JAMA®

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The effects of drug dependence on social systems has helped shape the generally held view that drug dependence is primarily a social problem, not a health problem. In turn, medical approaches to prevention and treatment are lacking. We examined evidence that drug (including alcohol) dependence is a chronic medical illness. A literature review compared the diagnoses, heritability, etiology (genetic and environmental factors), pathophysiology, and response to treatments (adherence and relapse) of drug dependence vs type 2 diabetes mellitus, hypertension, and asthma. Genetic heritability, personal choice, and environmental factors are comparably involved in the etiology and course of all of these disorders. Drug dependence produces significant and lasting changes in brain chemistry and function. Effective medications are available for treating nicotine, alcohol, and opiate dependence but not stimulant or marijuana dependence. Medication adherence and relapse rates are similar across these illnesses. Drug dependence generally has been treated as if it were an acute illness. Review results suggest that long-term care strategies of medication management and continued monitoring produce lasting benefits. Drug dependence should be insured, treated, and evaluated like other chronic illnesses.

JAMA. 2000;284:1689-1695   www.jama.com

MANY EXPENSIVE AND DISturbing social problems can be traced directly to drug dependence. Recent studies[1-4] estimated that drug dependence costs the United States approximately $67 billion annually in crime, lost work productivity, foster care, and other social problems.[2-4] These expensive effects of drugs on all social systems have been important in shaping the public view that drug dependence is primarily a social problem that requires interdiction and law enforcement rather than a health problem that requires prevention and treatment.

This view is apparently shared by many physicians. Few medical schools or residency programs have an adequate required course in addiction. Most physicians fail to screen for alcohol or drug dependence during routine examinations.[5] Many health professionals view such screening efforts as a waste of time. A survey[6] of general practice physicians and nurses indicated that most believed no available medical or health care interventions would be "appropriate or effective in treating addiction." In fact, 40% to 60% of patients treated for alcohol or other drug dependence return to active substance use within a year following treatment discharge.[7-9] One implication is that these disappointing results confirm the suspicion that drug dependence is not a medical illness and thus is not significantly affected by health care interventions. Another possibility is that current treatment strategies and outcome expectations view drug dependence as a curable, acute condition. If drug dependence is more like a chronic illness, the appropriate standards for treatment and outcome expectations would be found among other chronic illnesses.

To explore this possibility, we undertook a literature review comparing drug dependence with 3 chronic illnesses: type 2 diabetes mellitus, hypertension, and asthma. These examples were selected because they have been well studied and are widely believed to have effective treatments, although they are not yet curable. Our review searched all English-language medical and health journals in MEDLINE from 1980 to the present using the following key words: *heritability*, *pathophysiology*, *diagnosis*, *course*, *treatment*, *compliance*, and *ad-*

herence, *relapse,* and *reoccurrence*. Importantly, our definition of *drug* and our review criteria included all over-the-counter (alcohol and nicotine), prescription (benzodiazepines, amphetamines, opiates), and illegal (heroin, marijuana, cocaine) drugs.

The review is presented in 2 parts. The first part considers some characteristic aspects of chronic illness, such as diagnosis, heritability, etiology, and pathophysiology. The second part reviews recent advances in the medical treatment of drug dependence and considers treatment response, particularly medication adherence and relapse or recurrence. Although we are aware that arguments by analogy are limited, we believe this comparative analysis of drug dependence with other chronic illnesses offers some instructive and provocative implications.

DIAGNOSIS, HERITABILITY, ETIOLOGY, AND PATHOPHYSIOLOGY
Diagnosis
Most adults have used alcohol and/or other drugs, sometimes heavily to the point of abuse but rarely to the point where that use could reasonably be called an illness. There is no laboratory test for dependence, but the diagnostic differentiation of use, abuse, and dependence has been operationally refined and repeatedly shown to be reliable and valid.[10,11]

Dependence or what is commonly called *addiction* is operationally defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[10] as a pathologic condition manifested by 3 or more of 7 criteria. Two of these criteria, tolerance and withdrawal, indicate neurologic adaptation or so-called physiologic dependence. However, as has been pointed out,[12] physiologic adaptation (tolerance or withdrawal) by itself is neither necessary nor sufficient for a diagnosis of substance dependence. Indeed, those receiving a dependence diagnosis are required to show a "compulsive desire for and use of the drug(s) despite serious adverse consequences" such as "use

instead of or while performing important responsibilities."[10,11]

There are several short (<5 minutes of patient or practitioner time) questionnaires that can screen for alcohol and other drug dependence disorders with high rates of sensitivity and specificity.[13] Following a positive screening result, standardized diagnostic checklists can be applied during the medical evaluation. Diagnoses that result from these standardized and easily applied criteria have been reliable and valid across a range of clinical and nonclinical populations.[11]

Genetic Heritability
One of the best methods for estimating the level of genetic contribution is to compare the rates of a disorder in monozygotic and dizygotic twins. Heritability estimates from twin studies[14,15] of hypertension range from 0.25 to 0.50, depending on the sample and the diagnostic criteria used. Twin studies of diabetes offer heritability estimates of approximately 0.80 for type 2[16] and 0.30 to 0.55 for type 1 diabetes mellitus.[17] Finally, twin studies[18,19] of adult-onset asthma have produced a somewhat broader range of heritability estimates, ranging from 0.36 to 0.70.

Several twin studies[20-23] have been published in the substance dependence field, all showing significantly higher rates of dependence among twins than among nontwin siblings and higher rates among monozygotic than dizygotic twins. Published heritability estimates include 0.34 for males dependent on heroin, 0.55 for males dependent on alcohol, 0.52 for females dependent on marijuana, and 0.61 for cigarette-dependent twins of both sexes.[20-23] More studies of heritability are needed across drug types and sexes, but the evidence suggests significant genetic contribution to the risk of addiction comparable to that seen in other chronic illnesses.

Role of Personal Responsibility
Since the use of any drug is a voluntary action, behavioral control or willpower is important in the onset of de-

pendence. Thus, at some level an addicted individual is at fault for initiating the behaviors that lead to a dependence disorder. Doesn't this voluntary initiation of the disease process set drug dependence apart, etiologically, from other medical illnesses?

There are many illnesses in which voluntary choice affects initiation and maintenance, especially when these voluntary behaviors interact with genetic and cultural factors. For example, among males, salt sensitivity is a genetically transmitted risk factor for the eventual development of one form of hypertension.[24,25] However, not all of those who inherit salt sensitivity develop hypertension. This is because the use of salt is determined by familial salt use patterns and individual choice. Similarly, risk factors such as obesity, stress level, and inactivity are products of familial, cultural, and personal choice factors.[24,25] Thus, even among those with demonstrated genetic risk, a significant part of the total risk for developing hypertension can be traced to individual behaviors.

There are also involuntary components embedded within seemingly volitional choices. For example, although the choice to try a drug may be voluntary, the effects of the drug can be influenced profoundly by genetic factors. Those whose initial, involuntary physiologic responses to alcohol or other drugs are extremely pleasurable will be more likely to repeat the drug taking than those whose reaction is neutral or negative. Work by Schuckit[26] and Schuckit and Smith[27] has shown that sons of alcohol-dependent fathers inherit more tolerance to alcohol's effects and are less likely to experience hangovers than sons of non–alcohol-dependent fathers. In contrast, the inherited presence of an aldehyde dehydrogenase genotype (associated with alcohol metabolism) causes an involuntary skin "flushing" response to alcohol.[28-30] Individuals who are homozygous for this allele (approximately 35% of the Chinese population, and 20% of Jewish males in Israel) have an especially unpleasant initial reaction to

voluntary alcohol use to the point where there are virtually no alcoholics found with this genotype.[28-30]

Pathophysiology

The acute effects of alcohol and other drugs have been well characterized. However, even a complete understanding of these acute effects cannot explain how repeated doses of alcohol and other drugs produce paradoxically increasing tolerance to the effects of those drugs concurrent with decreasing volitional ability to forgo the drug. As suggested by Koob and Bloom,[31] the challenge is to find an internally consistent sequence by which molecular events modify cellular events and in turn produce profound and lasting changes in cognition, motivation, and behavior. Research on the neurochemical, neuroendocrine, and cellular changes associated with drug dependence has led to remarkable findings during the past decade, as summarized in the recent literature.[32-35] Herein, we summarize just 3 areas of investigation.

Addictive drugs have well-specified effects on the brain circuitry involved in the control of motivated and learned behaviors.[31-36] Anatomically, the brain circuitry involved in most of the actions of addictive drugs is the ventral tegmental area connecting the limbic cortex through the midbrain to the nucleus accumbens.[35,36] Neurochemically, alcohol, opiates, cocaine, and nicotine have significant effects on the dopamine system, although through different mechanisms. Cocaine increases synaptic dopamine by blocking reuptake into presynaptic neurons; amphetamine produces increased presynaptic release of dopamine, whereas opiates and alcohol disinhibit dopamine neurons, producing increased firing rates. Opiates and alcohol also have direct effects on the endogenous opioid and possibly the γ-aminobutyric acid systems.[31-36]

Significantly, the ventral tegmental area and the dopamine system have been associated with feelings of euphoria.[31,36] Animals that receive mild electrical stimulation of the dopamine system contingent on a lever press will rapidly learn to press that lever thousands of times, ignoring normal needs for water, food, or rest.[36] Cocaine, opiates, and several other addictive drugs produce supranormal stimulation of this reward circuitry.[31-36]

Given the fundamental neuroanatomy and neuropharmacology of this system, it is understandable that addictive drugs could produce immediate and profound desire for their readministration. Less clear is why simply preventing the administration of these drugs for some period would not correct the situation, return the system to normal, and lead to a "sadder but wiser" individual who would be less instead of more likely to reuse those drugs.

It is known that use of these drugs at some dose, frequency, and chronicity will reliably produce enduring and possibly permanent pathophysiologic changes in the reward circuitry, in the normal levels of many neurochemicals, and in the stress response system.[31,35,37-41] Volkow et al[37,42] found impairments in the dopamine system of abstinent former cocaine users 3 months after their last use. Other studies[39,40] have documented sustained changes in the stress response system following abstinence from opiate or cocaine dependence. Researchers do not know how much drug use is required to create these changes or whether these effects ever return to normal. Somatic signs of withdrawal last several days, motivational and cognitive impairments may last several months,[33] but the learned aspects of tolerance to the drug may never return to normal.[35,36,41]

A second explanation for the enduring pathology seen among drug-dependent persons and their tendency to relapse lies in the integration of the reward circuitry with the motivational, emotional, and memory centers that are colocated within the limbic system. These interconnected regions allow the organism not only to experience the pleasure of rewards but also to learn the signals for them and to respond in an anticipatory manner.[36,41,43] Repeated pairing of a person (drug-using friend), place (corner bar), thing (paycheck), or even an emotional state (anger, depression) with drug use can lead to rapid and entrenched learning or conditioning. Thus, previously drug-dependent individuals who have been abstinent for long periods may encounter a person, place, or thing that previously was associated with their drug use, producing significant, conditioned physiologic reactions, such as withdrawal-like symptoms and profound subjective desire or craving for the drug.[43,44] These responses can combine to fuel the "loss of control" that is considered a hallmark of drug dependence.[10]

These conditioned physiologic responses have been shown in laboratory studies[41,45,46] of currently abstinent former opiate, cocaine, and alcohol–dependent individuals. Childress et al,[43] using positron emission tomography, examined limbic and control brain regions of detoxified, male, cocaine-dependent subjects and cocaine-naive controls during videos of cocaine-related scenes. During the video, these currently abstinent former cocaine-dependent subjects experienced increased craving and showed a pattern of limbic increases and basal ganglia decreases in regional cerebral blood flow that mimicked the effects of the drug itself. This pattern did not occur in cocaine-naive controls or among the formerly cocaine-dependent patients in response to a neutral video.[43] Thus, even artificial video scenes of cocaine-related stimuli, presented in the sterile context of a positron emission tomography laboratory, produced excitation of brain reward regions and triggered drug craving.

TREATMENT RESPONSE

A central question in the comparison of drug dependence with other illnesses is whether dependence will decrease without treatment and whether it will respond to medications and other interventions. There is a large research literature on drug dependence treatment outcomes.[7-9,34,35,47-49] The treatment of addiction has been described in a manual[50] and 2 detailed vol-

umes.[51,52] Space permits only a few examples from that literature, addressing questions of particular import to physicians.

Untreated Persons

Examinations of untreated, dependent persons offer some indication of the natural course of addiction. For example, Metzger et al[53] measured drug use, needle-sharing practices, and human immunodeficiency virus (HIV) infection rates of 2 large samples of opiate-dependent persons in Philadelphia, Pa. The in-treatment (IT) group included 152 patients randomly selected at admission to a methadone maintenance program. Out-of-treatment (OT) subjects were also heroin-dependent individuals matched to the IT group by age, race, sex, neighborhood, and other relevant background factors, although none of the 103 OT subjects had received treatment. Both groups were interviewed and tested for HIV status every 6 months for 7 years. At the initial assessment, 13% of the IT sample and 21% of the OT sample were HIV positive. By 7 years, 51% of the OT group but only 21% of the IT group tested HIV positive.[53] Of course, even this substantial between-group difference does not prove that treatment participation was the causal agent. It is likely that the OT subjects lacked the motivation for change found among the treated patients. Thus, lack of desire for personal change, rather than the effects of the treatment itself, could have produced the differences seen.

One way to separate the effects of drug dependence treatment from the effects of motivation is to compare treated and untreated substance-dependent individuals who were explicitly not interested in treatment. Booth and colleagues[54] studied 4000 intravenous drug users seeking HIV testing as part of a multisite acquired immunodeficiency syndrome initiative in 15 cities. Subjects were randomly assigned to either standard HIV testing alone or to standard testing plus 3 sessions of motivational counseling from a health educator. At 6-month follow-up, those who received additional counseling showed half the rate of drug injection (20% vs 45%), 4 times the likelihood of abstinence (confirmed by urinalysis), and significantly lower arrest rates (14% vs 24%) than those randomly assigned to receive just HIV testing.[54] Studies of other illnesses show that screening and brief advice from physicians can affect the motivation for change among patients and the longer-term course of their health. The data of Booth et al suggest this is true even for seriously addicted individuals.

Svikis et al[55] studied drug abuse treatment in pregnant, cocaine-dependent women who did not originally apply for treatment. All women had simply applied for prenatal care and were found to be positive for cocaine use on a routine drug screen. They were compared with 46 pregnant, demographically matched women who tested positive for cocaine use and received standard prenatal care during the year before the opening of the experimental treatment program. Drug dependence treatment consisted of 1 week of residential care followed by twice-weekly addiction counseling in the context of the scheduled prenatal visits.

At delivery, 37% of the treated patients tested positive for cocaine use compared with 63% of the untreated women. Infants of the treated women averaged higher birth weights (2934 vs 2539 g) and longer gestational periods (39 vs 34 weeks) than those of the comparison group. Following delivery, 10% of infants in the treated group required care in the neonatal intensive care unit (mean, 7 days). In comparison, 26% of infants in the untreated group required intensive care (mean, 39 days). Average costs of care were $14 500 for the treated group and $46 700 for the comparison group. These data indicate that drug-dependent women can be screened and motivated during prenatal care and that drug dependence treatment can be combined with traditional prenatal care in an extremely cost-effective manner.

Medications

In addition to medications for nicotine dependence, such as nicotine gum and patch and bupropion hydrochloride, medications for alcohol and opiate addiction have been developed under Food and Drug Administration guidelines, have been researched in randomized clinical trials, and have reached the market. Herein, we discuss a few recent developments, but a complete review has been published by the Institute of Medicine.[35]

Opioid Dependence. Opioid agonists, partial agonists, and antagonists are the 3 primary types of medications available for the treatment of opioid dependence, all acting directly on opioid receptors, particularly μ-receptors.[35] Agonist medications, such as methadone hydrochloride, are prescribed in the short-term as part of an opioid detoxification protocol or in the long-term as a maintenance regimen. Double-blind, placebo-controlled trials[56,57] have shown methadone to be effective in both inpatient and outpatient detoxification, although the long-term effects of detoxification alone, without continuing treatment, have been uniformly poor. As a maintenance medication, methadone's oral route of administration, slow onset of action, and long half-life have been effective in reducing opiate use, crime, and the spread of infectious diseases, as was recently validated by a National Institutes of Health Consensus Conference.[58]

The partial agonist buprenorphine hydrochloride is administered sublingually and is active for approximately 24 to 36 hours.[59] Large double-blind, placebo-controlled trials of buprenorphine have shown reductions in opiate use comparable with methadone but with fewer withdrawal symptoms on discontinuation.[60] Importantly, the combination of buprenorphine plus naloxone hydrochloride, designed to reduce injection use, will soon be released for prescription in primary care settings.[61]

Opioid antagonists such as naltrexone block the actions of heroin through competitive binding for 48 to 72 hours, producing neither euphoria nor dysphoria in abstinent patients.[62,63] Nal-

trexone is used as a maintenance medication, designed as an "insurance policy" in situations where the patient is likely to be confronted with relapse risks. Naltrexone in combination with social or criminal justice sanctions is routinely used in the monitored treatment of physicians, nurses, and other professionals.[63] In a recent controlled trial, Cornish and colleagues[64] showed that naltrexone added to standard federal probation produced 70% less opiate use and 50% less reincarceration than standard probation alone.

Alcohol Dependence. Naltrexone has been found effective at 50 mg/d for reducing drinking among alcohol-dependent patients.[65,66] It works by blocking at least some of the "high" produced by alcohol's effects on μ-opiate receptors. More recently, European researchers have found encouraging results using the γ-aminobutyric acid agonist acamprosate to block craving and relapse to alcohol abuse.[67] Alcohol-dependent patients prescribed acamprosate showed 30% higher abstinence rates at 6-month follow-up than those randomized to placebo. Furthermore, those who returned to drinking while receiving acamprosate reported less heavy drinking ($\geq$5 drinks per day) than those receiving placebo.[67]

Stimulant Dependence. Although there are not yet effective medications for the treatment of cocaine or amphetamine dependence,[35] there are proven behavioral treatments.[68-71] There also are promising animal studies of a potential vaccine that binds to and inactivates metabolites of cocaine,[72] but clinical trials will not be scheduled for several years.

Comparing Treatments for Drug Dependence With Treatments for Other Chronic Diseases

There is no reliable cure for drug dependence. Dependent patients who comply with the recommended regimen of education, counseling, and medication have favorable outcomes during and usually for at least 6 to 12 months following treatment.[47-50] Favorable outcomes typically continue in patients who remain in methadone maintenance or in abstinence maintenance through participation in Alcoholics Anonymous (AA) or other self-help programs.[48,50-52] However, because of insurance restrictions, many patients receive only detoxification or acute stabilization with no continuing care.[3,6,9] Others drop out of rehabilitation-oriented treatment and/or they ignore physician advice to continue taking medications and participating in AA. Thus, 1-year, postdischarge follow-up studies[47-52,73] have typically shown that only about 40% to 60% of discharged patients are continuously abstinent, although an additional 15% to 30% have not resumed dependent use during this period. Problems of low socioeconomic status, comorbid psychiatric conditions, and lack of family and social supports are among the most important predictors of poor adherence during addiction treatment and of relapse following treatment.[47-52,74]

Hypertension, diabetes, and asthma are also chronic disorders, requiring continuing care throughout a patient's life. Treatments for these illnesses are effective but heavily dependent on adherence to the medical regimen for that effectiveness. Unfortunately, studies have shown that less than 60% of adult patients with type 1 diabetes mellitus fully adhere to with their medication schedule,[75] and less than 40% of patients with hypertension or asthma adhere fully to their medication regimens.[76,77] The problem is even worse for the behavioral and diet changes that are so important for the maintenance of gains in these chronic illnesses. Again, studies indicate that less than 30% of patients with adult-onset asthma, hypertension, or diabetes adhere to prescribed diet and/or behavioral changes that are designed to increase functional status and to reduce risk factors for recurrence of the disorders.[75-78] Across all 3 of these chronic medical illnesses, adherence and ultimately outcome are poorest among patients with low socioeconomic status, lack of family and social supports, or significant psychiatric comorbidity.[75-79]

Perhaps because of the similarity in treatment adherence, there are also similar relapse rates across these disorders. Outcome studies indicate that 30% to 50% of adult patients with type 1 diabetes and approximately 50% to 70% of adult patients with hypertension or asthma experience recurrence of symptoms each year to the point where they require additional medical care to reestablish symptom remission.[75-80]

COMMENT

Few persons who try drugs or regularly use drugs become dependent. However, once initiated, there is a predictable pathogenesis to dependence marked by significant and persistent changes in brain chemistry and function. It is not yet possible to explain the physiologic and psychological processes that transform controlled, voluntary use of alcohol and other drugs into uncontrolled, involuntary dependence. Twin studies indicate a definite role for genetic heritability. Nonetheless, personal choice and environmental factors are clearly involved in the expression of dependence. In terms of vulnerability, onset, and course, drug dependence is similar to other chronic illnesses, such as type 2 diabetes, hypertension, and asthma.

Our review of treatment response found more than 100 randomized controlled trials of addiction treatments, most showing significant reductions in drug use, improved personal health, and reduced social pathology but not cure.[7-9,34,35,47-52,81,82] Recent treatment advances include potent, well-tolerated medications for nicotine, alcohol, and opioid dependence[35,58,61,65-67] but not marijuana or stimulant dependence. There is little evidence of effectiveness from detoxification or short-term stabilization alone without maintenance or monitoring such as in methadone maintenance or AA.[47-52,57] However, as in treatments for other chronic disorders, we found major problems of medication adherence, early drop-out, and relapse among drug-dependent patients. In fact, problems

of poverty, lack of family support, and psychiatric comorbidity were major and approximately equal predictors of non-compliance and relapse across all chronic illnesses examined.[74-83]

Thus, our review suggests that drug dependence shares many features with other chronic illnesses. We are aware that arguments by analogy are limited, and even marked similarities to other illnesses are not proof that drug dependence is a chronic illness. Nonetheless, these similarities in heritability, course, and particularly response to treatment raise the question of why medical treatments are not seen as appropriate or effective when applied to alcohol and drug dependence. One possibility is the way drug dependence treatments have traditionally been delivered and evaluated.

Many drug dependence treatments are delivered in a manner that is more appropriate for acute care disorders. Many patients receive detoxification only.[3,35,48,49] Others are admitted to specialty treatment programs, where the goal has been to rehabilitate and discharge them as one might rehabilitate a surgical patient following a joint replacement.[47] Outcome evaluations are typically conducted 6 to 12 months following treatment discharge. The usual outcome evaluated is whether the patient has been continuously abstinent after leaving treatment.

Imagine this same strategy applied to the treatment of hypertension. Hypertensive patients would be admitted to a 28-day hypertension rehabilitation program, where they would receive group and individual counseling regarding behavioral control of diet, exercise, and lifestyle. Very few would be prescribed medications, since the prevailing insurance restrictions would discourage maintenance medications. Patients completing the program would be discharged to community resources, typically without continued medical monitoring. An evaluation of these patients 6 to 12 months following discharge would count as successes only those who had remained continuously normotensive for the entire postdischarge period.

In this regard, it is interesting that relapse among patients with diabetes, hypertension, and asthma following cessation of treatment has been considered evidence of the effectiveness of those treatments and the need to retain patients in medical monitoring. In contrast, relapse to drug or alcohol use following discharge from addiction treatment has been considered evidence of treatment failure. The best outcomes from treatments of drug dependence have been seen among patients in long-term methadone maintenance programs[49,50,58,83] and among the many who have continued participating in AA support groups.[84,85]

IMPLICATIONS

For primary care physicians, this review suggests that addiction screening, diagnosis, brief interventions, medication management, and referral criteria should be taught as part of medical school and residency curricula and routinely incorporated into clinical practice.[86,87] For those in health policy, our review offers support for recent insurance parity initiatives.[88] Like other chronic illnesses, the effects of drug dependence treatment are optimized when patients remain in continuing care and monitoring without limits or restrictions on the number of days or visits covered. Although it is unknown whether care delivered in a specialty program or coordinated through primary care will provide the maximal benefits for patients and society, it is essential that practitioners adapt the care and medical monitoring strategies currently used in the treatment of other chronic illnesses to the treatment of drug dependence.

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