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Neurobiology of addiction: treatment and public policy ramifications

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In the United States, efforts to treat addiction are hampered by prejudice and a public view that treats it as a disorder of self-control, not a disease. We highlight select advances in addiction research that, if disseminated to the public, could reverse these misconceptions and facilitate changes in policy to improve treatment access and care delivery for this highly prevalent disease.

The infrastructure to treat addictive illness, when compared with treatment for other traditional medical illnesses, is lacking in the United States. This situation is tolerated by a public that views addiction more as a social problem than an actual disease, despite scientific evidence supporting a disease concept of addiction based on neuronal mechanisms, heritability, treatment responses and a characteristic progressive clinical course[1]. Pejorative views toward addicted individuals also exist and contribute to policies that would be simply unacceptable if applied to 'real' medical disorders. These policies have created limited access, insufficient capacity and a dearth of trained providers in most geographical regions, especially for adolescent patients who might avoid progressive addiction with appropriate treatment. Even patients with access to treatment typically discover that its duration is severely limited by insurance company policies (managed care), even though addiction is a chronic illness requiring sustained aftercare. Imagine limiting treatment duration for diabetes, chronic heart failure or hypertension.

Stigma and misconception create formidable obstacles to a more enlightened public policy toward addictive illness. Rather than being treated as patients, afflicted individuals are often blamed for their illness, discriminated against and readily criminalized. Specialized treatment for addiction is even viewed as unnecessary (why not 'just say no' to drugs?) or misperceived as being ineffective. In contrast, treatment response does not dictate availability of care for other medical conditions like cancer, stroke and heart failure. Why should it be considered an appropriate standard for the availability of addiction treatment? This blatant discrepancy in access suggests that, despite therapeutic advances and improved clinical outcome, treatment parity will not be achieved until addiction is widely viewed as a disease.

Much of our knowledge about addiction neurobiology is based on decades of animal studies that model the dynamic clinical components of the illness. Elegant study designs assessing self-administration, conditioned place preference, reinstatement (after cues, stress and drug priming) and intracranial self-stimulation have provided a tremendous amount of behavioral and neurochemical information. Although this research has identified neuronal mechanisms underlying drug reward, craving, relapse and hedonic dysregulation, the predictive value of animal models varies considerably. Naltrexone treatment for alcohol dependence stemmed directly from animal studies showing that opioid antagonists reduce alcohol self-administration. On the other hand, the robust phenomenon of sensitization has received considerable emphasis even though its clinical significance is questionable, and it has not produced new treatments. Neuroimaging may ultimately circumvent the limitations of animal models and delineate brain mechanisms associated with clinical features of addictive illness. Scientific discoveries that substantiate the biological basis of addiction and improve treatment outcome should ultimately erode entrenched societal attitudes that prevent addiction from being evaluated, treated and insured as a medical disorder.

Addiction is best conceptualized as a disease of brain reward centers that ensure the survival of organisms and species[2]. Given their function, reward centers have evolved the ability to grip attention, dominate motivation and

compel behavior directed toward survival goals, even in the presence of danger and despite our belief that we are generally rational beings. By activating and dysregulating endogenous reward centers, addictive drugs essentially hijack brain circuits that exert considerable dominance over rational thought, leading to progressive loss of control over drug intake in the face of medical, interpersonal, occupational and legal hazards. There is even evidence that denial, once thought to be purely 'psychological', may be associated with drug-induced dysfunction of the prefrontal cortex[3].

Loss of control is both the hallmark of addiction and the source of its societal stigma. An uneducated yet strongly opinionated public does not understand the technical field of addiction neurobiology and is more likely to conceptualize addiction as a character flaw (for example, addictive personality) than a brain disease. Therefore, the dissemination of understandable information about this brain disease could change public perceptions and hence public policy toward addictive illness. Considerable emphasis has been placed on the prevention of addiction through widespread educational initiatives targeting children, adolescents and parents, but much less emphasis has been placed on the disease of addiction. Addiction is a disease of brain regions that are intrinsically interesting to the general public because they subserve the human experiences of pleasure, craving and motivation. Fascination with this topic could be exploited by educational initiatives to gain ground against moralistic attitudes that stigmatize, ostracize and often criminalize patients with addictive illness.

Access to treatment for millions of addicted patients is a costly proposition. However, there would be offset savings in the cost of medical care, lost productivity, neighborhood destruction, crime and prison capacity[4]. Even though the United States has a disproportionate number of prisoners, and most have been incarcerated for drug-related crimes, their addiction is seldom treated within the prison walls or, more importantly, after they are released to a drug-infested environment. Similarly, although medical complications of addiction are commonly encountered in clinical practice, their cause is seldom addressed and treated[5]. By fully integrating addiction treatment into our medical care delivery and judicial systems, we could dramatically improve medical care and justice.

Here we highlight select areas of addiction research that illustrate brain involvement and would probably stimulate public interest if conveyed in an understandable fashion. Perhaps the dissemination of these and other examples of current knowledge could begin to reverse popular misconceptions about addictive illness, increase compassion and tolerance and facilitate changes in public policy that improve treatment access and care delivery for this highly prevalent disease.

The cycle of addiction

Addiction neurobiology ties clinical phenomena of the illness to specific neuronal

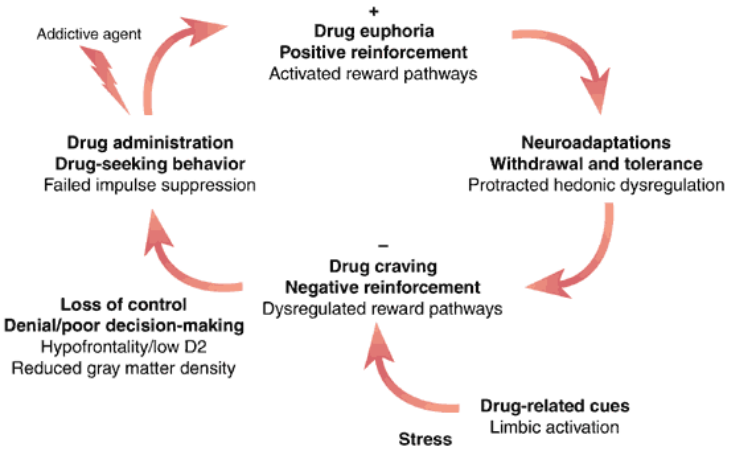

Fig 1. The cycle of addiction is positively reinforced by drug euphoria and negatively reinforced by withdrawal, craving and hedonic dysregulation.
Drug-related cues and stress increase craving, and loss of control may stem in part from prefrontal cortical dysfunction. Neuronal mechanisms for these cardinal components of addiction have been increasingly delineated with animal models and human neuroimaging studies.

Addictive drugs produce euphoria by activating brain pleasure centers, and it is noteworthy that diverse agents (for example, opioids, stimulants, alcohol, nicotine, marijuana) all increase extracellular dopamine (DA) levels in the shell of the nucleus accumbens (NAc). Drug-induced euphoria in humans has also been closely linked to DA receptor (D2) binding by several elegant positron emission tomography (PET) studies[6]. Animal studies demonstrate that natural rewards (sex, food, water) also elevate DA levels in the NAc, although to a lesser extent, and human neuroimaging studies report that DA release in the dorsal striatum correlates with meal pleasantness[7]. These studies link drug euphoria to natural reward centers that have evolved to ensure survival.

Once experienced, drug euphoria promotes the repeated use of an addictive drug, especially if genetic traits enhance the pleasurable experience. For instance, there is considerable evidence that individuals with a genetic predisposition toward alcoholism experience more pleasure from this drug because it produces an exaggerated β-endorphin response. Over time, addictive drugs disrupt reward circuits and produce dysphoric states such as withdrawal, craving and hedonic dysregulation that provide negative reinforcement, and alternate with the positive reinforcement of euphoria to drive the cycle of addiction (Fig. 1).

Chronic exposure to heroin, cocaine or alcohol produces a number of common neuroadaptations[8], including DA hypoactivity, that contribute to a remarkably similar clinical course in severely addicted individuals. The cycle of addiction becomes etched in midbrain and frontal structures that reinforce the pursuit of survival-related behaviors by dominating attention and decision-making. Addictive illness reminds us that desire and pleasure can be impervious to rational thought, clashing with deeply engrained cultural values placed on stoicism and self-control.

Craving is a complicated phenomenon that can be dramatically amplified by stimuli (cues) that have become associated with drugs through conditioned learning. Neuroimaging studies of addicted human patients demonstrate a fascinating link between brain function and cue-induced craving, which is arguably the most persistent and insidious clinical component of addictive illness. Cues associated with diverse substances (for example, cocaine, heroin, alcohol and nicotine) produce robust activation of limbic structures on PET and functional magnetic resonance imaging (fMRI). Images depicting limbic activation during cue-induced craving provide an interesting and graphic means of demonstrating the neuronal basis of cue-induced craving to the general public (Fig. 2).

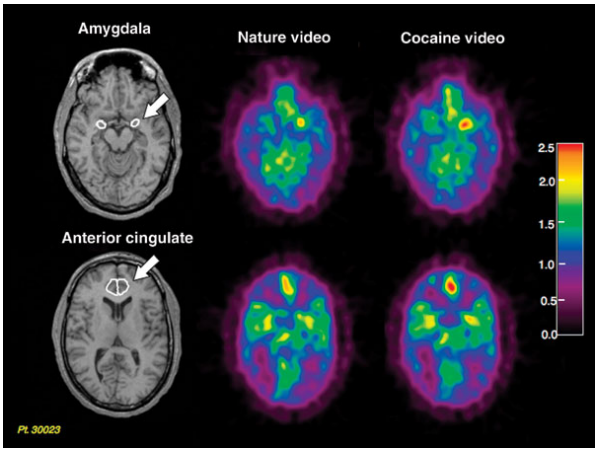

Fig 2. Cue-induced craving (produced by a cocaine video compared to a nature video) is associated with significant limbic activation on PET, which graphically demonstrates the neuronal basis of this important clinical component of addictive illness.

Another interesting neuroimaging finding associated with addictive illness is that of hypofrontality (reduced baseline metabolism in the prefrontal cortex)[6]. Baseline hypofrontality involves the same frontal regions that become hypermetabolic during cue-induced craving, and the exaggerated change (Δ metabolism; peak minus baseline) in frontal metabolism might contribute to the remarkable salience of drug-related cues[3]. In addition to hypofrontality, cocaine-addicted individuals show reductions in frontal gray matter density[9] and poor performance on

neuropsychological tests assessing prefrontal cortical function[3]. As the seat of executive function in the brain, the prefrontal cortex is involved in decision-making, risk/reward assessment, impulse control and perseverance. Functional and structural abnormalities in the prefrontal cortex might therefore contribute to clinical characteristics of addicted patients (such as poor impulse control, lack of resolve, faulty decision making) that are viewed prejudicially by the general public. Hypofrontality is associated with reduced D2 receptor availability on PET, which may be a marker for reduced DA function in addicted patients.

The next sections review specific neurobiological findings that are likely to be of great interest to the general population and convey the biological basis of addiction. It is not widely known that the brain produces opioids and opioid receptors, that heroin binds to these receptors, and that alcohol pleasure involves opioid function. Also unappreciated is the importance of cue-induced craving, its basis in limbic activation, and evidence that addicted individuals have impairments in executive and hedonic function. These findings should be disseminated to the general public in understandable and interesting forums to promote the disease concept of addiction.

Endogenous opioids

Endogenous opioid pathways activated by addictive drugs are involved in pain, pleasure, appetite, sexual function and natural drive states, and it is noteworthy that separate and antagonistic enkephalin and dynorphin populations of medium spiny cells in the NAc are involved in addictive illness[8]. Although alcohol is ubiquitous in our society, few people know that alcohol reward is mediated by endogenous opioids and influenced by genetic factors affecting opioid function. One of the earliest reports[10] pertaining to this topic was published in 1980, showing that naltrexone pretreatment extinguishes alcohol self-administration in rhesus monkeys. Several lines of animal research subsequently demonstrated that alcohol acutely increases opioid activity, especially in animals bred to prefer alcohol, and that alcohol is not self-administered by -opioid receptor knockout mice[11].

Human studies also demonstrate involvement of endogenous opioid systems in alcohol reward. Compared with normal subjects, individuals with a genetic predisposition for alcoholism have low baseline blood β-endorphin levels and enhanced β-endorphin release and euphoria after alcohol administration[12]. Enhanced release of β-endorphin against low baseline levels constitutes a surge in the concentration of this rewarding endogenous opioid that may explain why these individuals experience more pleasure from alcohol. Other studies corroborate an interaction between β-endorphin levels and alcohol consumption. Cerebrospinal levels of β-endorphin are three times higher in normal subjects than in patients with chronic alcoholism, and there is evidence that β-endorphin levels might become depleted after chronic alcohol intake[13]. Alcoholics experiencing withdrawal symptoms have plasma β-endorphin levels only half as high as those in normal subjects, yet their levels normalized after several weeks of sobriety[14]. In addition, abstinent alcoholics show increased -opioid receptor binding in the ventral striatum that correlates with the severity of their reported craving for alcohol[15]. Thus, both genetic and alcohol-induced alterations in β-endorphin are important in the neurobiology of alcoholism. The involvement of endogenous opioids in alcoholism led directly to the development of naltrexone as an approved treatment for this condition.

Cue-induced craving and limbic activation

We have known for decades that environmental stimuli (people, places and things) associated with drug use can trigger intense craving in addicted patients. Aside from perpetuating active drug use, cue-induced craving triggers relapse after protracted abstinence because it persists for months or years, and even perhaps indefinitely, as a direct avenue to recidivism. Seeing a syringe in the doctor's office, smelling a cigarette, or glancing at a vodka advertisement are innocuous experiences for most of us but can be painfully compelling for vulnerable individuals. Largely unknown to the general public, neuroimaging studies have demonstrated dramatic limbic responses to drug-related cues that correlate with the degree of reported craving. This phenomenon graphically demonstrates the biological nature of addictive illness and provides one of the most fascinating examples of the mind/brain interface.

Neuroimaging studies of patients addicted to various substances demonstrate the activation of similar frontal regions as a common pathway of cue-induced craving. Cocaine-dependent patients have been studied extensively in PET and fMRI experiments, and they consistently show activation of the amygdala and anterior cingulate cortex that correlates closely with their reports of craving severity[3]. Alcoholic subjects also show activation of the anterior cingulate, medial prefrontal cortex and striatum in response to alcohol-related cues on fMRI[16, 17], and the intensity of the cue reactivity correlates with their likelihood of relapse[18]. PET studies of heroin-dependent subjects also

demonstrate a strong correlation between cue-induced opioid craving and hypermetabolic responses in the inferior frontal and orbitofrontal cortex[19], and patients with nicotine dependence show increased metabolism in the anterior cingulate on fMRI during exposure to cigarette-related cues[20]. These studies demonstrate a common neuronal response to cues associated with diverse substances, and they justify the commonly held notion that various drug dependencies should be conceptualized as a single disorder.

Natural drive states are also associated with activation of glutamate-rich cortical regions. Remarkably, the same frontal regions that are activated by cocaine-related cues in cocaine-dependent patients are also activated in normal subjects viewing sexually explicit videos[21]. Furthermore, neuroimaging studies demonstrate that the subjective report of hunger in response to food-related cues is temporally associated with marked activation of frontal regions[22]. These studies link drug-related craving with natural drive states, and graphically support the idea that addictive drugs hijack endogenous reward circuits that have evolved to ensure survival.

Prefrontal cortical regions that are activated during cue-induced craving receive DA projections from neurons originating in the ventral tegmentum. A series of elegant single-cell recording studies demonstrate that these midbrain DA neurons fire during unpredicted hedonic activity, but their firing habituates to predictable reward and shifts instead to cues that reliably predict impending reward[23]. These and other studies reviewed elsewhere[3] suggest that DA firing is correlated with cue-induced limbic activation. Interestingly, studies demonstrate that DA firing in the ventral tegmentum plunges below baseline when anticipated reward is not delivered, linking DA hypoactivity to an animal model of acute deprivation (craving). Furthermore, animals chronically exposed to stimulants, alcohol or opioids show dramatic depletion of extracellular DA in the NAc[24], and DA depletion might contribute to craving and hedonic dysregulation in addictive illness[8].

Because cue-induced craving is associated with DA firing and hypermetabolic responses in glutamate-rich cortical regions, medications that reduce DA neurotransmission have been widely proposed as potential treatments for this phenomenon. Glutamatergic neurotransmission is also implicated in cue-induced craving, and glutamate-releasing neurons in the orbitofrontal cortex (which receive reward-related sensory input from the thalamus) fire during cues related to natural rewards and send excitatory projections to the VTA and the NAc[25]. Cue-induced craving often leads directly to relapse, and an effective treatment for this phenomenon should dramatically improve outcome. DA and glutamate antagonists should be tested in the laboratory before concluding that they reduce limbic activation during cue presentation, especially as addicted patients may already be DA depleted. Indeed, limbic activation during drug-related cues provides a unique biological marker that should be exploited with further targeted research.

The D2 story

One of the most interesting findings in addiction research is the reduced availability of striatal D2 receptors in patients with addictive illness. PET studies using [^{11}C]raclopride, a radioligand that competes with DA at D2 receptors, demonstrate persistently low striatal D2 availability (↓D2) in patients addicted to cocaine[26], alcohol[16], methamphetamine[27] or opioids[6]. Individuals with morbid obesity also have ↓D2 that is inversely related to their body mass index[28].

It is not known whether ↓D2 in addicted patients precedes or results from their drug exposure, and there is evidence that both possibilities may occur. That ↓D2 persists beyond detoxification from alcohol and opiates suggests that it might be a predisposing factor or at least a persistent drug-induced finding[6]. The possibility that ↓D2 represents an inherited trait is compelling because D2 binding varies considerably across individuals, and nonaddicted individuals with ↓D2 report significantly more pleasure after receiving stimulant drugs[6]. Similarly, monkeys with ↓D2 are significantly more likely to self-administer cocaine than those with increased striatal D2 receptor availability on PET (↑D2; ref. 29). Indeed, ↑D2 may protect against addiction because alcohol intake is significantly reduced in rats after D2 receptor expression has been increased with an adenoviral vector[30]. The importance of genetic factors in addictive illness, especially those affecting the intensity of drug reward, reinforces the biological basis of this disorder.

Although ↓D2 may represent a consti-tutional trait and addiction vulnerability, it can also result from cocaine exposure because chronic cocaine treatment produces ↓D2 in monkeys. In addition, D2 varies with social

dominance rank in cynomolgus monkeys and is reduced with social demotion, leading to an increased propensity to self-administer cocaine[31]. There is considerable evidence from animal studies supporting DA hypoactivity after chronic exposure to stimulants, opioids, and alcohol[24, 32, 33], and human studies also report DA hypoactivity in alcohol-[34], heroin-[35] and cocaine-addicted patients[6], with the latter group showing evidence of DA hypoactivity on neuroimaging and a host of neuroendocrine and autopsy studies reviewed elsewhere[25]. DA hypoactivity after chronic cocaine administration is associated with the downregulation of D2 autoreceptors that are abundant in the striatum[3]. Consequently, ↓D2 may reflect autoreceptor downregulation and may serve as a marker for DA dysregulation in addictive illness.

Autoreceptor downregulation might also contribute to the controversial finding of sensitization, which has unclear relevance to addictive illness despite its considerable emphasis by many animal researchers[36]. Whereas tolerance is defined as a reduced dose response after repeated drug administration, sensitization involves accentuated responses, classically in the form of enhanced locomotion with a repeated fixed dose of a stimulant or opioid agent. Enhanced cocaine-induced elevations of DA[37] and glutamate[38] in the NAc of cocaine-pretreated animals are associated with sensitization and could be explained by persistently downregulated D2 (ref. 3) and mGluR2/3 (ref. 39) autoreceptors, especially as mice lacking D2 expression (having no autoreceptor function) show strikingly enhanced striatal DA levels after the administration of cocaine and morphine[40]. Thus, sensitized DA and glutamate responses to cocaine, often invoked as a rationale for testing DA- or glutamate-inhibiting agents, may merely reflect a homeostatic autoreceptor response to DA hypoactivity. Sensitization in animals has led some researchers to speculate that cocaine euphoria actually increases over time, even though patients typically report the opposite and escalate their daily consumption of cocaine. This area of research provides an excellent example of why animal models must be reconciled with clinical experience.

In cocaine and methamphetamine abusers, ↓D2 is correlated with reduced metabolism in the orbitofrontal cortex[6]. As previously noted, hypofrontality in cocaine-dependent patients may contribute to poor impulse control, elements of denial and compulsive drug use[2, 6]. Cocaine-dependent subjects with reduced anterior cingulate and right prefrontal cortical metabolism have concomitant difficulty controlling impulses during formal neuropsychological testing[41]. These findings suggest that agents that increase metabolic activity in frontal regions, such as modafinil, might improve impulse control in addicted patients[3].

Through animal models and human neuroimaging studies, researchers are elucidating neuronal mechanisms that underlie the dynamic clinical elements of addictive illness. First, this body of research strongly supports the disease concept by linking the activity of reward-related structures in the brain to clinical manifestations of this disease. Common neurobiological phenomena also justify categorizing addiction to diverse agents under a single general disorder. Diverse agents like cocaine, heroin and alcohol increase striatal DA levels during intoxication, whereas chronic exposure to these agents is associated with DA hypoactivity, ↓D2 and limbic activation during cue-induced craving. Addiction also has genetic determinants and a similar progressive clinical course across various substances. These attributes are certainly consistent with the idea that addiction is a brain disorder, despite popular misconceptions.

Pharmacological treatments for addiction

Several approved and promising treatments for addiction have been identified through neurobiological research[3, 42]. Pharmacological strategies are emerging that target specific clinical components of addiction, including drug-induced euphoria, hedonic dysregulation, cue-induced craving and even denial. The development of treatments that dramatically improve clinical outcome should reverse social stigma and justify an expanded care delivery system. However, the clinical impact of new treatments also depends on their translation into clinical practice. Treatments for nicotine dependence (such as bupropion and the nicotine patch) have been promoted by the pharmaceutical industry, are often prescribed by primary care physicians and are covered by some insurance plans. Naltrexone treatment for alcoholism, on the other hand, has not been sponsored by industry, is seldom prescribed by primary care physicians, and is greatly underused.

Naltrexone (an opioid receptor antagonist) was originally developed to treat heroin dependence by blocking euphoria, an established pharmacological strategy that improves outcome by weakening the addiction cycle. However, this strategy has been limited in opioid dependence because naltrexone does not convincingly ameliorate

opioid craving, and patients often stop the drug and resume heroin use. Still, reducing opioid reward with naltrexone provides benefits for some patients, and adherence has recently been addressed with the development of depot delivery systems that allow for monthly medication injections.

The initial controlled study of naltrexone in alcoholics reported a reduction in clinically significant daily drinking and alcohol craving in active versus placebo groups[43]. After these findings were replicated at another site[44], naltrexone gained FDA approval for the treatment of alcoholism. Since then, most controlled studies have reported significant reductions in daily drinking with naltrexone treatment. Furthermore, the efficacy of naltrexone might be more dramatic in a subgroup of genetically defined alcoholics. One of the polymorphisms (Asp40) for the gene encoding the -opiate receptor produces a receptor with high affinity for β-endorphin, and individuals with this variant have increased risk of alcoholism[45] and heroin addiction[46]. Alcoholics with this variant are reported to be significantly more likely to benefit from naltrexone than patients without the variant are[47]. If this finding is replicated, clinicians will have an available genotype to match alcoholic patients with effective treatment.

Studies showing naltrexone efficacy in alcoholic outpatients prompted laboratory testing to assess how the beneficial effects are mediated. One of these studies suggests that naltrexone diminishes alcohol-induced craving, which fuels the common phenomenon in which the first drink leads to uncontrollable drinking. This controlled study evaluated the effect of naltrexone pretreatment on baseline and alcohol-induced craving[48], finding that placebo- versus naltrexone-treated patients reported higher alcohol craving at baseline and after alcohol priming. This study also tested drinking behavior after the priming dose of alcohol by asking subjects to choose either alcohol or money, and the placebo group chose alcohol significantly more often. Conversely, the naltrexone group reported less craving, even after the priming dose when additional alcohol was available, consumed fewer drinks and drank more slowly. Therefore, the tendency for alcoholics to lose control once they begin to drink is an important clinical feature of alcoholism that may be specifically ameliorated by naltrexone.

Although naltrexone represents a success story that stemmed directly from neurobiological research, this treatment for alcoholism is markedly underused in clinical practice. One problem has been patient nonadherence, sometimes in response to side effects but more often to recapture the experience of alcohol-induced euphoria. This issue is being addressed by the development of depot delivery systems that will eliminate the need for patients to make a daily decision about naltrexone. However, the greatest translational problem likely stems from a curious lack of awareness among primary care physicians regarding naltrexone. Despite FDA approval for alcoholism since 1994, naltrexone is not widely prescribed to the enormous population of active alcoholics, even though alcohol often produces the very illnesses for which these patients seek medical treatment[5].

Pharmaceutical companies have just begun to view alcoholic patients as an important population, and the recent approval of acamprosate might signal a change in industry attitudes toward addictive illness. Acamprosate modulates *N*-methyl-D-aspartate (NMDA) receptor subunit expression[49]. However, the pharmaceutical industry is still reluctant to develop treatments for illegal addictions, exemplified by the fact that cannabinoid receptor antagonists have not been made available for testing in marijuana-dependent patients. Our government may also be reluctant to promote treatments for illegal addictions. Buprenorphine, an effective partial -opioid agonist that was recently approved for office-based treatment of opioid dependence, has many advantages over methadone, a full agonist with many legal restrictions. Nonetheless, its use is curtailed by FDA rules stipulating which physicians can prescribe the drug and how many patients they can treat.

New pharmacological strategies that target specific elements of the addiction cycle are currently under intense investigation. Modafinil has been reported to attenuate cocaine euphoria in two controlled studies and is under investigation in three large clinical trials[3]. Cocaine euphoria is also being targeted with cocaine vaccines that prevent the drug from entering the brain[50], and other promising medications for cocaine dependence (disulfiram, topiramate, propranolol and baclofen) are being tested[3]. Cue-induced craving in cocaine, opioid, heroin and nicotine dependence is a logical target for candidate medications that might be screened in the neuroimaging laboratory before being tested in large clinical trials. Potential pharmacological treatments for other clinical components of addiction, including stress-induced craving, hedonic dysregulation and hypofrontality, will likely be identified through expanding research[3].

Public policy implications

Changes in public policy are needed to improve the access, capacity and quality of addiction services. These changes would be facilitated by public acceptance of the disease concept and through the development of more effective treatments. Both goals could be attained with advances in addiction neurobiology and continued funding in this essential area of research. Animal and human research should be closely coordinated and focused on developing practical treatment interventions. Animal models with demonstrated relevance to the clinical setting, especially those assessing self-administration and reinstatement, should be prioritized as a means of guiding treatment development. It is also imperative that research findings in this technical area be made available to the public in an understandable manner that conveys the biological nature of addiction. We have reviewed select findings from this research that illustrate brain involvement in alcohol euphoria, cue-induced craving and the genetic vulnerability to addiction. These interesting examples are largely unknown to the general public, and their dissemination is now indicated to promote the disease concept of addiction.

Even when effective treatments for addiction have been identified, as illustrated by naltrexone treatment for alcoholism, they have not always been adequately translated into clinical practice. The pharmaceutical industry has recently become interested in alcohol and nicotine dependence, and their considerable resources could potentially expand addiction treatment. Addiction treatment should also be integrated into mainstream medicine. Although medical complications of substance abuse are commonly encountered in clinical practice, addiction and medical treatments are seldom coordinated[5]. Primary-care physicians are essential in this regard and should have a much greater role in the assessment and treatment of addicted patients. The training of physicians to assess and treat addiction should be expanded in our medical schools and residency programs. We cannot allow the stigma of addiction to influence training policies, as it undoubtedly has, if we wish to provide comprehensive and effective medical care. Primary-care physicians should competently evaluate their patients for addictive illness, especially those with addiction-related medical conditions, and view pharmacological treatments as part of their clinical arsenal. Referrals to addiction specialists should be made with the same frequency as those to other medical specialties. The general quality of care delivery in this country will be improved to the extent that addiction treatment is placed in the mainstream of medicine.

The judicial approach to addicted patients is another area in dire need of guidance and policy change. Active addiction often involves criminal behaviors related to drug use and procurement, and addicted patients typically engage in activities they would never consider during recovery. Such individuals should receive innovative judicial interventions that promote treatment over criminalization and recovery over incarceration. The judicial system should develop an integrated interface with specialized treatment teams to ensure that appropriate interventions are closely coordinated. Addicted patients already incarcerated should receive treatment within the prison walls, and drug testing of inmates and correctional officers should be applied to eliminate the widespread use of drugs within our prisons. Ending inappropriate criminalization of this disease would produce tremendous financial and humanitarian benefit to our society.

Education designed to prevent addiction is already integrated into our schools and should be further developed with research-based interventions. Because perceived risk is an important determinant of drug experimentation, the dangers of drugs should be conveyed accurately and credibly to our youth. Schools provide a natural setting for these interventions and a means of identifying students who may require treatment. Unfortunately, there are few practitioners qualified to evaluate and treat adolescent substance abusers in most geographical regions. Given the progressive nature of addiction, and the opportunity of early intervention, inadequate access to treatment for adolescent substance abusers is entirely unacceptable.

Public-policy changes that improve access, capacity and quality in addiction treatment will require significant investment in our health delivery system. Treatment for this chronic disorder is labor intensive, requiring a comprehensive assessment by qualified practitioners, as well as ongoing individual, group and family interventions. Although pharmacological treatments for addiction will continue to improve and streamline treatment, a 'magic bullet' for this chronic debilitating disorder will probably not be found. If and when the public begins to view addiction as a medical disorder, the need for treatment parity could be added to arguments regarding the cost of untreated addiction in dollars and lives. It remains to be seen whether improvements in our care delivery system will occur in a climate that focuses more on cost savings than quality enhancement.

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