SUPPLEMENT

What Is Addiction, What Is Alcoholism?

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The title of this article, contributed by my friend and colleague, Michael Lucey, MD, of the University of Wisconsin, entails 2 general concepts that are my focus. The first states that there is such a thing as addiction, or addictive disorder, and that what we commonly refer to as alcoholism is a form of this phenomenon. Because alcoholism is second in prevalence only to nicotine addiction in the general population and is the most frequent addictive disorder for which persons seek liver transplantation, I will use it as the principal example of what addictive disorders, more generally considered, entail.

The second general concept locates us in the realm of clinical diagnosis. My goal, therefore, is to present a discussion of current theoretical understanding that is at the same time clinically useful when seeing patients. In this regard, I will not simply reiterate constructs from easily available sources such as the 4th revised edition of the American Psychiatric Association's *Diagnostic and Statistical Manual*[1] (DSM-IV-TR). It simply outlines the phenomena common to all addictive disorders and expects the practitioner to fill in the blanks for specific agents of use. Instead, I will work from the general ideas that compose the Platonic nature of addiction and use specific alcohol-related phenomena to illustrate them.

In the interest of brevity, I will not spend much time discussing other substances of abuse. In addition, I will use the medical model of addictive disorders as disease states. Other models, such as moral choice, habit and reinforcement, or learned behavior, make up useful discussions in other arenas.

Let me begin by defining *alcoholism.* The term, which is often used in popular speech, may call to mind alcoholic liver disease, alcoholic cardiomyopathy, alcohol dementia, alcohol amnestic disorder or Wernicke-Korsakoff disease, alcohol intoxication, or alcoholic amnesia (blackouts). Although diagnosis may involve considering some or all of these things, it is not the thing itself. In clinical diagnosis, alcoholism refers to alcohol dependence (AD). By the same token, diagnosing any clinical addiction means establishing that a patient is dependent on a specific substance. Our first task, then, is to define dependence. It is, first, a series of specific behavioral manifestations. Second, the diagnosis of AD does not depend directly on the quantity and frequency of alcohol drunk, either acutely or over time.

DIAGNOSIS

The diagnosis of AD requires evidence of phenomena in 3 clinical domains: (1) physiological dependence, including tolerance and withdrawal; (2) loss of control of alcohol use, often erroneously referred to as craving; and (3) decline in physical functioning, social functioning, or both. Of the 7 dependence criteria listed in the DSM-IV-TR,[1] for example, 2 refer to physical dependence, 2 to loss-of-control phenomenon, and 3 to social or physical impairment. But for my purposes, the 3 large symptom domains offer an easier way of remembering and assessing symptoms relevant at the bedside or in the clinic.

PHYSIOLOGICAL DEPENDENCE: TOLERANCE AND WITHDRAWAL

Tolerance refers to the ability of the central nervous system (CNS) to approximate normal functioning in the presence of ever-increasing doses of ethyl alcohol. Clinically, the person reports needing more alcohol to get the same effect once noticed at a much lower dose earlier in the natural history of drinking. To assess this, the physician must establish a baseline effect that has changed over time. This necessitates careful attention to the details of the patient's drinking history.

One useful approach may be to ask what the effect of alcohol was when a person first began drinking on his

Abbreviations: DSM-IV-TR, 4th revised edition of the American Psychiatric Association's *Diagnostic and Statistical Manual;* AD, alcohol dependence; CNS, central nervous system; DT, delirium tremens; AA, alcohol abuse.

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TABLE 1. Likely Timing of Occurrence of Alcohol Withdrawal Phenomena[2]

Time	Phenomenon
6–12 hours	Acute withdrawal syndrome begins
24 hours	Withdrawal seizures begin
≥72 hours	DT begins
5–7 days	Course of uncomplicated withdrawal
1–4 weeks	Course of withdrawal complicated by DT or other conditions

Abbreviation: DT, delirium tremens.

or her own. Results include such things as nausea, feeling high, or other unique descriptors that the patients can provide regarding what they noticed after 1-2 standard alcohol drinks. A standard drink may be roughly defined as a 12-oz can or bottle of beer; a 6-oz glass of table wine; or a 1.5-oz shot of whiskey or other spirits.

After establishing a baseline, the interviewer may then ask how many standard drinks the person required to achieve the same effect at the time when his or her drinking was at its greatest. Formal DSM-IV-TR criteria require a 50% increase. In the case of alcohol, most will describe a doubling or more of the amount required for the initial effect. Many AD patients will describe amounts several times greater than those drunk in the state naive to alcohol. This signals that the CNS has adapted to heavy alcohol use—that is, it has reached tolerance.

Alcohol withdrawal accompanies tolerance in most individuals. In those who report no withdrawal symptoms despite a history of clear tolerance to alcohol, the clinician must ask whether the patient is drinking in the morning before withdrawal symptoms manifest themselves. Also, ask whether the patient is regularly taking some other CNS depressant, such as a benzodiazepine or an anticholinergic agent, that covers withdrawal symptoms. Only rarely will the physician encounter patients who have little or no withdrawal symptoms despite clear tolerance development.

In general, any drug withdrawal state follows a preexisting CNS tolerance. Short-acting CNS depressants, such as ethanol and short-acting tranquilizers, are particularly dangerous after a sudden lowering of levels in the blood. This is theoretically because of the rapid suppression and then release of inhibitory neurotransmitter systems in the brain. A rapid decrease of circulating levels in a tolerant brain can include life-threatening generalized seizures and, in the case of ethyl alcohol, potentially fatal delirium, including delirium tremens (DT).

The physician's first question should always be, "When was your last drink?" The time since last alcohol use offers a rough projection of when to expect the untoward reactions that may occur during alcohol withdrawal (Table 1). Frequencies will vary from the nearly ubiquitous occurrence of acute withdrawal symptoms to the relatively rarer production of seizure or DT.

TABLE 2. Signs and Symptoms of Alcohol Withdrawal[2]

anxiety
nausea and vomiting
sweating

tachycardia pulse >110
tachypnea
fever, temperature >99.6°F
hypertension, diastolic pressure >90 mm Hg

tremor
hyperactive deep tendon reflexes
ankle clonus

A rapid decrease in the blood ethanol level sets the process of the acute alcohol withdrawal syndrome in motion, one that lasts 5-7 days in uncomplicated cases. Because ethanol is a CNS depressant, its quick removal triggers CNS hyperactivity both centrally, as by a subjective sense of jitteriness or impending disaster (anxiety), and peripherally, through the symptoms of sympathetic nervous system discharge. Table 2 lists acute withdrawal symptoms.

Because the process of alcohol withdrawal involves an extended interaction between ethanol and its effect on the CNS, wide variations will occur in the frequencies of symptoms from case to case. Some may have all of the symptoms and signs, whereas others may have only one or two. Medical teams like to focus on vital signs as targets for treatment because these can be measured. Subjective anxiety, often described by patients as a jittery or shaky feeling, is one of the most subtle manifestations of withdrawal and one that the wise clinician will not ignore.

Either of 2 clinical signs usually points to worsening CNS function: hyperactive deep tendon reflexes and ankle clonus sustained for more than 2 beats. These usually indicate pathophysiologic impairment of the upper motor neurons. This impairment in turn is frequently associated with the onset of generalized seizure activity. Either sign, especially that of ankle clonus, indicates that aggressive treatment of withdrawal should be initiated in order to prevent seizures.

Standard treatment for the alcohol withdrawal syndrome is founded on the strategy of replacing alcohol's gamma-aminobutyric acid agonist actions with longer-

acting agonist medicines that can be withdrawn slowly over the same time course seen in uncomplicated cases. In most cases, this requires dose titration of long-acting benzodiazepine agents, such as chlordiazepoxide, until symptoms resolve. Because withdrawal can present an accelerating course of illness progressing to life-threatening conditions in the most serious cases, it should be treated aggressively within the first day, or when the condition is first recognized, with gradual tapering of the medicine over 5-7 days.

For initial treatment in cases uncomplicated by clonus, seizure history, previous severe withdrawal, or age >60 years, 50 mg of chlordiazepoxide provided orally is generally a good starting dose. When clonus, seizure history, or history of previous severe withdrawal are present, or when withdrawal symptoms occur even though ethanol is still present in the blood, 100 mg provided orally is indicated. For an elderly person, 25 mg provided orally is likely a better beginning dose. Symptoms and signs must be checked again in 2 hours and the dose repeated if there is no change. By repeated doses and reassessment, the target symptoms should come under control within 6 hours. The dose required to achieve this can be extrapolated to 24 hours—multiplying times 4—and given in divided doses during the first day, unless the patient appears drowsy or somnolent. The goal of sedation is to achieve a state of comfort with the symptoms resolved and vital signs in the normal range, without oversedation or somnolence that may lead to aspiration pneumonia or other complications. After establishing the dosage for the first day, the amount may be reduced by 25% of the original and given on each successive day—for example, 400, 300, 200, and 100 mg daily, and the medication withdrawn on day 5. Long-acting agents will be stored in lipid tissues and will still be present in most cases through days 6 and 7. If symptoms or signs return at the end of the course, small doses (in the range of 50 mg) can be added to cover them.

In cases with little stress on hepatic metabolism (e.g., hepatic failure), or when parenteral medication is required (e.g., when gastritis or nasogastric tube placement obviates oral administration), lorazepam can be titrated in the same manner. The starting dose can be 1-3 mg, depending on the clinical presentation, and the effect can be judged quickly (after 30 minutes). A first-day dose range may be 8-10 mg, or more if the severity is high. Because lorazepam has an intermediate half-life ranging 6-8 hours, it must be given in divided doses, usually 4 times a day. It can also be titrated downward during the course of withdrawal, but at a slower rate of approximately 15% of the Day 1 dosage over a 6-7-day period because it is not stored in the body.

Titration of the dose on a case-by-case basis is the key to successful management of alcohol withdrawal. Relying on initial standing doses of benzodiazepines is generally of little use because it does not address the wide individual variations of CNS compromise.

DT constitutes the most extreme CNS dysfunction in alcohol withdrawal. This condition manifests as profound confusion, perceptual disorders characterized by visual or other hallucinations, and extreme increases in vital signs. DT may occur in as many as 5% of withdrawal cases, and patients who are left untreated or partially treated have a 10-15% mortality rate. This diagnosis indicates admission to the intensive care unit and aggressive provision of benzodiazepine coverage sufficient to return the vital signs to normal. Gradual tapering may then occur until the patient is out of danger. In such cases, however, the mental confusion may clear gradually, often well past the acute need for benzodiazepines.

Taken together, tolerance and withdrawal constitute physiological addiction to ethyl alcohol. One current hypothesis derived from basic studies suggest that tolerance, mediated by the brain's reward systems, and withdrawal, mediated by the brain's stress response systems, exist in a compensatory balance. When alcohol is removed, the reward system resets itself at a lower, more normal level of functioning, and the stress response system moves in a similar fashion to retain the equilibrium. This is referred to as *allostatic equilibrium*, and the CNS will act to maintain it. The allostatic imbalance is thought to account for the stress system's production of withdrawal symptoms in the CNS as well as in the sympathetic nervous system.[3]

The loss-of-control phenomenon is the essence of any addiction and certainly of AD. This refers to the inability of the AD person to predict with any degree of certainty how much he or she will imbibe from one drinking episode to the next. Clinically, once the drinking episode starts, the AD person will be unable to stop in the middle of the episode without a very great struggle. Useful questions at interview include asking 1) whether patients feel compelled to continue drinking or find it very hard to stop drinking; 2) once they start, whether they find themselves drinking more than they wanted to or had planned to; and 3) whether they make rules to attempt to control their drinking through external means.

It is important to distinguish the loss-of-control phenomenon from craving. The former has to do with the inability to stop drinking once started. Craving, as classically defined, refers to the episodic and often intense desire or compulsion to drink at some time after a drinking bout, and should not be confused with the search for alcohol to treat withdrawal symptoms.

The loss-of-control phenomenon occurs *within* a drinking episode. Forms of craving occur *between* drinking episodes. The loss-of-control phenomenon continues to be a scientific puzzle. Despite ongoing research inquiry over many years, neuroscience has yet to define the CNS changes underlying the loss-of-control phenomenon that characterizes dependence. Clinically, however, longitudinal studies of abstinence make it clear that once the control of drinking behavior departs, it does not return in most cases.[4] It cannot be relearned or reconstituted. In this sense, a diagnosis of dependence signals a permanent condition—including a permanent risk of uncontrolled drinking.

When diagnosing AD or other drug dependence, therefore, it is important to establish whether the loss-

of-control phenomenon exists in each case. Its absence, even in the face of a clear history of tolerance, for example, strongly suggests the lesser diagnosis of alcohol abuse (AA). In that case, 2 things often occur: the person achieves and maintains abstinence without a struggle, and the risk of relapse over the long term appears considerably lower.

Social or physical decline results from the sustained heavy drinking that follows the combination of physical addiction and loss of control. The clinician asks whether drinking has become a problem with respect to family relationships, legal status, work, friendships, or physical health. The physician will be especially attuned to the last of these because the physical sequelae of AD can often result in frequent clinical visits and hospitalizations. In this setting, a useful approach is to assess the time course of the alcohol-related illness and to document the points at which other doctors or caregivers have advised against further alcohol use. This often yields useful information regarding where the patient may be in his or her course toward resolving alcohol addiction in favor of abstinence.

AD, then, may be reliably diagnosed when evidence in all 3 domains presents. The DSM-IV-TR diagnostic criteria do not require evidence in all 3 domains and therefore will cast a somewhat wider diagnostic net. Although either approach is defensible, the physician will do well to use both concurrently. I usually take the more conservative approach, especially in the setting of a life-threatening illness, for which there is only one treatment alternative, as in the case of liver or other solid organ transplantation.

As noted, many patients will manifest some symptoms of AD, but not enough to receive a formal diagnosis. The diagnosis of AA again pertains: although full addiction has not occurred, the behavioral process of moving toward loss of control and dependence appears to be in place. In most cases, AA refers to the presence of either tolerance or social dysfunction in the absence of withdrawal, or the loss-of-control phenomenon. Generally speaking, AA offers a much better prognosis with respect to treatment than does AD. Although the lesser diagnosis may be less clearly defined, it is the generally more optimistic diagnosis to make. But let us keep this and other issues in perspective in a field vulnerable to misunderstanding.

ADDRESSING COMMON MISCONCEPTIONS

AD is a hopeful and treatable diagnosis. Longitudinal studies show that up to 45% with the AD diagnosis reach abstinence annually, either through treatment or self-help groups. To monitor this, we developed a systematic method for transplant teams to follow alcohol use.[5]

A caring physician beats medicinal agents for AD. Most pharmacologic agents are weakly effective against AD.[6] A recent multisite longitudinal study found the physician's presence to be stronger than medication.[7]

A high proportion of those described as alcoholic will not merit the AD diagnosis. When Dr. Lucey and I compared notes some time ago only approximately 75% of those he saw with alcoholic liver disease fit the AD diagnosis when I interviewed them.[8] Conversely, only approximately 80% of those referred to me as alcoholics met the AD diagnosis. Of the remaining 20%, half fit the AA diagnosis and half did not merit either. This was especially true of women who, because of a greater vulnerability to alcoholic liver disease, may injure the liver without reaching AD.

Diagnosis is only one component in assessing prognosis. As pointed out long ago, the path out of AD has much to do with where a patient is in the course of illness. Like cancer, earlier diagnosis leads to better survival: physical decline is less severe, and social resources are more abundant. Prognosis can be assessed confidently.[4]

In summary, liver transplantation remains the only successful treatment for liver failure. Transplant teams have, in my experience, acted fairly and compassionately in providing organ grafts for those with AD. I applaud their wisdom in proceeding empirically.[9]

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