dimensions	Levels of Service									
	Level 0.5 Early Intervention	Level 1 OTP Opioid Treatment Program	Level I Outpatient Services	Level 2.1 Intensive Outpatient	Level 2.5 Partial Hospitalization	Level 3.1 Clinically-Managed Low Intensity Residential Services	Level 3.3 Clinically-Managed Pop Specific High Intensity Residential Services	Level 3.5 Clinically-Managed High Intensity Residential Services	Level 3.7 Medically-Monitored Intensive Inpatient Services	Level 4 Medically-Monitored Intensive Inpatient Services
Dimension 1: Alcohol Intoxication and/or Withdrawal Potential	No withdrawal risk	Withdrawal prevented by OTP	Minimal risk of severe withdrawal Level 1WM	Minimal risk of severe withdrawal Level 2WM	Minimal risk of severe withdrawal Level-2-WM	No withdrawal risk	Moderate withdrawal risk (not severe) Level 3.2WM	Moderate withdrawal risk (not severe) Level 3.2WM	Moderate risk of severe withdrawal Level 3.7WM	Severe withdrawal risk Level 4WM
Dimension 2: Biomedical Conditions and Complications	None or stable	None or stable	None or stable	None or stable	None or stable	None or stable	None or stable	Stable; may need medical monitoring	Medical monitoring required	Needs 24 hour medical care
Dimension 3: Emotional/Behavioral or Cognitive Conditions and Complications	None or stable	None or manageable in outpatient structure	None or stable	Mild severity; needs monitoring	Mild to moderate severity; needs monitoring	None or minimal	Mild to moderate severity	Unable to control impulses	Moderate severity	Severe problems needs 24 hour Psychiatric care
Dimension 4: Readiness to Change (insight)	Has insight into use affecting goals	Requires structure therapy to progress	Cooperative, but needs motivation and monitoring	Moderate resistance structure required	Significant resistance; more structure needed	Needs structure to maintain therapeutic gains	Little insight; needs motivating strategies	No insight may not believe treatment is necessary	High resistance and poor impulse control	Not applicable for this level of care
Dimension 5: Relapse/ Continued Use or Continued Problem Potential (automaticity)	Need skills to change current use	High relapse risk without OTP	Able to maintain abstinence	Higher automaticity; needs monitoring and support	Significant automaticity; needs more monitoring and support	Understands relapse, but still needs structure	Higher automaticity requiring 24 hour monitoring	Inadequate skills to prevent immediate relapse	Unable to control use with dangerous consequence	Not applicable for this level of care
Dimension 6: Recovery/ Living Environment	Good social support	Supportive recovery environment	Supportive recovery environment	Less supportive structure needed to cope	Environment unsupportive; higher structure improves patient coping	Environment unsupportive; higher structure improves patient coping	Dangerous environment; structure permits success in recovery	Dangerous environment; structure permits success in recovery	Dangerous recovery environment; structure permits success in recovery	Not applicable for this level of care

Figure 1: Adult Admission Criteria: Crosswalk of Levels 0.5 through 4. Adapted from the ASAM Criteria 3rd Ed pp: 175-176 [45].

The next lower level (3.7) permits the use of critical pathways and order sets that allow the physician to order and monitor treatment without having to manage the patient as intensely. Although facilities that provide care at the 3.7 level have 24-hour nursing care, these are frequently not full hospitals that have laboratory, radiology and on-call medical personnel readily available at all hours. **Level 3.7** services are less expensive than the hospital, but prices vary greatly depending on clientele and funding source**.**

Level 3.5 is high intensity "Clinically managed" treatment. Care is often provided by licensed psychologists, social workers or therapists, with medical services available on an as-needed basis. The programs providing a higher intensity of service often have providers with a broad range of technical expertise in a comfortable treatment setting or therapeutic community. **Level 3.3** is a "Population specific" high intensity level of residential treatment, often with amenities, structure, or range of services designed to address specific issues (such as cognitive impairment). **Level 3.1** is considered low intensity residential treatment. This treatment level is most often used as a step-down or transitional stage for patients that need structure and a safe living environment to maintain gains made at a higher service level. Patients often begin working or going to school again while in this treatment level, and process work related stressors with their recovering peers and therapists. Sometimes level 3.1 treatment facilities provide banking services to help patients budget and use their money wisely.

Level 2.5, the "Partial hospitalization program" is the most structured therapy in an outpatient setting. Level 2.5 programs provide the treatment of a medium to high intensity residential program during the day, with the patient going home at night. Time spent in treatment at this level is usually more than 20 hours per week. **Level 2.1** (the next lower step) is also known as the intensive outpatient program (IOP). IOPs have several groups or individual sessions per treatment day and often address co-occurring disorders (some have more, some have less). The intentional flexibility of Level2.1 allows treatment to be provided in the evenings and/or weekends in addition to the usual daytime weekday hours. Time spent in treatment at this level is usually 9-19 hours per week.

Level 1 is outpatient based treatment, with the frequency of office visits being decided by the provider and the patient. Patients with co-occurring psychiatric disorders or behavioral issues that might interfere with the group dynamic may respond better to individual therapy in an office visit setting**.** Time spent in treatment at this level is usually less than 9 hours per week. **Opioid Treatment Programs (OTPs)** with methadone or buprenorphine are a separate heading. OTPs can be very structured with daily visits, regular drug screens, and counseling sessions. They could also be relatively unstructured, with monthly office visits for prescription renewals and no therapy requirements.

Level 0.5 (single office based intervention) is the lowest treatment level. This level of intervention is designed to address patients who may not meet the criteria for a substance abuse or dependence diagnosis, but are noted to be at risk. Patients may be referred to recovery groups for support, but are not scheduled for follow-up sessions to address alcohol or other substance misuse. Which treatment level to use is based on the patient's performance on a 6-dimensional assessment.

Dimension 1 is alcohol intoxication and/or severe of alcohol/other drug withdrawal symptoms. Patients with severe withdrawal symptoms necessitating 24 hour medical care require hospitalization. Patients with less severe symptoms can be considered for less intensive and less costly treatment options. The ASAM Criteria includes several tables and charts that correlate level of care needed based on the severity of withdrawal symptoms and need for withdrawal management (WM). Levels of withdrawal management correspond to the levels of treatment, with the exception of level 3.2-WM which relates to both 3.3 and 3.5 levels of treatment.

Dimension 2 is biomedical conditions and complications. Patients with traumatic injuries or uncontrolled medical issues (e.g. malignant hypertension, diabetic ketoacidosis or hyperosmolar non-ketotic hyperglycemia, decompensated cirrhosis, etc.) generally require treatment in the Level 4 setting.

Dimension 3 is emotional, behavioral, or cognitive conditions and complications. Patients with co-occurring psychiatric, behavioral or cognitive disorders that impair perception of reality, or those at significant risk of harming themselves or others require addition treatment in a setting that allows concomitant treatment of both processes. This care is often provided in a hospital-based locked psychiatric ward or medical ward with one-to-one observation.

Dimension 4 is readiness to change. The keyword that summarizes this dimension to the authoris insight. The question providers must ask regards the patient's motivation to change. Is the request for treatment more related to the avoidance of external consequences or internal desire to change? Interestingly, dimension 4 responses do not qualify patients for Level 4 services. It makes sense that the hospital is not the correct level of care to impart insight. In the absence of Dimension 1,2,or 3 factors, this issue is best addressed in a lower, less costly level of care.

Dimension 5 is relapse, continued use, or continued problem potential. The keyword that summarizes this dimension to the author is automaticity. The patient may be able to sit in a counseling or group session, understand, and verbally ascend to willingness to change but then may be unable to resist alcohol use when confronted with cues or stressors associated with drinking in the past. Inability to resist impulse is not a reason for hospitalization, but may, in some cases (depending on severity) preclude the use of outpatient treatment settings.

Dimension 6 is recovery environment. This dimension is

closely related to dimension 5 in that a lonely or unsupportive environment can exert pressure on the patient to return to the same escape mechanism (alcohol, other drugs or behaviors) used before the treatment intervention. The benefits of a supportive recovery environment cannot be overstated as a dangerous environment that encourages relapse can rapidly undermine gains made in treatment. Sometimes a safe environment can be built by attending sobriety meetings and/or developing a network of sober accountability partners and friends. Other times more drastic measures are necessary, such as removal of the patient from a destructive home or exposure to negative influences from friends and/or family members.

Case Example

Initial Presentation

A 64y/o man voluntarily presents to the emergency room tremulous and agitated with a blood alcohol level of 320 mg/dl. He is noted to have a blood pressure of 210 /120 mmHg and pulse is 120 Beats Per Minute (BPM). He complains of nausea with vomiting, headache, and a prickly sensation on his arms and legs. He is unkempt, disheveled, and malodorous. Funduscopic, heart, lung and abdominal exams are normal. CBC and chemistry panel are normal and urine toxicology screen is pending. Addiction consultation is called to assist with appropriate treatment and disposition. What level of treatment does this patient require?

Treatment Recommendations

The patient requires Level 4 treatment at this time. His elevated pulse and blood pressure, along with vomiting make him unsuitable for a lower level of care. He may be placed on a protocol or symptom triggered detoxification regimen, and given fluids, thiamine, antinauseants, and antihypertensives as needed.

Background

The next day, the patient is feeling much better, though he still feels tremulous and anxious. He continues to have headaches and the prickly skin sensation, but nausea is improved and there has been no vomiting overnight. The BP is now 140/80 mm Hg, and pulse is 96 bpm. The patient is now ready to tell his story. He has been using alcohol since his teenage years, and has never had previous addiction treatment. He married his college sweetheart after graduation. During his 20s he would binge drink weekends while watching sports with his friends. During his 30s he discovered wine tasting, and would share a bottle of wine every evening while still binge drinking on weekends with friends. During his 40s and 50s his work promotions allowed business lunches with alcohol use. He began meeting clients and co-workers after work for drinks before coming home and drinking wine before, during and after dinner. He would go out with "Bar buddies" but lost interest in any previously enjoyable activities (movies, evening walks, sex) after getting home for the evening. He began having arguments with his wife about his heavy drinking, and boring lifestyle. He retired from work at the age of 62 and stayed home most days, starting his drinking with mimosas in the morning and continuing use all day. Fights with his wife escalated. Approximately three weeks prior to the admission, he physically assaulted his wife during an argument. She called the police who removed him from his home. She changed the locks, secured the doors and windows, and installed an alarm system. She is charging him with domestic violence, has requested a restraining order, and has not spoken to him since. He has been living with his "Bar buddies" and drinking non-stop. He knows he needs to change but does not know how. He is very angry at his wife. What is the next treatment step for him?

Diagnosis and Treatment Plan

He has type 1 alcohol use disorder as manifested by multiple negative consequences (fights with spouse including a legal intervention for domestic violence), tolerance, and withdrawal symptoms. He wants to get away from his consequences but his internal motivation to change is questionable (angry at wife). His automaticity is unknown, but his recovery environment is dangerous. The plan is to complete detoxification and address any remaining medical issues, and then transition him into a residential treatment facility (3.3 or 3.5) depending on what is available through his insurance provider.

Follow-Up

Patient returns after one month in a medium-intensity residential treatment facility (level 3.3). He has enjoyed attending the groups and recovery activities. He reports no desire to drink alcohol anymore and does not feel tempted when he passes the grocery store or the bar. He understands that he hurt his wife and that he needs to make amends. He has joined Alcoholic Anonymous (AA) and just obtained sponsor. He asks to stay in treatment another month because he doesn't want to go back to live with his "Bar buddies". The program has contacted his wife who is amenable to the possibility of a reconciliation, but "Not yet." What is the next treatment step for him?

Assessment and Plan

He has developed insight and does not report problems with automaticity. His major issue is Dimension 6--the dangerous recovery environment. He could transition to the lower cost 3.1 level of treatment. Now that he understands his role in damaging his marriage, it may be possible to explore involving the wife in her own recovery program. As they both recover, the potential for outpatient couples therapy and reunion exists.

Types of Treatment

Many treatment strategies have been tried to treat people with alcohol use disorders ranging from quick one hour sessions or one weekend seminars to life-long therapies. Proper treatment depends

on proper diagnosis, and understanding that there is a spectrum of drinking disorders. The NIDA concept of addiction as a chronic brain disease is important once the diagnosis of dependence is established. Patients not exhibiting criteria for addiction frequently respond to brief counseling and motivational interviewing/ enhancement to facilitate self-change. As consequences mount in frequency and severity, the strategy should be adjusted. This section discusses treatment tools including behavioral therapies, pharmacologic therapies, complementary and alternative therapies, and support groups.

Detoxification

Patients that present in alcohol withdrawal often require pharmaceutically assisted detoxification. Withdrawal symptoms can begin hours to days after cessation of heavy, prolonged alcohol use. The symptoms should not be due to another medical or psychiatric disorder, and should cause clinically significant impairment of function. Two of the following 8 criteria listed in the DSM-5 should be noted within several hours to a few days: [5]

1. Autonomic hyperactivity
2. Worsening tremor
3. Insomnia
4. Nausea or vomiting
5. Transient visual, tactile, or auditory hallucinations or illusions
6. Psychomotor agitation
7. Anxiety
8. Generalized tonic-clonic seizures

Symptoms result from an unmasking of the chronic suppression of excitatory neurotransmitters (predominantly glutamate) by GABA [46,47]. Delirium Tremens (DTs) is defined by systemic autonomic instability in addition to the hallucinosis and CNS hyperactivity. Withdrawal seizures are usually generalized tonic-clonic, and occur most often between 12-48 hours after cessation of alcohol use, the same time frame as acute alcoholic hallucinosis. DTs usually begin between 48 to 96 hours after cessation of alcohol use and have a mortality rate of up to 5 percent. Common electrolyte abnormalities include hypokalemia, hypomagnesemia, and hypophosphatemia which can lead to rhabdomyolysis, cardiac arrhythmias, and further systemic decompensation. Uncomplicated DTs may last up to 7 days, and frequently requires treatment in the intensive care unit.

Treatment of alcohol withdrawal is predominantly supportive, with use of sedatives to prevent seizures and alleviate CNS hyperactivity. Benzodiazepines and barbiturates have both been used successfully in the treatment of acute, severe alcohol withdrawal. Both are $GABA_A$ agonists, and increase the flow of the chloride ion through the channel causing inhibition of excitatory biogenic amines [48]. Barbiturates cause the channel to stay open (increasing potential for overdose), while benzodiazepines allow the channel to open and close at a more rapid rate. Because of the improved safety profile, benzodiazepines are the most commonly used sedative to manage alcohol withdrawal. Barbiturates (phenobarbital) or propofol can be added to benzodiazepines to treat refractory DTs.

In 1997, a working group from ASAM published an evidence based practice guideline on the pharmacological management of alcohol withdrawal [49]. This was a meta-analysis reviewing 134 articles including 65 prospective controlled trials involving 42 medications. Outcomes reviewed included severity of withdrawal syndrome, DTs, withdrawal seizures, completion of withdrawal, entry into rehab, and cost. Benzodiazepines (chlordiazepoxide, diazepam, lorazepam, oxazepam) were considered equally efficacious in reducing seizures and DTs, and were recommended for moderate to severe withdrawal. Thiamine administration on admission was also recommended, as was use of individualized treatment regimens.

The choice of benzodiazepine is often made based on the experience of the provider and unique characteristics of the patient. Diazepam and chlordiazepoxide are, long acting, benzodiazepines which are metabolized in the liver to other active compounds. Diazepam is usually given in 5-10mg doses while chlordiazepoxide is usually given in 25-50mg doses. These agents may take several weeks to be completely cleared from the body after a 3 to 5 day course (3-6 doses per day), and provide a smooth, gradual self-taper.

Lorazepam and oxazepam are short/intermediate-acting benzodiazepines that do not have active metabolites and may be a safer alternative in patients who are elderly or have decompensated liver disease or respiratory compromise. Lorazepam is usually given in 1-2mg doses, while oxazepam is given in 15-30mg doses. They may also be dosed 3-6 times per day but late-onset withdrawal symptoms and seizures may occur [50]. Clonazepam (0.5 -1mg per dose) is a long acting benzodiazepine also metabolized in the liver but without active metabolites. Benzodiazepines may be given proactively in front-loaded or fixed-dose protocols, or reactively to treat patient symptoms.

Carbamazepine and divalproex have both been used successful to treat less severe alcohol withdrawal symptoms, and may be considered in milder withdrawal situations with outpatient protocols [51-54]. Although protocols vary significantly, non-benzodiazepine detoxification may start at around 200mg for carbamazepine or 250mg for divalproex, given 3-4 times per day for the first day or two then tapered off over a period of 7 to 10 days. Doses may need to be lower in elderly patients.

Gabapentin, a medication with FDA approval for treating postherptic neuralgia and epilepsy, has been shown to be successful

in the treatment of mild to moderate alcohol withdrawal in the outpatient setting in recent studies [55]. It has also been shown to improve sleep and mood, particularly post-withdrawal dysphoria, in those who are quitting or reducing their alcohol intake. There are no established treatment protocols thus far, but typical doses may start at 900mg to 1800mg twice daily for 3 to 4 days then tapered [56]. Additional studies have shown benefit with long term gabapentin use as an anti-craving agent to decrease the risk of relapse. Despite the lack of serious adverse drug-related events in these studies, gabapentin does have known and reported side effects and the benefits of use must be weighed against the risks.

Several quantifying instruments have been developed and used to better assess risk of morbidity and mortality from alcohol withdrawal. The most well know, and most commonly used is the Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) Scale [57]. This scale has well documented validity and reliability. CIWA-Ar has 10 sign/symptoms categories, 9 of which are scored from 0-7 and the tenth 0-4 for a total possible 67 points. A score of less than 8-10 points indicates mild withdrawal, while a score of 15 or higher indicates severe symptoms [50]. Some have chosen to use a mild (0-8), moderate (9-15), severe (>15) scale, and base decisions whether to use medications, outpatient detoxification, or inpatient treatment based on the score. Others use a mild (<10) vs significant (≥10) to determine whether or not to use pharmaceutically assisted detoxification. The 10 parameters measured by the CIWA-AR are as follows:

1. Nausea/vomiting 0-7
2. Tremor 0-7
3. Paroxysmal sweats 0-7
4. Tactile disturbances 0-7
5. Auditory disturbances 0-7
6. Visual disturbances 0-7
7. Anxiety 0-7
8. Agitation 0-7
9. Headache, fullness in head 0-7
10. Orientation and clouding of sensorium 0-4

The CIWA-Ar can be administered by a trained provider in approximately 2 minutes. No points are given for abnormal pulse or blood pressure. The CIWA-Ar has been used to measure symptoms to determine the need for medication using symptom-triggered detoxification protocols. Patients receiving symptom-triggered protocols have been shown to use less medication and have a shorter treatment period than patients on fixed-dose protocols [58,59]. One issue with using short-acting benzodiazepines in symptom-triggered detoxification protocols is that they require patient assessment to be performed regularly and sometimes frequently. Sometimes this is difficult to accomplish on a general medical ward, leading to protocol errors [60]. The staff must be able and willing to use assessment tools in a correct and timely manner.

Stages of Change and Motivational Interviewing

Detoxification (separation of the patient from alcohol) may be considered the beginning of substance abuse treatment, but the terms are not synonymous. Time in detoxification can be used to determine the next appropriate level of treatment, type of treatment, and whether or not "Anti-craving" pharmacologic therapy will be used. The treatment provider should work with the patient to optimize motivation to change. This can be done through techniques of motivational interviewing. Use of open-ended questions, affirmations, and reflective questioning will allow the interviewer to determine the patient's insight and readiness to change. The "Stages of Change" give us a framework with which to better define this process [61,62]. The **first stage is precontemplation**. This stage may be categorized by rationalization, and denial of the severity of consequences. Patients in this stage may feel that the effort of changing is not justified by the reward. The **second stage is contemplation**. Patients in this stage are becoming more aware of the benefits of changing their behavior, and understanding the severity of the consequences of avoiding change. The **third stage of change is preparation**. In this stage, the patient comes to the realization that change may not be easy, but is still necessary. The patient makes mental and physical adjustments necessary to make the change. The **fourth stage is action**. In this stage, the individual makes observable changes necessary to reduce or eliminate consequences. The **fifth stage is maintenance**. This stage may be categorized as relapse prevention. The patient learns the stresses and triggers of temptation to return to old behavior, and utilizes new behaviors (learned in the action step) to prevent relapse. The **sixth** and **final stage of change is termination**. This is the theoretical stage in which there is no longer a temptation or chance to relapse. Sometimes patients with severe physical, social, or legal consequences of alcohol dependence feel that they have reached this stage of change after detoxification, without having worked through the preceding stages.

During a motivational interview, the provider gives information which may relate to the physical or social consequences of alcohol abuse. The provider may also dispel preconceived ideas about addiction treatment, making the idea of changing behavior less frightening to the patient. By helping the patient understand the severity of their consequences and lower the fear related to change, the provider can facility movement towards action. The provider then affirms the patient's "Change talk," being careful not to belittle their ideas, motivation, or plans. An open, honest, non-judgmental relationship is the building block for further conversation if the first attempt at behavioral change is unsuccessful.

Behavioral Therapies

Once the patient is ready to move towards action, the various therapeutic options must be considered. There are several models primarily used for the treatment of alcohol (and other substance) abuse [63]. Many treatment programs offer group therapy sessions as part of their treatment model. Recovery groups can be educational, support related, therapeutic, or focused on skill development. Many programs combine different types of groups. **Educational recovery** groups may use lecture or videos in addition to discussion to provide information to improve the understanding of addiction, the process of recovery, and prevention of relapse. **Support related** twelve step or secular facilitation groups encourage participation in outside support groups to develop a network including sponsor and accountability partners. The most widely established support groups are Alcoholics/Narcotics Anonymous, but other support groups such as Celebrate Recovery, Life Ring, or SMART Recovery also encourage development of a community based support system. **Therapy groups** may include use Motivational Enhancement Therapy (MET) [64] to help patients resolve ambivalence about changing behaviors, increasing their commitment to recovery. They may also be insight oriented, with a goal of raising insight and self-awareness of stressors and relapse triggers. **Skills groups** may use Cognitive Behavioral Therapy (CBT) [65] or Dialectic Behavioral Therapy (DBT) to reverse maladaptive thoughts and beliefs that support substance use or other problem solving and stress management techniques. Other therapies such as individual counseling, family therapy, and contingency management (giving intermittent small rewards for achieving objective recovery goals) are often used in addition to groups by many recovery programs.

Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity) was a multicenter clinical trial designed to discover whether matching patient characteristics to treatment option would improve outcomes. The study included 1726 alcohol dependent patients (two parallel groups either directly admitted outpatients or stepping down from inpatient or day treatment program) who were randomly assigned to Twelve Step facilitation (TSF), Cognitive Behavioral Therapy or Motivational Enhancement Therapy for a treatment period of 12 weeks. One-year follow-up interviews were performed with over 90% of patients. Significant and sustained improvements in drinking outcomes were achieved from baseline by patients in all 3 treatment groups, with little difference in outcome by type of treatment. In the outpatient study arm, those with lower psychiatric severity did better in TSF than CBT [66]. A secondary analysis demonstrated that patients with a high anger score treated in MET had better post-treatment outcomes than CBT, and patients with high alcohol dependence did better in TSF than CBT. Patients with low alcohol dependence did better in CBT [67]. A three-year follow-up (for 952 patients) was subsequently performed, revealing the high anger patients continuing to do better after MET. With regard to overall outcomes, the reductions in drinking observed after one year were sustained in the third year. Although few differences were seen among the 3 cohorts, the research group noted a possible slight advantage to those receiving TSF [68].

Pharmacologic Therapies Approved by the U.S. Food and Drug Administration (FDA)

Although several models of therapy based substance abuse treatment have demonstrated evidence of effectiveness, [69] considerable room for improvement still exists. Several pharmacologic therapies for alcohol abuse have demonstrated benefit in reduction of hazardous drinking, and should be considered. The U.S. Food and Drug Administration (FDA) has approved 4 medications for the treatment of alcohol dependence. These are disulfiram, acamprosate, oral naltrexone, and injectable long-acting naltrexone. A thorough literature review can be found in TIP 49 "Incorporating Alcohol Pharmacotherapies into Medical Practice: A Review of the Literature" from the US Department of Health and Human Services [70]. Disulfiram is an anti-craving drug approved nearly 60 years ago that inhibits the conversion of acetaldehyde to acetate by aldehyde dehydrogenase. This can cause nausea, vomiting, flushing, and headache with alcohol intake. A black box warning states that disulfiram should not be given to patients whom have ingested alcohol within the preceding 12 hours. The dose range is 125 mg to 500 mg daily, but it has been used in higher doses at less frequent intervals. Recent literature reviews have showed only modest short term reductions in alcohol use [71]. One study demonstrated significantly better abstinence with observed dosing during the initial phase (12 weeks), but results were similar to naltrexone and acamprosate during the second phase (52 weeks) of treatment [72]. Patients who agree to supervised disulfiram use have better abstinence rates and improved outcomes [73].

Acamprosate was approved by the FDA in 2004, but has been used in Europe since the 1980s. The exact mechanism of acamprosate is unclear, but it is structurally similar to GABA and thought to modulate the effects of glutamate at the N-methyl D-aspartate (NMDA) receptors in the brain. It has been studied in doses from 1332to 3000mg per day, but the usual dose is 666mg (2 tabs) three times a day (1998mg per day). Acamprosate has no black box warnings and no pharmacokinetic differences due to gender or degree of alcohol dependency. No dosage adjustments are needed with mild to moderate hepatic impairment or mild renal disease. Dose adjustment is necessary in moderate renal disease (creatinine clearance of 30-50mL/min), and it is contraindicated in severe renal disease (<30mL/min). The 3 European studies that served as pivotal trials [74-76] all underwent FDA reanalysis that demonstrated improved outcomes in complete abstinence, time to first drink, and percent days abstinent [77]. Several good, multicenter studies in the United States have demonstrated variable improvement in outcomes [78,79]. Despite this, the meta-analyses done on the many world-wide trials demonstrate a significant

reduction in drinking frequency [80,81]. Acamprosate has been shown to reduce the risk of returning to any drinking and improving duration of abstinence. It is considered to be a moderately effective medication in the treatment of alcohol use disorder [82,83].

Oral naltrexone was approved by the FDA in 1994 as an anti-craving medication for treatment of alcohol dependence. Naltrexone is an Opioid Mu Receptor (OPRM1) antagonist, thought to work by blocking the brain reward contribution from the opioid system. This effect may be most prominent in a subset of patients with certain genetic polymorphisms (Asp40 allele) [33]. There is a black box warning not to use naltrexone in patients with acute hepatitis or hepatic failure. Caution should be used in patients with severe liver or renal disease, but no dosage adjustment is recommended. Patients that use naltrexone should not be using opioids for the treatment of chronic pain, and should carry a card informing medical providers they are on an opioid receptor blocking agent.

Seminal articles by Volpicelli [84] and O'Malley [85] published in 1992 demonstrated a significant decrease in relapse drinking with naltrexone. The interesting paradigm shift of using "Less heavy drinking days" as a measure of success was advanced by these studies. Many clinicians at that time felt that the only measure of treatment success was complete abstinence and did not acknowledge the clinical significance of these study results. Naltrexone has been administered at doses of 25mg/day to 100mg/day, with the usual dose being 50mg/day. In the last two decades oral naltrexone has been extensively studied with most studies showing increased efficacy over placebo, though some have not [70].

The COMBINE study [78] was an NIAAA sponsored multicenter study randomized, controlled study that evaluated the efficacy of medications (oral naltrexone and acamprosate), behavioral therapies and their combinations for the treatment of alcohol dependence. The study included 1383 patients from 11 academic sites. Subjects were randomized to either 100mg of oral naltrexone, 3g of acamprosate, both, or neither. Behavioral therapies consisted of either Combined Behavioral Intervention (CBI), Medical Management(MM), both, or neither. Medication placebo groups were included. The study was conducted for 16 weeks, with reevaluation 1 year after treatment. The investigators concluded that "Within the context of medical management, naltrexone yielded outcomes similar to those obtained from specialist behavioral treatment (i.e. CBI)". They found no evidence of increased efficacy for acamprosate alone or in combination with naltrexone, and found that placebo plus medical management was more effective than specialist CBI alone. The 1-year post treatment phase published in 2008 assessed drinking behavior and clinical status at weeks 26, 52 and 68. Patients treated with medical management and either combined behavioral intervention, naltrexone, or both had sustained benefit [86].

A critical factor in the efficacy of naltrexone for the treatment of alcohol dependence is patient compliance [87]. Unfortunately, medication adherence is generally not good, with a retrospective database review show that more than 85% of patients not refilling their naltrexone prescription at some point within the 6 months after starting treatment [88]. To assist patients overcome motivational difficulties with adherence, long acting implantable and injectable forms of naltrexone were developed. In April 2006, extended-release injectable naltrexone (XR-NTX) [89] was approved by the FDA for the treatment of alcohol dependence and the prevention of relapse to opioid dependence. This Polylactide-Co-Glycolide(PLG) microsphere formulation is administered intramuscularly and releases naltrexone for one month following injections. Comparing the 380mg dose with placebo, one study showed a 25% decrease in heavy drinking days over a 6-month period [90]. Medication adherence is a problem with XR-NTX as with the other approved alcohol dependence medications [91]. One study found that "Persistence days on medication" were significantly higher than the other three FDA approved medications [92]. This study also demonstrated that despite the higher up-front cost for XR-NTX (approximately $1100 per month), the number of emergency department visits and hospital days saved (due to relapse prevention) make it a cost-effective option. An open-label pilot study examining the use of XR-NTX in repeat DUI offender volunteers showed significantly less drinks per day and more abstinent days over the 3-month period [93].

Other Pharmacologic Therapies

The issues of poor adherence and moderate efficacy with the current FDA-approved medications have prompted the search for other options [94]. Topiramate, baclofen, ondansetron, sertraline, nalmefene, aripiprazole, zonisamide, quetiapine, varenicline, and levetiracetamare among the medications currently under investigation [95]. Topiramate is thought to work as a GABA agonist and glutamate antagonist [96]. Topiramatewas shown in a randomized controlled trial to have a lower percentage than placebo (by 16%) of heavy drinking days by participants (N = 371) [97]. In the study, participants randomized to topiramate were titrated from a starting dose of 25mg/day up to 300mg/day over a 6- to 8-week period. Adverse effects involving paresthesia, taste perversion, and anorexia were problematic. Other studies have also demonstrated significant benefit in study subjects using to piramate. Although not FDA approved for this indication, to piramate is considered by some to be a first line option in the treatment of alcohol use disorder [98]. Baclofen is a $GABA_B$ agonist currently under investigation. A retrospective open-label study assessed the proportions of high risk drinkers who were either abstinent or drinking at low levels one year after starting high dose baclofen therapy (129 $\pm$ 71mg/day) [99]. The authors were able to follow-up on 132 of 181 patients. Of the patients, 80% were either abstinent or drinking at low levels. Ondansetron is an antagonist of the serotonin type 3 receptor (5-HT3) and was approved for the treatment of nausea and

vomiting. One study randomized 283 alcohol dependent patients according to serotonin transporter (5-HTT) genotype (LL, LS, SS), with additional genotyping for another transporter polymorphism (TT/TG/GG). Participants received either ondansetron 4 μg/kg twice daily or placebo for 11 weeks plus CBT [100]. The investigators noted that individuals with the LL genotype had a lower mean number of drinks per day and a higher percentage of days abstinent than those receiving placebo, with the greatest effect being in individuals with the LL/TT genotypes. Sertraline, a selective serotonin uptake inhibitor approved for the treatment of depression, anxiety and other psychiatric disorders has also been evaluated for potential efficacy in alcohol use disorders. One study evaluated the effect of sertraline on alcohol dependent patients, separating them by phenotype (late onset/low vulnerability [LOA] versus early onset/high vulnerability [EOA]) and by serotonin transporter (5-HTT) genotype (LL, LS, SS) [101]. The patients (N = 134) were randomized to receive up to 200mg of sertraline or placebo daily during the 12-week study. The medication effect varied significantly by both phenotype and genotype with the LOA /LL patients reporting few drinking and heavy drinking days. The study participants were followed for 6 months post-treatment with continued significantly beneficial effects for the LOA/LL group only [102]. The opioid antagonist nalmefene was assessed in a randomized double-blind study in Finland [103]. Subjects (N = 242) took 10 to 40mg of nalmefene or placebo for the 28 week study with minimal psychosocial intervention. The study was extended another 24 weeks for 57 subjects in the nalmefene arm who were then randomized to either continue nalmefene or receive placebo. The study showed significantly decreased drinking for those receiving nalmefene over placebo in both phases. Aripiprazole is an atypical antipsychotic medication also approved for treatment of bipolar disorder, schizophrenia, irritability associated with autistic disorder, and Tourette syndrome. It is a partial agonist of the Dopamine2 (D2) and serotonin 1A (5-HT1A) receptors, and an antagonist for serotonin 2A (5-HT2A) receptor. In one study, alcohol dependent subjects not seeking treatment were randomized to either aripiprazole or placebo, with the dose titrated up to 15mg over a 14-day period [104]. Functional magnetic resonance imaging (MRI) was performed during exposure to alcohol-related cues. Brain activity was higher in the right ventral striatum of individuals receiving placebo and blunted in those receiving aripiprazole. Patients treated with aripiprazole also had significantly less heavy drinking during the 14-day period. Zonisamide, first synthesized in Japan in the 1970s, is an anticonvulsant medication approved as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. It is chemically classified as a sulfonamide, works to block voltage-dependent sodium and calcium channels, and is metabolized mainly by hepatic cytochrome 3A4 (CYP3A4). In a double-blind trial, 40 subjects with alcohol use disorder were randomized to receive combined zonisamide (up to 500 mg/d) plus psychosocial therapy or placebo plus psychosocial therapy for 12 weeks. Although there was not a statistically significant difference between groups in terms of abstinent days, there was a significant reduction in heavy-drinking days per week [105]. Varenicline, an FDA approved medication for the treatment of nicotine dependence has been shown at a 2mg/day dose to significantly reduce heavy-drinking days per week, drinks per drinking day, and alcohol craving in both smokers and non-smokers [106].

Complementary and Alternative Medicine (CAM)

Submitting to treatment for an alcohol use disorder can be difficult for the patient. When making the decision to take the first, most difficult step towards treatment, people have a natural tendency to wonder if perhaps there an easier or better option exists. Complementary and Alternative Medicines (CAMs) for addiction treatment are available worldwide, and have been gaining popularity in the United States [107,108]. Identifying and describing the wide variety of CAMs available would be a difficult process. Even the definition of CAM is challenging in this paradigm because behavior therapies, 12-step support groups, and stress relieving/relaxation techniques are a part of established non-alternative recovery programs. The National Center for Complementary and Integrative Health (NCCIH), formerly known as the National Center for Complementary and Alternative Medicine (NCCAM), was established in 1998 and is one of 27 centers that make up the National Institute of Health. Their 2016 Strategic Plan defines the following objectives [109]:

1. Advance fundamental science and methods development
2. Improve care for hard-to-manage symptoms
3. Foster health promotion and disease prevention
4. Enhance the complementary and integrative health research workforce
5. Disseminate objective evidence-based information on complementary and integrative health interventions

Studies using biofeedback [110] and electroacupuncture [111,112] indicate these therapies may be helpful. There is a paucity of randomized, placebo/sham controlled studies using these therapies. It is important to emphasize, however, that lack of evidence is different from lack of efficacy. Many testimonials of success have been shared by individuals who overcame their struggles with alcohol using CAM. Furthermore, companies with proprietary formulations or therapies have introduced CAM products directly to consumers using testimony as a marketing tool. The potential benefit of these therapies is difficult to report or compare as they often have not undergone the rigorous scrutiny required for presentation or publication in scientific meetings or journals.

Support Groups

A review article about alcohol use disorders would be remiss to not mention the very important role of support groups in recovery

history and process. The largest and most well-established group is Alcoholics Anonymous (AA), the idea of which was birthed in Akron, Ohio in 1935 by cofounders Bill Wilson and (Dr.) Bob Smith. The first "Big Book" of AA was published in 1939 and included the "12 Steps" with which AA, and many subsequent groups, would be identified. The 12 steps illuminate a spiritual (not religious) recovery path taken by millions of people worldwide. There are currently over 2 million people attending more than 115,000 AA recovery groups around the world. "Friends of Bill W." (a pseudonym for AA) find fellowship on cruise ships, in airplanes, and at many other spontaneous and interesting places. In the chapter "How it Works" of AA, the steps are listed [113]

1. We admitted we were powerless over alcohol-that our lives had become unmanageable.
2. Came to believe that a Power greater than ourselves could restore us to sanity.
3. Made a decision to turn our will and our lives over to the care of God as we understood Him.
4. Made a searching and fearless moral inventory of ourselves.
5. Admitted to God, to ourselves, and to another human being the exact nature of our wrongs.
6. Were entirely ready to have God remove all these defects of character.
7. Humbly asked Him to remove our shortcomings.
8. Made a list of all persons we had harmed, and became willing to make amends to them all.
9. Made direct amends to such people wherever possible, except when to do so would injure them or others.
10. Continued to take personal inventory and when we were wrong promptly admitted it.
11. Sought through prayer and meditation to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out.
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics, and to practice these principles in all our affairs.

Many other groups have used the steps in this spiritual recovery pathway to overcome other chemical and behavioral addictions such as Narcotics Anonymous, Gamblers Anonymous, Overeaters Anonymous, Co-dependents Anonymous, Sex and Love Addicts Anonymous, etc. Several other recovery groups in addition to these should be mentioned. Celebrate Recovery (CR) was founded by John Baker in 1991, and is intended to bring the 12-step recovery process to people admitting they need support to overcome "Hurts, hang-ups, and habits." It was designed to be broad enough to allow participants with behavioral issues (e.g. anger, gambling, past abuse, codependency, sex addiction, overeating, etc.) to benefit from the 12 step recovery process along with those with alcohol or other chemical dependencies. Celebrate Recovery is growing rapidly, and with about 29,000 groups meeting in the United States and 20 other countries, is now second to the Anonymous groups in size. CR has a program for teens (The Landing) and a "Pre-covery" program (Celebration Place) for children 5-12years of age [114]. Participants start the meeting together in a large group for a testimonial or step lesson, then separate into smaller gender- and issue-specific groups for individual sharing.

The spiritual nature of the 12-step programs has raised questions about the legality of court-mandated program attendance. Several circuit court decisions have upheld the assertion that mandated 12-step meeting attendance is a violation of the Establishment Clause in the First Amendment to the U.S. Constitution [115]. Several secular organizations have regular insight-oriented meetings. These include LifeRing, SMART Recovery, Women for Sobriety, Secular Organizations for Sobriety, and Moderation Management. These programs combine to offer about 3000 meetings in the U.S. and other countries.

Summary

Alcohol has been a part of human culture for many millennia. As long as people continue to use alcohol, a small subset will experience the consequences related to misuse and overuse. The purpose of this article is to provide clinicians with a basic understanding of the tools available to diagnose and treat this "Cunning and baffling "Brain and multisystem disease. Both genetic and environmental factors appear to play important roles in not only the initiation of alcohol use but also the susceptibility for misuse and the risk of developing a use disorder. There are FDA approved medications, behavioral therapies, and community support groups that have demonstrated promise in helping people overcome the consequences of alcohol use disorder.

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