Clinical issues play a critical role in National Institute on Drug Abuse’s (NIDA’s) entire research portfolio. There is not a division or branch within NIDA’s structure that is not somehow affected by clinical research; it is the common thread that permeates and influences our entire research agenda. Even the most basic research that we support is influenced by the questions that are derived from clinical practice and research settings. For example, although we know from clinicians and others who treat patients who are abusing drugs, such as MDMA (Ecstasy), that their patients seem to be addicted to the drugs, there have not yet been scientific studies of MDMA’s addictiveness. The clinical anecdotal evidence is there, but the basic researchers will have to do more definitive research to determine the abuse liability and addictiveness of this drug.

The best example of the important role that clinical research plays in NIDA’s research portfolio can be found in NIDA’s treatment portfolio, particularly in its newest infrastructure, the National Drug Abuse Treatment Clinical Trials Network (CTN). The CTN was established in 1999 to broaden and expand the testing of new treatments for drug addiction. The mission of the CTN is to conduct studies of behavioral, pharmacological, and integrated treatment interventions that have been shown to be effective in research settings, in rigorous, multisite clinical trials to determine effectiveness across a broad range of community-based treatment settings and diversified patient populations. Every node has at least five participating CTPs. The second part of the mission is to transfer the research results to physicians, providers, and their patients to improve the quality of drug abuse treatment throughout the country.

Prior to the establishment of the CTN, the efficacy of new treatments for drug addiction had been demonstrated primarily in specialized research settings, with somewhat restricted patient populations. Now therapeutic approaches, such as motivational enhancement treatment, can be tested in centers across the country.

The structure of the CTN is similar to clinical trial networks that have been established by other National Institutes of Health (NIH) institutes to expedite new and effective treatments for AIDS and cancer. The CTN currently is composed of 14 geographically diverse nodes (Delaware Valley, Florida, Great Lakes Regional, Long Island Regional, Mid-Atlantic, New England, New York, North Carolina, Ohio Valley, Oregon, Pacific Region, Rocky Mountain, South Carolina, and Washington). These regional research nodes work collaboratively with NIDA and community-based treatment providers (CTPs) to ensure that science-based treatments can be adapted for suitable implementation in community settings. Community treatment programs are typically non–university-based and have a proven track record of providing quality treatment to large and diverse patient populations. Every node has at least five participating CTPs.

As of October 2001, seven research protocols are in place, and almost 600 patients are enrolled in the various studies. The buprenorphine–naloxone protocol, for example, is fully launched at six sites across the CTN, and the motivational incentives protocol is fully launched at seven sites across five nodes. The findings and results of the implementation, adoption, and outcomes of these studies are immediately shared with the participants of the CTN through a number of mechanisms including symposiums; e-mails, electronic mailing lists, and Web sites; participation in special interest groups; and publications. Transferring the research results to physicians, providers, and their patients is critical to the success of the CTN.

**Medications Development**

Before a concept protocol such as buprenorphine–naloxone can even be considered to become an implementable
research protocol for the CTN, years of basic and clinical research have to go into its development. This is one of the many reasons why NIDA’s Medications Development Program (MDP) is so important.

NIDA’s MDP brings the critical mass of the nation’s knowledge of medicinal chemistry, molecular biology, brain function, and behavior to bear on the urgent public health problem of drug addiction. The program strives to accelerate the speed with which compounds are identified, evaluated, developed, and approved as new medications to treat drug addiction. The program has evolved into a portfolio that includes a wide variety of candidate treatment agents from novel synthesis all the way through Phase 3 clinical testing.

Fundamental breakthroughs in brain research are leading to significantly more predictable and rapid ways to identify and evaluate candidate compounds. For example, scientists know that most abused drugs exert their effects by interacting with specific brain sites and systems. The discovery of these sites and the chemicals that act on them has allowed NIDA researchers to identify the central nervous system areas involved in addiction to, and abuse of, a variety of drugs, including heroin, crack/cocaine, and marijuana. Armed with this knowledge, medical science and the NIDA MDP now have the unprecedented opportunity to explore rapidly and systematically methods to interrupt, modify, attenuate, or extinguish this process through a rational testing paradigm.

Medications are being developed for addictions and overdoses to many drugs of abuse, including methamphetamine, cocaine, heroin, nicotine, and other emerging drugs, such as gamma hydroxy butyrate. Developing medications for addiction to stimulants remains a high priority for NIDA. Last year, more than 208 compounds were screened as potential treatments for cocaine addiction. Two promising candidates, disulfiram and selegeline, are beginning Phase 3 clinical trials.

As part of its medications development process, NIDA makes a concerted effort to critically assess the needs of patients, clinicians, and state regulators in the development of medications that fulfill their needs. Meetings, interactions, and reviews involving the treatment and research communities, as well as state and regulatory and treatment agencies, are routinely undertaken and publicized. In this manner, NIDA’s MDP is able to both hear the concerns of those within the field and keep the field abreast of the latest research findings. It was, in part, through this process that NIDA and congressional leaders became more determined to bring effective medications directly to the treatment provider. The medication buprenorphine for opiate addiction epitomizes NIDA’s important role and commitment to making treatments that are more accessible to those in need.

Legislation was passed last year allowing qualified physicians to prescribe certain antiaddiction medications in an office setting, including buprenorphine and buprenorphine–naloxone (after approval by the Food and Drug Administration). Buprenorphine and buprenorphine–naloxone products are expected to increase the amount of treatment capacity available and expand the range of treatment options that can be used by physicians.

Behavioral Treatment Development

NIDA also continues to bring new behavioral treatments to fruition. Behavioral therapies are frequently the only treatments available to drug-dependent individuals. Even where medications are available, behavioral therapies can be an integral component of treatment. Recognizing the importance of behavioral therapies, NIDA has been supporting research in this area through its Behavioral Therapies Development Program (BTDP). The BTDP is intended to promote all of the necessary stages of behavioral therapy research so that new and more efficacious behavioral therapies are developed as advancements in cognitive and behavioral science are made and so that the best behavioral therapies may be effectively transported to the community treatment provider. It is NIDA’s intention to support scientifically sound and clinically relevant behavioral therapy research that will have a meaningful impact on improving the efficacy of drug abuse and dependence treatment.

Research indicates that many behavioral therapies for drug abuse and addiction are efficacious. However, no therapy has been shown to be completely efficacious for every individual. For many individuals, engagement and retention in treatment and relapse following treatment remain concerns. NIDA has undertaken the BTDP with the goal of addressing these concerns and substantially improving, for each individual, the efficacy of behavioral therapies for drug abuse and dependence.

NIDA’s BTDP delineates three stages of behavioral therapy research. Stage 1, the earliest stage of behavioral therapy development research, is viewed as an iterative process involving identifying promising clinical, behavioral, and cognitive science relevant to treatment; generating and formulating new behavioral therapies; operationally defining the therapies in manuals; and pilot testing and refining the therapies.

Stage 2 research consists of efficacy testing of promising therapies identified in Stage 1. Stage 2 may also involve studies examining the efficacy of components of therapies and studies examining individual differences in response to the therapies. Most of the behavioral therapy research that NIDA has supported in the past has been of this type. Stage 2 also involves the replication, at other sites, of efficacy studies with positive results.

Stage 3 research is aimed at understanding whether and how an efficacious therapy may be transported to the community. That is, one question relevant to Stage 3 research is whether a therapy maintains its potency when it is administered within community-based treatment programs. Another question relevant to Stage 3 research is the question of how therapists and counselors can be trained to administer a new therapy effectively. Thus, Stage 3 research may involve the development of training procedures and techniques to help teach therapists and counselors how to utilize new therapies and the testing of the utility of these procedures and techniques.
Behavioral therapies such as motivational enhancement and motivational interviewing, which have had a proven track record for improving treatment outcome and retention levels in small-scale studies, are now being tested in the CTN. NIDA realizes, however, that no matter how good one of our behavioral treatments or new medications are, because of the complexity of addiction, it is likely that many, if not all, addicts will require and benefit from a combination of pharmacological and behavioral interventions. For many addicts, the behavioral interventions used will have to address at least two sets of problems and use two types of therapies. One involves a cognitive approach that will help patients reframe how they relate to and view the world. The other approach is social rehabilitation.

Clinical Neurobiology of Addiction

Advances in neuroimaging are providing us with new insights into the human brain and are affecting how we conduct clinical research. In the past, we have had to rely solely on animal models for essential data on the neurobiological mechanisms of addiction. These animal models have served us well and have elucidated the basic processes of addiction at the molecular and cellular systems level. However, it is clear that animal studies cannot precisely model many of the complex aspects of addiction such as polysubstance abuse; comorbidity; effects of stress, violence, and poverty; and drug craving. Brain-imaging technologies, such as positron emission tomography and functional magnetic resonance spectroscopy, have provided us with a window into the brain. They are allowing us to visualize the effects of drugs on the brain and look at the structure and function of the human central nervous system following acute or chronic exposure to drugs of abuse, including studies characterizing brain changes during the different stages of drug abuse and addiction (e.g., drug use, dependence or addiction, withdrawal or abstinence, craving, and relapse).

Neuroimaging studies of addiction are now being applied to show what, if any, long-term effects drugs may have on the brain. This approach has been particularly useful as we attempt to understand the long-term effects on the brain of drugs being used increasingly across the country, such as MDMA. Through the use of these modern imaging techniques, we now have direct evidence in humans to support the voluminous animal literature showing a decrease in a structural component of serotonergic or brain 5-HT neurons in human MDMA users. In addition, we are now beginning to see signs that MDMA has residual effects as well—it has the ability to impair one’s cognitive abilities. Further, these techniques also can be used to help us understand whether the brain can fully recover from drug abuse and addiction. Are drug-induced brain changes permanent? Can abstinence or treatment allow the brain to change back to more normal structural and functional states? These are some of the questions we hope to be able to answer. These techniques and fields of research also will be useful to us as we assess human brain processes during development. For example, by conducting brain-imaging studies on children who have participated in NIDA’s multiyear cohort studies, researchers will be able to gain critical insights into brain structural and functional processes. This is a new area of clinical research that NIDA would like to further explore.

Clinical Research on AIDS

NIDA supports clinical studies of HIV and AIDS among drug users, including people in and out of drug abuse treatment. NIDA’s multidisciplinary research program involves studies of behavioral and biological factors associated with drug abuse and HIV infection. Current studies of HIV focus on HIV disease progression, treatment of HIV-infected drug users, linkage of drug abuse treatment and primary medical care, the relationship between HIV and other infectious diseases common among drug users, and HIV disease in pregnant women and their infants. The goal of the clinical research program is to understand the unique aspects of HIV and AIDS among drug users to develop better prevention and treatment strategies.

NIDA-funded clinical research has contributed substantially to current knowledge about HIV infection and disease progression in populations of drug users. For example, although basic research indicates that opioids can modulate (suppress or enhance) the immune response, clinical studies of HIV disease progression, as measured by decline in immune cell (CD4) counts, have not demonstrated that immune suppression is more rapid among actively injecting polydrug (cocaine and heroin) users than among other risk groups.

Conclusion

Much progress has been made by NIDA and other NIH institutes to facilitate clinical research. NIDA’s CTN provides the best example of how we are creating a supportive environment for the conduct of a broad agenda of high-quality clinical research. By blending the worlds of research and practice, we can only hope to improve treatment outcomes for our patients.

The success of clinical research in the 21st century will depend on access to complex, expensive research tools, a multidisciplinary and collaborative approach, and good information management systems. NIDA is using this recipe for success as it continues to expand its clinical research infrastructure.

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