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Drugs and alcohol: Treating and preventing abuse, addiction and their medical consequences

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Abstract

Recent advances in the fields of genetics, molecular biology, behavioral neuropharmacology, and brain imaging have dramatically changed our understanding of the addictive process and why relapse occurs even in the face of catastrophic consequences. Addiction is now recognized as a chronic brain disease that involves complex interactions between repeated exposure to drugs, biological (i.e., genetic and developmental), and environmental (i.e., drug availability, social, and economic variables) factors. Its treatment, therefore, requires, in general, not only a long-term intervention but also a multipronged approach that addresses the psychiatric, medical, legal, and social consequences of addiction. Also, because addiction usually starts in adolescence or early adulthood and is frequently comorbid with mental illness, we need to expand our treatment interventions in this age group both for substance abuse and psychiatric disorders.
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Keywords: Addiction; Dopamine; Prevention; Treatment; Mental illness; Adolescence

Abbreviations: ADHD, attention deficit/hyperactive disorder; CB, cannabinoid; CM, contingency management; DA, dopamine; FAS, fetal alcohol syndrome; GABA, gamma-amino butyric acid; GVG, gamma vinyl-GABA; IDU, injection drug use; Meth, methamphetamine; MPH, methylphenidate; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; PET, positron emission tomography.

Contents

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1. Introduction: the challenges of substance abuse today

Our views on the biological bases of drug and alcohol addiction have changed profoundly in recent years. To translate the new understanding into more effective prevention and treatment programs, the scientific and nonscientific communities will need to (a) coordinate efforts to curb the prevalence and high cost associated with alcohol and drug addiction, (b) study and reduce the phenomenon of early onset, (c) foster wider acceptance of the concept of substance addiction as a chronic relapsing brain disease, (d) engage pharmaceutical industry participation in the research and development of new and effective treatments for substance addiction, and (e) facilitate reimbursement of treatment costs by private medical insurance companies.

1.1. Prevalence, trends, and costs of substance abuse in America

According to 2003 data from the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration [SAMHSA], 2004b), 9.1% of the total population, or an estimated 21.6 million people aged 12 or older, can be classified with dependence or abuse of psychoactive substances (alcohol or illicit addictive drugs). Recent data also show that abuse of illegal drugs and of nicotine in young individuals has apparently begun to decline. According to Monitoring the Future (MTF), a survey that monitors drug use among high school students, current (past month) use of illicit drugs has declined 17% in the past 3 years in this group (Johnston et al., 2005). At the same time, MTF and other surveys also reveal disturbingly high levels of nonmedical use of prescription drugs (stimulant medications, opiate analgesics, and benzodiazepines), the rise of which has been most dramatic in the painkillers category. This is likely to reflect multiple factors, including the increase in the number of prescriptions for some of these medications, their frequent presence in the media, and their relatively easy and private access via web sites that do not require prescriptions (Lineberry & Bostwick, 2004). Another factor that is likely to contribute is a new pattern of drug abuse that is initiated not by the desire to get "high" but by the desire to improve performance. For example, stimulant medications are increasingly being abused by high school students to improve their scores on college entrance exams, by girls to achieve a body image that conforms to unrealistic standards, and by adults trying to cope in highly competitive environments.

Despite generally positive trends, the prevalence of substance abuse remains unacceptably high. Moreover, the economic impact of substance abuse is enormous. The estimated costs associated with illicit drugs are ~US$280 billion (including costs from crime, loss in productivity, health care, incarceration, and drug enforcement operation costs; Harwood, 2004), for alcohol, around US$185 billion (Harwood, 2000), and for nicotine, ~US$158 billion (CDC, 2005a, 2005b, 2005c). This brings the grand total estimated economic impact of substance abuse in the United States to over half a trillion dollars.

1.2. Obstacles in the treatment of addiction

Despite the fact that there are effective treatments for drug addiction, less than 15% of those addicted receive treatment (Gerada, 2005). This is likely a reflection not only of the addicted person's denial of there being a problem but also of the fear of stigmatization for being labeled an addict, as well as the lack of access to an acceptable treatment program. In this respect, the lack of reimbursement by private insurance companies hinders a wider involvement of the medical community in the early evaluation and treatment of drug addiction.

Another obstacle pertains to the limited range of medications currently available for the treatment of addiction. This reflects, in part, the limited participation of the pharmaceutical industry in the development of addiction medications. Understandably, the stigma associated with drug addiction, the lack of insurance reimbursement for drug-abuse treatment, and the perceived relatively small size of the users' market create an environment that is not conducive to active collaborations with industry.

Recognizing the impact of this gap, the Institute of Medicine has recommended the implementation of a program of targeted incentives for the pharmaceutical industry (Fulco et al., 1995). In the meantime, we continue to pursue collaborations with pharmaceutical companies in an effort to move their novel and promising compounds forward and into the process of clinical evaluations for the treatment of addictive disorders.

Whenever we are able to access and reevaluate medications developed to target other diseases (i.e., antiepileptics and antidepressants) for their potential application to

addiction, much valuable research and preliminary safety testing has already taken place, resulting in substantial savings of time and resources.

1.3. Drugs and HIV

Drug abuse and HIV/AIDS are intertwined epidemics (Schuster, 1992; McCoy et al., 2004). Injection drug use (IDU) accounts for ~1/3 of all the AIDS cases in this country (Fig. 1), and over 90% of HIV infected injection drug users are also infected with hepatitis C (Amin et al., 2004). However, that is only 1 part of the problem of HIV transmission because non-IDU drug abusers also show much higher rates of HIV infection than the general population (McCoy et al., 2004). There are many factors that contribute to such high rates, but chief among them is the risky sexual behaviors that many drug and alcohol abusers engage in due to changes in their mental state from drug intoxication. Basic research shows that certain drugs of abuse can also compromise the immune system (Zhu et al., 2000; Yu et al., 2003; Safdar & Schiff, 2004), putting users at greater risk of contracting the illness or suffering a more severe course. It is also reasonable to expect a synergistic, deleterious interaction between centrally acting psychoactive drugs and neurotoxic substances released during the course of an HIV infection (Nath et al., 2002).

Addiction treatment has been shown to be an effective way to prevent the spread of diseases, such as HIV/AIDS and hepatitis. Drug injectors who do not enter treatment, for example, are up to 6 times more likely to become infected with HIV than injectors who enter and remain in treatment (NIDA, 2000). Participation in treatment also offers good opportunities for screening, counseling, and referral for additional services, all of which can help reduce the spread of diseases to the general population.

NIDA research has shown that screening can be a cost-effective way to prevent and treat diseases, such as HIV/AIDS. When broad screening for HIV in health care settings is provided, early detection and active antiretroviral therapy result in increased life expectancy and reduced transmission rates (Paltiel et al., 2005; Sanders et al., 2005). For example, screening a person at 30 years of age could increase his/her life expectancy by almost 2 years. Furthermore, by screening larger segments of the population, HIV transmission rates can be decreased by about 20%.

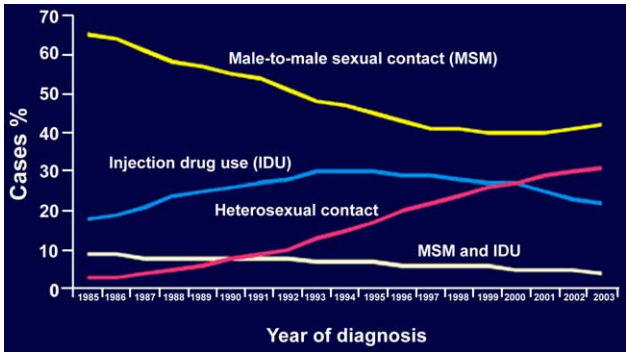

Fig. 1. Proportion of AIDS cases among adults and adolescents by exposure category and year of diagnosis 1985–2003, United States (CDC, 2005a).

The HIV/AIDS epidemic has taken a disproportionate toll on racial and ethnic minority populations. The CDC reports that during 2000–2003, HIV/AIDS rates for African American males were 7 times those for white males, and African American females had 19 times the rates for white females, exceeding the rates for males of all races/ethnicities other than African Americans (CDC, 2004a). NIDA has launched an initiative that is focused specifically on reducing HIV rates among African Americans, including conducting more studies in geographic areas where rates are highest and developing interventions that are ethnically appropriate. Further, because African American males are nearly 8 times more likely to be incarcerated than white males, supporting research on the intersection of drug use and criminal justice consequences in the African American population is a high priority.

2. The neurobiology of substance abuse and addiction

2.1. Developmental aspects

In addressing the neurobiology of drug abuse and addiction, it is critical to consider the influence of specific developmental stages. Experimentation with illicit use of addictive substances during childhood and adolescence is not only dangerous but also disturbingly common (Johnston et al., 2005). To a large degree, initiation for most youth results from the convergence of social influences and the typically rebellious behaviors that appear around the preteen and teenage years. Research shows that periods of enhanced risk for seeking drugs coincide with major transitions in children's lives (NIDA, 2003). As children navigate through these developmental stages, they face not only increased social, emotional, and educational challenges but also greater access to addicting substances.

Overlaying these behavioral and social risk factors is the recent finding showing that brain development continues well beyond childhood and adolescence (Fig. 2; Sowell et al., 2004). The adolescent brain is characterized by vigorous changes in growth and connectivity. The continuous pruning and fine-tuning that eventually create the adult brain coincide with the commonly observed shifts in adolescent behavior and thought processes that compromise the early adolescent's ability to consistently carry through with intended and planned choices (Luna & Sweeney, 2004). Recent imaging data revealed that one of the last areas of the brain to mature is the prefrontal cortex (Gogtay et al., 2004), which is an area involved in judgment, decision making, and control of emotional responses. It is reasonable to hypothesize a link between the immaturity of the adolescent brain, the ensuing high level of risk taking and novelty

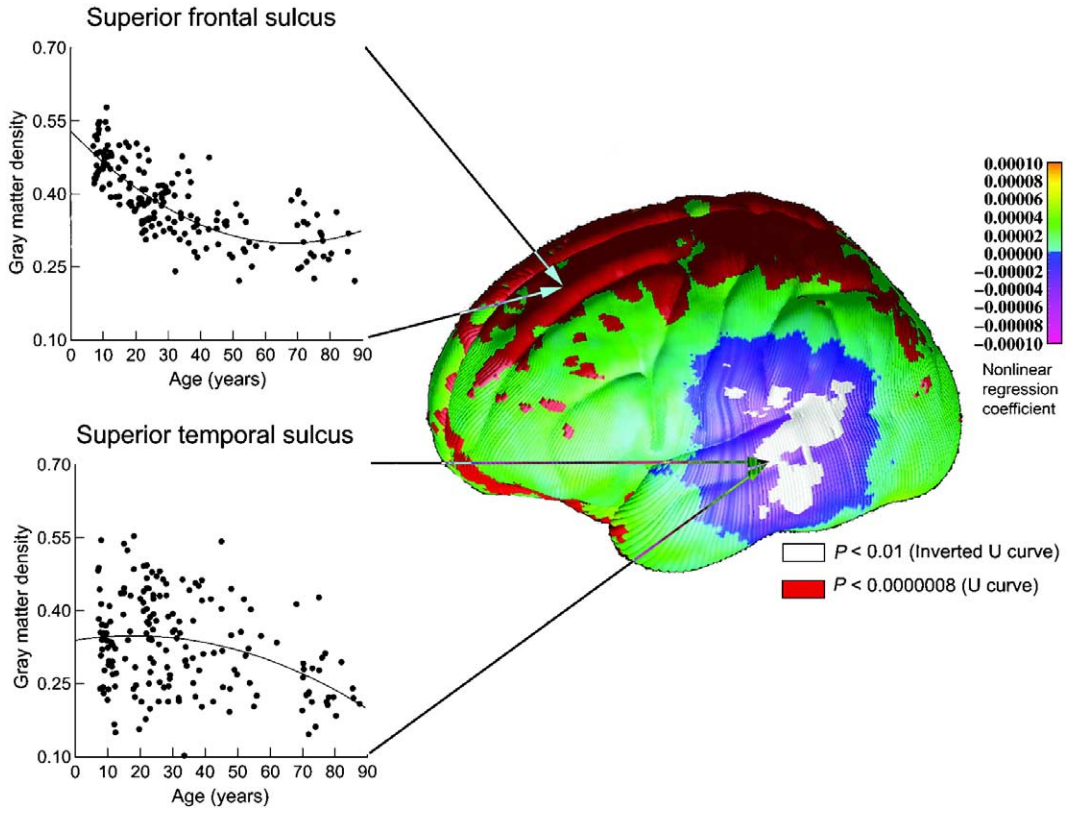

Fig. 2. Non-linear effects of age on gray mater density (GMD) on the lateral brain surface. This statistical map (left frontal view) shows age effects on GMD on the lateral surface of the brain between childhood and old age. Regions shown in either red or white correspond to regression coefficients that have significant positive or negative nonlinear age effects, respectively. Representative scatter plots of age effects with the best-fitting quadratic regression line are shown for sample surface points in the superior frontal sulcus and the superior temporal sulcus. See original article for more details (Sowell et al., 2004). Reprinted with permission.

seeking, and the increased morbidity and mortality observed in adolescence when compared with adults (Resnick et al., 1997; Kelley et al., 2004).

Exposure to drugs of abuse at such active developmental stages may increase a child's vulnerability to the effects of drugs and may adversely impact brain development. Exposure of young animals to nicotine, for example, has been found to induce changes in their brains that lead to an increased effect of nicotine later in life (Belluzzi et al., 2004). Epidemiological evidence also shows that youth who begin abusing substances early in their lives constitute the group at highest risk for later development of chronic addiction to drugs (Spear, 2000) and alcohol (Grant et al., 2001).

Both NIDA and NIAAA are studying the effects of drugs and alcohol on brain development in a variety of ways. We support basic research with animals to directly examine the effects that early exposure to drugs and alcohol can have on brain development and behavior. Both NIDA and NIAAA support research in adolescents, focusing on cognition (e.g., learning, judgment, and decision making) and emotion (e.g., social reinforcers, motivation, and stress responses), which should enhance our ability to create effective messages and interventions to discourage teens from abusing alcohol and drugs.

NIDA participates, along with NICHD, NIMH, and NINDS, in the NIH-Magnetic Resonance Imaging (MRI) Study of Normal Brain Development, the goal of which is to determine the path of normal brain development and its relationship to cognitive and behavioral maturation. The hope is to capitalize on the findings of research to facilitate the investigation of how drugs and alcohol affect developmental trajectories.

2.2. Substance abuse in pregnancy

By extension, it is equally important to evaluate the specific vulnerabilities and risks associated with earlier stages in life. Indeed, alcohol and drug use by pregnant women are known to pose significant risks to brain development; 4.3% of pregnant women between the ages of 15 and 44 report past month use of illicit drugs (SAMHSA, 2004b), while the prevalence of any alcohol use among pregnant women was about 10% (CDC, 2004b). While these rates are significantly lower than those among the nonpregnant, child-bearing age female population (10% and 53%, respectively), extrapolation from CDC pregnancy rate data (Ventura et al., 2004) reveals the disturbing fact that close to 800,000 fetuses in the United States could be exposed to the harmful effects of alcohol and drugs every

year. Similarly, the rate of pregnant women who smoke during pregnancy, estimated to be ~18% (SAMHSA, 2004b), is still unacceptably high. Therefore, the identification and measurement of each substance's contribution to potentially adverse cognitive, emotional, and behavioral outcomes are top priorities.

Suspected early consequences of drug and alcohol use during pregnancy include brain growth alterations and withdrawal symptoms. Subsequent behavior, development, and neurologic function may also suffer from prenatal and/or childhood exposure. Also, medical complications during delivery are much more frequent in mothers who used during pregnancy (Huestis & Choo, 2002).

As new experimental tools become available, we are gaining more confidence in our ability to assess scientifically the effects of substance abuse on the developing brain. Thanks to these tools, we now know, for example, that the neuronal loss underlying fetal alcohol syndrome (FAS) is more severe and much more widespread (affecting many brain regions, spinal cord, and retina) than previously thought. Animal studies clearly show that such deficits hinge on ethanol's ability to enter the fetal brain and disrupt synaptogenesis, a process whose blockage activates a cellular cascade that drives a large number of neurons to undergo unscheduled programmed cell death (Olney, 2004). This finding could explain the smaller brains and the neurobehavioral and cognitive disturbances associated with the well-studied human FAS (Ikonomidou et al., 2000). A related mechanism is also likely to underlie the observed disruption of brain surface and gray matter density asymmetry patterns in adolescents that have been prenatally exposed to large quantities of alcohol (Sowell et al., 2002).

Many other psychoactive drugs traverse the placental and fetal brain barriers unimpeded and potentially affect the developing brain directly (Fig. 3; Benveniste et al., 2005). This possibility, which has been the focus of prospective epidemiological studies, remains hard to assess in humans. Results must be interpreted in light of multiple confounding factors, such as a drug users' tendency to use combinations of various substances (e.g., alcohol, tobacco, and marijuana). Additional risks can result from exposure to deleterious environmental factors, such as toxins and poor nutrition, often linked to low socioeconomic status and known to influence various parameters of cognitive development.

In contrast, complementary and properly controlled studies using nonhuman primates have produced some evidence of the potential harmful effects of alcohol and drugs on the developing fetus. For example, a recent review of several such studies, in 4 different rhesus monkey models, indicates possible detriments in overall growth in newborns exposed to relatively high levels of cocaine in utero. The primate models of oral cocaine administration demonstrate that prenatal exposure can result in detectable neurobehavioral deficits, but only when assessed beyond the first week after birth (postnatal weeks 2 and 4; Lidow, 2003). Intriguingly, 1 study showed a delayed and long-lasting impaired ability to adapt to new environmental contingencies in monkeys that had been prenatally exposed to cocaine 6 years earlier, yet no other discernible cognitive effects were observed (Chelonis et al., 2003). This result is reminiscent of a human study that found no significant effects of prenatal cocaine exposure on the growth, intellectual ability, academic achievement, or teacher-rated classroom behavior of 6-year-olds, but deficits in their ability to sustain attention on a computerized vigilance task were detected (Richardson et al., 1996). Similarly, 1 prospective report shows no association between prenatal cocaine exposure and lower IQ scores but hint at persistent attentional and other cognitive deficits, as exposed children grow older (Singer et al., 2004). Interestingly, the same study showed that the quality of the care-giving environment could have a significant compensatory effect. It seems reasonable to hypothesize that the ultimate impact of prenatal cocaine will reflect the combined influence of many factors, including the dose and pattern of exposure as well as the postpartum environment in which the child will be raised.

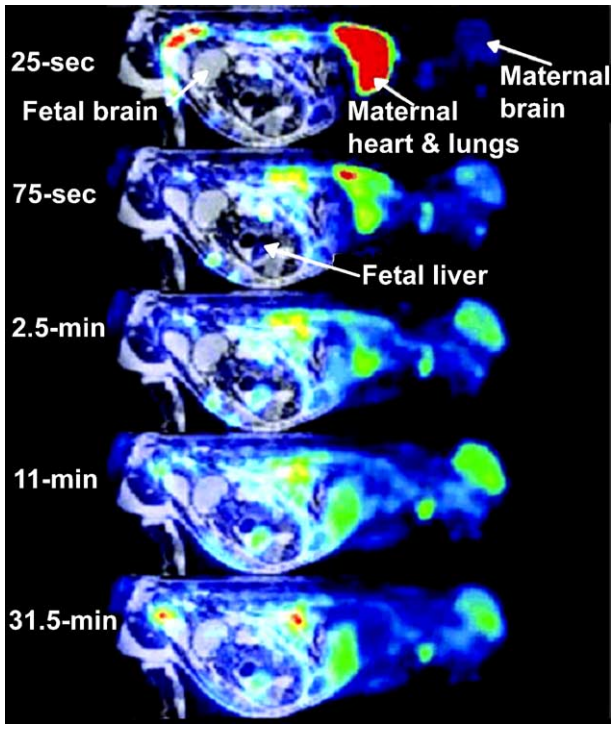

Fig. 3. Time series of ^{11}C-cocaine positron emission tomography (PET) scans from third-trimester pregnant *Macaca radiata*. Each PET frame is coregistered to corresponding MR image. Early PET frames (25 sec, 75 sec, and 2.5 min) clearly show early ^{11}C uptake in placental vessels, maternal heart, lungs, and kidneys. Later time frames demonstrate uptake in fetal liver (Benveniste et al., 2005). Reprinted with permission.

Use of methamphetamine (meth) during pregnancy is of particular concern because of its prevalent use among women of child-bearing age (SAMHSA, 2004a). Moreover its ability to cause long-lasting changes in brain function in chronic users (Hanson et al., 2004) and its neurotoxic effects on select dopaminergic and serotonergic terminals in the rat

brain (Cadet et al., 2003) suggest that meth use during pregnancy could have serious implications for fetal brain development.

In a recent study, structural abnormalities were observed in regions of the brain associated with cognition and emotion in meth abusers (Thompson et al., 2004). Moreover, prenatal meth exposure has been associated with abnormal brain metabolism (Smith et al., 2001), and a group of meth- and cocaine-exposed newborns displayed significantly reduced visual recognition memory, compared with unexposed controls (Hansen et al., 1993). Another MRI study provides evidence of an association between prenatal meth exposure and smaller volumes in discrete subcortical structures, which correlated with poorer performance on sustained attention and delayed verbal memory (Chang et al., 2004).

Clearly, more research is needed to establish the individual contributions of all the factors influencing the long-term impact of substance abuse, by pregnant women, on the developing brain. NIDA is currently funding longitudinal studies with children who have been prenatally exposed to marijuana, cocaine, and nicotine to gain information about their cognitive and emotional development, as well as their vulnerability to drug abuse and addiction later in life. Additionally, NIDA has recently launched the first large-scale study of the developmental consequences of meth exposure, which includes 7 hospitals in Iowa, Oklahoma, California, and Hawaii.

The long-term effects of prenatal alcohol exposure throughout pregnancy have been well documented and reviewed (Nordstrom-Klee et al., 2002; Day & Richardson, 2004). A current emphasis of NIAAA is the exploration of behavioral methodologies that could improve the neurocognitive performance of children diagnosed as having fetal alcohol spectrum disorder (FASD).

2.3. Neural substrates of substance abuse and addiction

All compounds with abuse potential have the ability to disrupt the processing of information in the brain by subverting 1 or more of the common neurotransmitter systems (i.e., gamma-amino butyric acid [GABA], glutamate, acetylcholine, dopamine [DA], serotonin, and opioid peptides). However, an (early) increase in DA signaling has been one of the most consistent observations across studies of the reinforcing effects of drugs of abuse.

Not surprisingly, acute drug intoxication is accompanied by highly localized and dynamic patterns of brain activation and deactivation (Breiter et al., 1997; Stein et al., 1998), as well as complex cascades of transcriptional reprogramming (Zhang et al., 2002; Yuferov et al., 2003). These changes are rapid and robust and can dramatically alter the function of regions neuroanatomically connected with DA systems known to be involved in reward, memory, motivation, drive, and self-control. Dopaminergic involvement is likely an equally important factor in the progression to alcohol addiction, since the reinforcing properties of ethanol appear to rely on increased opioid neurotransmission, which can indirectly enhance DA release (Oswald & Wand, 2004).

Imaging technologies, such as MRI and positron emission tomography (PET), now allow us to investigate the anatomical and functional changes that characterize the process of drug addiction in the human brain (Fig. 4). The

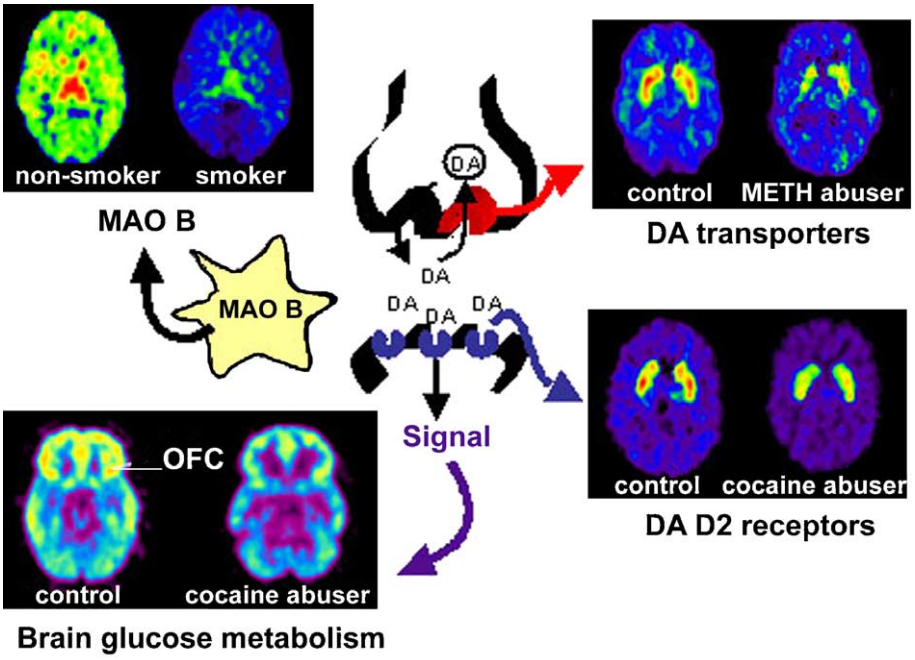

Fig. 4. Brain imaging tools such as PET allow for an unprecedented view of the pathological process that an addicted brain is subjected to. The images provide solid evidence for the deleterious functional (i.e., enzymes, transporters, and receptors) and metabolic effects of various drugs of abuse (Volkow et al., 2003).

result has been a growing series of studies that largely corroborates the widely held notion that disruption of dopaminergic neurotransmission is a key event in the initiation and maintenance of the adverse effects stemming from substance abuse, both acute and chronic.

Paradoxically, it has also been shown that, in contrast to the increases in DA neurotransmission observed in the brain reward centers during initial acute administration, chronic drug use leads to measurable decreases in dopaminergic activity (Volkow et al., 1997), which can persist for months after detoxification, and is associated with dysregulation of frontal brain regions (Volkow et al., 2004). Furthermore, preclinical studies show that chronic drug exposure can dramatically change the expression (Zhang et al., 2005) and activity (Hu et al., 2005) of various proteins involved in DA signaling.

Thus, the current understanding of the addiction cycle as a behavioral process gone awry can explain much of the reinforcing properties of addictive substances during initiation and early use. It also provides testable hypotheses regarding the specific structural changes in the brain associated with the impaired decision making that facilitates substance abuse even in the face of serious adverse consequences (Volkow et al., 2002).

Imaging and behavioral studies suggest the involvement of at least 4 interacting brain circuits in mediating the 3 states of the drug addiction process: intoxication, craving, and withdrawal. The first circuit is located in the nucleus accumbens (Di Chiara, 2002) and the ventral pallidum and mediates the reward process (Volkow et al., 2003). A second circuit that maps onto the orbitofrontal cortex (OFC) and the subcallosal cortex is responsible for the generation of motivation and emotional responses. The third circuit, in the amygdala and hippocampus, spawns memories and supports conditioned learning. The last circuit is in charge of high-level cognitive control and executive function and is located in the prefrontal cortex and the anterior cingulate gyrus (Volkow et al., 1993). In addition, imaging studies are providing increasing evidence of the involvement of the temporal insula in addiction (Wang et al., 1999; Franklin et al., 2002). Since the insula is a cortical region involved in processing autonomic responses, it may serve to underlie the strong peripheral responses that occur during drug craving (Wang et al., 1999).

The 4 underlying circuits receive direct innervation from DA neurons but are also connected with one another through direct or indirect projections that are mostly glutamatergic (Kalivas, 2004a). Predictably, there are experimental data that support a significant glutamatergic contribution to the orchestration of maladaptive responses to drugs and alcohol. Animal studies show that glutamatergic pathways play an important role in mediating drug craving and relapse (Kalivas, 2004b). This finding is consistent with the drug-dependent modulation of glutamatergic transmission in the prefrontal cortex, nucleus accumbens (McFarland et al., 2003), and amygdala (Lu et al., 2005), as well as with the drug-induced deregulation of proteins involved in pre- and postsynaptic glutamate transmission (Kalivas et al., 2005).

Thus, excitatory networks, as embodied in cortical and corticofugal glutamatergic projections, may play a more important role in substance abuse dependent neuroadaptation processes than previously thought (Kalivas, 2004b). Unfortunately, the lack of radiotracers for imaging glutamate function in the human brain has prevented the assessment of glutamatergic pathways in drug addicted subjects.

2.4. Genes, environment, and their interactions

There is little doubt that genetic factors play an important part in determining vulnerabilities to drug seeking and addictive behavior. The fact is that not everyone who takes drugs becomes addicted, and both NIDA and NIAAA are funding research to understand why some individuals become addicted while others do not.

Evidence for the involvement of genes in the process of drug addiction comes from classical epidemiological and genetic approaches. Twin studies, for example, have shown robust genetic components for alcohol, opiate, cocaine, and tobacco addictions (True et al., 1999; Kreek et al., 2004). On the other hand, studies with various knockout mouse strains have illuminated the role of specific gene products, such as Homer 2 (Szumlinski et al., 2004), opioid receptors (Chefer et al., 2004), and alpha 4 nicotinic receptors (Tapper et al., 2004), in conferring either protection from or increased risks of falling prey to drug addiction.

However, the contribution of single genes is only a small part of the picture. Genes exert their effects in the context of genetic networks, which are typically under the influence of environmental factors. As a result, the assignment of strong linkages between genetic polymorphisms and enhanced vulnerabilities to the addictive properties of drugs has proven to be a difficult goal to achieve.

Fortunately, the genetic research landscape is undergoing a radical transformation, and our efforts to better define the genetic underpinnings of substance abuse will likely benefit as a result. The newer screening techniques provide us with powerful tools to explore global transcriptional changes in response to drug administration (Nestler, 2004) and allow for the rapid identification of candidate genes whose modulation may signal the induction of long-lasting changes in the brain (McClung et al., 2004). By the same token, completion of the human genome project will permit an unbiased search for candidate genes from among all possible human coding sequences. When this dataset is combined with the massive throughput screening techniques now available, it will be possible to scan through millions of single nucleotide polymorphisms (SNPs), in hundreds of samples. The first genetic screens taking advantage of such an approach demonstrate unprecedented power and sensitivity (Hinds et al., 2005).

Better designs in primary data collection, combined with increased computing power, will make it possible to develop genetic risk analysis tools that take into account specific environmental risks and protective factors, long established to affect the trajectory of drug addiction. With this approach in mind, we plan to embark on cooperative efforts to identify genes associated with abuse to specific substances, evaluate their contributions to a persistent addictive behavior, and assess how they might interact with other genes and the environment.

2.5. Comorbidity with mental illness

The challenge of drug abuse research, particularly in the context of genetic screening, becomes even more daunting when the high incidence of comorbid mental illnesses is taken into account. For drug abusers, other than nicotine and alcohol, mood disorders were found to be 4.7 times more prevalent than in the entire population (Regier et al., 1990). On the other hand, abuse of other drugs, including cocaine, sedative hypnotics, and opioids, is also greater in individuals with depression compared with those without it, and those with the highest risk seem to be the ones with comorbid anxiety disorders (Goodwin et al., 2002). Similarly, the comorbidity between mental illness and nicotine addiction is alarmingly high (Lasser et al., 2000). NIAAA and NIDA have also joined forces to establish and deploy the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), designed to determine the extent of alcohol use disorders and their associated disabilities in the general population (Grant et al., 2004).

Both epidemiological and preclinical studies suggest that developmental factors are likely to play an important role in establishing these comorbidity linkages. The preliminary evidence suggests that early exposure to substances of abuse, during periods in which the brain is still undergoing significant changes, could lead to neurobiological changes associated with depression, enhanced sensitivity to stress, and decreased sensitivity to natural reinforcers (Volkow, 2004).

Genes and environment are key contributors to the connections between substance abuse and other mental disorders. Genetic components linking substance abuse and vulnerability to depression and to anxiety disorders were suggested by human (e.g., adoption, twin) and animal (e.g., using genetically altered strains of mice) studies. On the other hand, several environmental factors, such as family disruption, poor parental monitoring, acute and chronic stress, and low social class of rearing, have all been found, predictably, to contribute to the manifestation of substance abuse and certain comorbid mental illnesses (Tarter et al., 1995).

The neurobiological substrate for comorbid phenomena is likely to reside in or involve various limbic and paralimbic structures. Drug-induced changes in these regions have been implicated in the induction of the negative emotional symptoms that often occur during early phases of withdrawal from many psychoactive substances. Similarly, it is likely that a significant anatomical overlap exists with brain regions mediating the diverse symptoms of depression. Brain imaging studies of human depression as well as of substance abusers have demonstrated changes in the activity of numerous areas, including regions involved in mood regulation (e.g., ventral cingulate gyrus), cognitive operations (e.g., prefrontal cortex), memory (e.g., hippocampus), reward (e.g., ventral striatum), and arousal (e.g., thalamus; Drevets, 2001; Liotti & Mayberg, 2001).

We recognize the real obstacles that we confront in this area: the difficulty in describing complex phenotypes and the typically unknown sequence of events that lead to their manifestation. Yet, we will continue to support the research needed to tease apart the contribution of specific vulnerabilities to the occurrence of comorbid conditions.

3. Strategies to optimize the use of science

The knowledge derived from research in substance abuse has the potential to impact the lives of millions of individuals. However, in order to focus these efforts, it is important to ensure that the products of research are not just useful (effective) but also accepted and used by the community. Blending research with practice is one of the main goals of both our Institutes, which are working in concert with other organizations and federal agencies.

3.1. Prevention

Epidemiological data shows consistently that the longitudinal trends of drug abuse and perceived risk of harm maintain a close inverse correlation, namely, the use of addicting substances tends to rise whenever the perception of their harmfulness drops. In addition, 25 years of epidemiological research has clearly identified distinct socioeconomic and cultural factors that can either compromise or enhance a person's ability to reject the use of addictive drugs. It follows that prevention should be at the forefront of our strategies to mitigate the personal and societal burden of drug addiction.

To be efficacious, prevention must be rooted in scientific evidence: The multifaceted nature of the vulnerabilities for addiction, the high frequency of comorbid conditions, and the long-lasting neurobehavioral impact of drugs of abuse on the brain all play a critical role in shaping our prevention efforts.

The ability to investigate the motivational processes at work in the adolescent brain can provide valuable information regarding the drive and decision to drink and to use drugs, as well as unique opportunities to evaluate and select intervention strategies that are more likely to succeed. Accordingly, both NIDA and NIAAA allocate significant

resources on prevention programs that target children and adolescents.

The Adolescents Training and Learning to Avoid Steroids (ATLAS) and Athletes Targeting Healthy Exercise and Nutrition Alternatives (ATHENA) programs, 2 examples of evidence-based prevention strategies, have demonstrated that sport teams are effective vehicles for delivering gender-specific, peer-led curricula that promote a healthy lifestyle. These interventions have been very successful at reducing steroid and other drug use among high school athletes (Goldberg et al., 1996; Elliot et al., 2004).

As children become adolescents, the role of their peer groups in influencing their behavior becomes more prominent. Those who begin using substances early become part of a culture that engages in illegal activities, pitting themselves squarely against the criminal justice system. The ethos associated with drug abuse often encourages other forms of risky behaviors, including sexual activities that can expose youth to HIV, hepatitis, and sexually transmitted diseases. Indeed, it is estimated that about half of new cases of HIV crop up in people younger than 25 (CDC, 2005b).

NIDA-supported researchers also found that many of the risk-taking behaviors of adult women who contract HIV were associated with childhood sexual abuse (Klein & Chao, 1995), suggesting that early-learned behaviors, negative or positive, can impact later disease outcomes. Early exposure to stress or trauma is also known to be a risk factor for both substance abuse and mental health disorders (Kendler et al., 2000). For these reasons, it is critical that we devote more resources to developing preventive interventions geared toward protecting children and adolescents who may be at high risk for comorbid disorders.

The HIV epidemic and drug addictive disorders disproportionately affect incarcerated individuals. This is an unfortunate but well-established fact, which NIDA recognizes as a unique opportunity for the optimization of effective interventions. Several NIDA-supported projects have been initiated to develop and test models for an integrated approach for the treatment of criminal offenders suffering from HIV infection and/or drug addiction.

3.2. Pharmacotherapies

Clinical trials to assess the effectiveness of medications or of behavioral interventions should be based on the conceptualization of addiction as a chronic disease (McLellan et al., 2000). As for patients with other chronic diseases, most addicted subjects will require some type of continued therapeutic support (McLellan et al., 2005).

The evolving view of the neurobiological basis of the effects of substance abuse on the brain is continuously expanding the list of potential targets for intervention. The following medications are good examples of effective or promising treatments that emerged from a better understanding of the molecular and physiological bases of the reward, craving, withdrawal, and relapse phases of addiction.

Buprenorphine (Fudala et al., 2003) is a relatively recent addition to the list of effective medications for the treatment of heroin addiction. Because it is a partial opioid agonist, buprenorphine has the additional advantage that it is more difficult to overdose with it unintentionally. And, because it is the first office-based treatment option for opiate dependence, buprenorphine shows great promise as a detoxifying and treatment agent. The NIDA Clinical Trials Network (CTN) sponsored 2 clinical trials assessing buprenorphine–naloxone for short-term opioid detoxification. These trials provided an unprecedented field test of its use in 12 diverse community-based treatment programs.

Modafinil, a novel medication for the treatment of narcolepsy, is also being tested as a potential treatment for cocaine and methamphetamine dependence. Though the mechanism of action of modafinil is not properly understood, it is believed that it has both dopaminergic as well as glutamatergic effects. Hence, it has been proposed that modafinil could help counteract the cocaine-induced neuroadaptations on DA and glutamate reward circuits that, in turn, could help alleviate cocaine withdrawal symptoms (Dackis et al., 2003).

While cocaine administration primarily stimulates the central "reward system", many of its behavioral effects rely upon cortical circuits, making them attractive targets for pharmacologic intervention. Topiramate, an anticonvulsant that facilitates GABAergic neurotransmission and inhibits glutamatergic activity, can affect these circuits and has recently shown potential usefulness for the treatment of alcohol and opiate addiction. In a small pilot trial (Kampman et al., 2004), topiramate offered an efficacious and safe way to treat cocaine addiction as well.

Gamma vinyl-GABA (GVG, vigabatrin) is another antiepileptic medication that is used in Europe and other nations (but not in the United States), which increases the amount of GABA in the brain. Preclinical studies with GVG revealed that it interferes with drug-induced increases in DA in the nucleus accumbens in the brain (Schiffer et al., 2003). A preliminary open clinical trial in cocaine-addicted subjects reported that their cravings for cocaine disappeared within 2–3 weeks after starting GVG treatment (Brodie et al., 2003).

Baclofen, a GABA agonist, was shown to reduce acquisition of cocaine self-administration (Campbell et al., 2002) and to attenuate the reinforcing effects of the psychostimulant D-amphetamine in rats (Brebner et al., 2005). Recent clinical reports show that baclofen treatment could block craving in alcoholics (Addolorato et al., 2000) and improve abstinence in drug abusing patients (Shoptaw et al., 2003). These preclinical and limited clinical findings have prompted further studies of baclofen in human addiction. Although in their early stages, some studies in cocaine populations suggest a promising future for this and other $GABA_B$ agonists (Brebner et al., 2002).

Disulfiram (Antabuse), originally marketed for the treatment of alcoholism, was tested as a strategy to reduce

alcohol use among cocaine users (Higgins et al., 1993). It later became evident that the drug appeared to facilitate maintenance of cocaine abstinence in humans, showing promise for reducing cocaine use and addiction, particularly when combined with cognitive behavioral treatment (Carroll et al., 1998).

Naltrexone is an opioid antagonist that blocks the subjective effects of opioids. Its potential as an effective treatment for alcoholism and opiate addiction derives from the fact that, compared with other maintenance therapies, naltrexone is nonaddicting, has only subtle adverse effects, and is seldom traded in the illicit drug market (Greenstein et al., 1997). In spite of its demonstrated effectiveness (Kirchmayer et al., 2003), naltrexone success has been rather limited to patients who are highly motivated to rein in their addiction. For other patients who lack a strong external incentive to stop using drugs, noncompliance has been a significant obstacle to naltrexone achieving its full potential. However, evidence consistently suggests that behavioral therapies can significantly improve the retention of patients treated for either opiate (Carroll et al., 2001) or alcohol (Balldin et al., 2003) dependence.

During the past decade, the understanding of the cellular, molecular, and genetic mechanisms underlying alcohol addictive behavior has increased rapidly. It is now known that alcohol-seeking behavior and drinking is influenced by an array of neurotransmitter systems as well as neuromodulators, hormones, and several intracellular signal transduction pathways. As a result, multiple molecular targets have been identified for novel drug development. (Litten et al., 2005) A diversity of new medications is now being tested clinically for alcoholism treatment. These include the anticonvulsants topiramate, valproate and gabapentin, agents that facilitate GABA and inhibit glutamine activities; the 5-HT3 antagonist ondasterone; the GABAB agonist baclofen; aripiprazole, a partial dopamine D2 agonist; and kudzu, a medicinal plant used in traditional Chinese medicine (Litten et al., 2005). In additon, there are many promising targets that are being investigated preclinically in the hope of developing new lead compounds. These targets include corticotrophin-releasing factor receptors CRF1 and CRF2; neuropeptide Y receptors NPY1, NPY2 and NPY5; adenosine A1 and A2 receptors; cholinergic nicotinic and muscarinic receptors; and nociceptin and neurokinin receptors (Litten et al., 2005). Finally, research efforts are also focused on identifying neurocircuits responsible for different aspects of alcoholism, such as craving, positive reward, protracted withdrawal symptoms, impaired control, tolerance, and psychological and cognitive components. Targeting specific sites within these circuits may lead to novel compounds that could alleviate certain aspects of alcoholism.

The fast pace of discoveries has also led to the identification of novel pharmacotherapeutic targets. For example, research on the cannabinoid (CB) receptor system has demonstrated its involvement in reward, learning, and memory. Research on the CB system has not only provided new insights into how marijuana disrupts memory traces, but has also led to the recognition of connections between the cannabinoid system and the neuronal processes underlying reward. The new science of CB receptor biology has triggered the development of rimonabant, the first CB1-specific cannabinoid receptor antagonist, and a potential medication for the treatment of a variety of ailments, including obesity and the metabolic syndrome (Van Gaal et al., 2005), pain, and addictive disorders. Rimonabant blocks the subjective high elicited by marijuana and may also be useful in preventing relapse to other drug use (Le Foll & Goldberg, 2005).

The related CB2 receptor was identified in a recent study as an exciting pharmacotherapeutic target (Ibrahim et al., 2005). The activation of the CB2 receptor was found to inhibit acute, inflammatory, and neuropathic pain responses, but the absence of CB2 receptors in the brain prevents any unwanted effects in the central nervous system (CNS). This discovery heralds the possibility of a potent pain medication without addiction liability.

The last example comes from recent examination of the connections between stress and substance addiction. It has been hypothesized that compounds that can dampen the stress response could be useful because of the important role that stress plays during a relapse to abusing drugs, alcohol, and nicotine. Such medications are currently being developed for the treatment of anxiety disorders and depression, but they may also have a role in the treatment of drug addiction. Indeed, several compounds, known as corticotropin-releasing factor (CRF) receptor antagonists, have recently been shown to block the initiation of the stress response in the brain. These compounds have also shown a remarkable ability to block the initiation of drug taking in animals and the stress-induced reinstatement of drug-seeking behavior for a number of drugs of abuse (Koob, 1999). These positive observations have prompted NIDA to move Antalarmin, the most promising among these, through preclinical development.

3.3. Behavioral therapies

Many years of field experience show that substance abuse treatment programs can significantly increase treatment adherence and help the patients remain abstinent. By offering group and individual counseling opportunities and encouraging them to participate in complementary 12-step programs, such as Alcoholic or Narcotics Anonymous, these intervention opportunities can produce impressive gains in treatment outcomes (Fiorentine & Hillhouse, 2003). Historically, the concept and principles of 12-step programs have strongly influenced the development of modern substance abuse treatments. However, as of today, there have not been any large clinical trials done to assess the active components relevant to the therapeutic effectiveness of these programs.

Studies clearly indicate that social context can affect brain dopaminergic function and the probability of succumbing to the addictive allure of psychoactive substances

(Shively et al., 1997; Morgan et al., 2002). It is not surprising then that behavioral therapies have evolved to the point of offering effective treatment for the uncontrollable craving and frequent relapse characteristic of many alcohol and drug addicts.

In behavioral approaches, patients are typically ushered into a process that motivates them to initiate a personal recovery. The details and stringency of the strategies vary among the different modalities, which include cognitive, motivational, family, and couple therapies. Controlled studies have clearly shown the extent to which these therapies can help addicted individuals. In the late 1990s, for example, 4 different intensive psychosocial interventions for cocaine-dependent patients were compared by NIDA in the Collaborative Cocaine Treatment Study, and all treatments were found to be efficacious and to significantly reduce cocaine use by about 70% at 12-month follow-up (Crits-Christoph et al., 1999).

A similar outcome was obtained from Project MATCH, an NIAAA-sponsored large clinical trial designed to assess if different kinds of alcohol-dependent individuals fared better when assigned to different kinds of treatments (Babor and Del Boca, 2002).

The Matrix Model (Rawson et al., 1995) is another success story: an outpatient integrated therapeutic approach developed in the 1980s in response to an overwhelming demand for stimulant abuse treatment services. Over 5000 cocaine addicts and over 1000 meth users were treated by therapists who fostered a positive, encouraging relationship with the patient and used that relationship to reinforce positive behavioral changes. The model has been extended more recently to include alcohol and opiate addicted individuals. NIDA-funded projects (Rawson et al., 1995; Rawson et al., 2002) have demonstrated that participants treated with the Matrix model show statistically significant reductions in drug and alcohol use, improvements in psychological indicators, and reduced risky sexual behaviors associated with HIV transmission. Currently, projects are being conducted in 12 states and 4 countries employing this approach in treatment settings for stimulant, opiate, and alcohol users.

A commonly encountered obstacle to the successful treatment of people addicted to but trying to remain abstinent from heroin, alcohol, or other drugs of abuse is that they often fail to stay in treatment. Contingency management (CM) is a new empirically based treatment, based on positive reinforcement approaches, that has been specifically developed to address this issue. CM can interface with an array of substance addiction treatment programs already in place in the community. The implementation of CM programs involves the collaboration of scientifically oriented researchers and clinicians from NIDA's Clinical Trials Network (CTN). CM has been attracting a lot of attention lately as studies have begun to produce scientific evidence for its efficacy in the treatment of diverse drug abusing populations (Petry, 2000; Higgins et al., 2002).

Because of the multiplicity of brain circuits underlying the various substance addiction syndromes, a multimodal approach, when validated, has emerged as the modality of choice, offering the best chance to successfully treat drug addiction. Consequently, and in the context of increasingly more effective interventions, psychosocial therapies ought to be regarded as critical components of a comprehensive substance abuse treatment (SAMHSA, 1999).

Both NIDA and NIAAA will continue to support research on the synergistic interactions between medications and behavioral interventions that target different underlying causes so that subjects could benefit from mutually enhancing effects.

3.4. Treating comorbidity

As mentioned before, a great number of individuals simultaneously suffer from substance abuse and mental illness, as well as other medical or physical disorders, such as chronic pain, hepatitis C, and AIDS. Unfortunately, our current health care system is not designed to identify and optimally address co-occurring drug and health problems.

The high prevalence of comorbidity between drug abuse and mental illness suggests common contributing factors. Thus, both NIDA and NIAAA are committed to support more research on the neurobiological underpinnings of co-occurring disorders and the risk and protective factors that influence these phenomena.

We are interested, for example, in assessing whether some mentally ill patients might enter the cycle of drug and alcohol addiction as a result of self-medication practices. On the other hand, it is critical to carefully evaluate whether any currently used medication has the potential to put a patient at increased risk of developing an addiction problem. The first line of treatment for non-comorbid Attention Deficit/Hyperactive Disorder (ADHD), for example, consists of psychomotor stimulants, such as methylphenidate (MPH; Ritalin™) and dextroamphetamine (Adderall™), which are drugs that have reinforcing potential and can lead to addiction and abuse. These psychostimulants are prescribed with increasing frequency and for longer periods of time, so that understanding their long-term effects, both adverse and beneficial, has become an urgent priority. Specifically, do ADHD medications pose increased risks of substance abuse later in life? Interestingly, a recent meta-analysis concluded that adolescents treated for ADHD with methylphenidate appear to be 50% less likely to later develop drug abuse problems, compared with untreated individuals (Wilens et al., 2003). This is likely to reflect, in part, the protection afforded by associated changes in school performance, criminality levels, and self-worth (Fone & Nutt, 2005). More research is needed to assess the true direct impact of psychostimulant drugs on the vulnerability toward drug addiction later in life, particularly in those individuals that may have been misdiagnosed as ADHD and treated with stimulant medications.

It is hard to overestimate the importance of accurately assessing the demographics and prevalence of co-occurring diseases, such as HIV/AIDS, mental illness, chronic pain, or hepatitis C in guiding research, prevention, and intervention programs. The co-occurrence of drug addiction together with many other disorders greatly enhances the vulnerability of at-risk populations, particularly the very young. Accordingly, there is a pressing need to support research on the development of more evidence-based strategies to address the problem of comorbidity.

4. Meeting the challenges

Ultimately, our efforts should reduce the number of people entering the cycle of drug and alcohol addiction and increase the number of treatment options to help afflicted individuals recover from their disease and reclaim a life free of hurtful stigmas. While it is essential that we keep supporting the production of new knowledge to achieve these goals, it is clearly not sufficient. Our Institutes' outreach efforts are designed to maximize the transfer of knowledge back into society and educate the public about the emerging model of drug addiction as a chronic disease and the best strategies to prevent and treat addiction.

This goal appears more urgent than ever, as we enter an era when gaining a competitive edge is an end that justifies any means. Increasingly, medications such as steroids or stimulants are being used not just to cure ailments, but to improve perceived deficiencies, delay the effects of aging, and enhance cognitive and physical performance. NIDA will rise to the challenge of constantly updating its dissemination efforts, which must remain relevant in the face of changing patterns of drug abuse across the Nation.

In this context, we hope that the implementation of cooperative initiatives with state authorities, community treatment centers, and the Substance Abuse and Mental Health Services Administration (SAMHSA) will also help us deliver a much more focused and accurate message.

Our efforts to meet the challenges identified in this article are being multiplied by our participation in cross-institutional programs for the development of tools and strategies designed to benefit all neuroscience-related diseases. NIDA and NIAAA are engaged in active collaborations towards the implementation of the NIH Neuroscience Blueprint and Roadmap initiatives, and in the continuous monitoring of population survey figures and community derived epidemiological information, for the identification of emerging alcohol and drug-related threats to public health.

5. Summary

Recent research has increased our knowledge of how drugs can affect gene expression and neural circuitry in the brain, and how these changes ultimately alter human behavior. It has shed new light on the relationship between drug abuse and mental illness and the roles played by heredity, age, and other factors in increasing vulnerability to addiction. One of the main corollaries of such research efforts has been the clear understanding that substance addiction is a chronic and relapsing brain disease. At the individual level, this paradigm shift suggests that therapy approaches should be multi-pronged and attempt to (a) reduce drug's rewarding effects, (b) enhance the rewarding effects of alternative reinforcers, (c) block drug-associated conditioned learning, and (d) engage cognitive and motivational control in treatment. At a higher level, the new concept should elicit society's commitment to de-stigmatize drug and alcohol addictions.

In spite of the tremendous progress made so far, much remains to be done. We are still delineating the brain's circuits involved in making addicted individuals more vulnerable to the effects of addictive substances. Thanks to the increased availability of high-resolution brain-imaging technologies and growing genetic databases, addiction researchers will be able to define, in ever increasing detail, the critical issues surrounding the maladaptive processes leading to addiction, craving, and relapse. We are beginning to explore the complex interactions among genes, and between genes and the environment, that influence the trajectory of the addiction process and the underlying factors that predispose to comorbid conditions. The information gained from these efforts should revolutionize the way clinicians approach the prevention and treatment of addiction and accelerate the development of individually tailored interventions that take into account socioeconomic, cultural, age, gender, and genetic factors.

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