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Penn/VA Center for Studies of Addiction

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The Penn/VA Center was founded in 1971 because of great concern over the number of Vietnam veterans returning home addicted to heroin. At that time little was known about the science of addiction so our program from the very beginning was designed to gather data about the nature of addiction and measure the effects of available treatments. In other words, the goals were always a combination of treatment and research. This combination has continued to the present day. A human laboratory for the study of addiction phenomena such as conditioned responses was also founded in 1971. The key clinician investigators in this group have remained in the Center since the 1970s with most of the research staff continuing to work together. Important new investigators have been added over the years. Treatment was empirically based with randomized, controlled clinical trials as the gold standard for determining evidence-based treatment.

The patients coming to treatment do not distinguish between abuse of alcohol and other drugs so the treatment and research programs have always focused on all drugs including ethyl alcohol and the combination of ethyl alcohol with other drugs such as cocaine and opioids. Most of the patients coming for treatment also suffered from additional psychiatric disorders such as depression, anxiety, bipolar disorder or schizophrenia. Thus, the addiction treatment program in 1980 absorbed the rest of the VA Psychiatry Service into the Substance Abuse Program forming a new Behavioral Health Service with responsibility for over 9,000 patients.

The integration of substance abuse treatment with overall mental health care was the most efficient way to handle patients with complicated combinations of disorders. While this continues to be the best way to treat patients, it has proven difficult in practice. The main reason for this difficulty is that most mental health therapists whether they are psychiatrists, psychologists or social workers feel very inadequate to handle substance abuse problems.

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Unless they have had specialized training in addictive disorders, therapists are likely to be uncomfortable if substance abuse is one of the diagnoses while they may be quite comfortable treating other complex disorders such as schizophrenia. This lack of education of clinicians remains a major problem for our field.

Some of the findings that came out of both the Penn/VA laboratory and clinical studies are now widely accepted and form the basis of standard clinical practice. These concepts and evidence will be briefly reviewed below.

Addiction is a chronic disease of the brain

Data from animal models indicated that drugs that were abused by human beings were also strong reinforcers in animals. These drugs reinforced behavior according to an operant conditioning paradigm as well as by producing classically conditioned effects. Animal models showed that environmental cues associated with drug availability could provoke conditioned withdrawal symptoms and reinstatement of drug taking (Goldberg and Schuster, 1970). The Penn/VA human laboratory showed in human beings, for the first time, that opiate withdrawal symptoms (tearing of the eyes, runny nose, tachycardia, nausea, vomiting) and subjective craving for heroin could be produced as a conditioned response in the laboratory (O'Brien et al., 1977). One of the papers demonstrating this phenomenon was published in *Science* and consisted of training trials in which an odor was paired with a small dose of naloxone given to methadone-maintained volunteers. The conditioning stimulus (odor or CS) acquired the ability to produce craving and withdrawal symptoms (CR-conditioned response) when presented alone and this response continued long after the training trials had ended.

Subsequent studies showed that drug-free former addicts would report craving when presented with cues associated with their prior drug use whether the drug was alcohol, nicotine, amphetamines or other drugs of abuse. This demonstration of subjective symptoms of craving and objective signs of drug withdrawal showed that these are learned phenomena that persist long after the last dose of the drug. Thus simple detoxification does not treat the addiction which, at its base, is a memory trace involving a change in brain circuits. Subsequently the mechanisms of craving have been further elucidated using brain imaging technology. Conditioned activation of specific structures in the brain's reward system has been demonstrated by changes in regional cerebral blood flow measured by PET or functional MRI (Childress et al., 1999) (Franklin et al., 2007). More recently, in a collaboration with the Volkow group, dopamine release measured indirectly with C_{11} labeled raclopride was shown to be occurring in critical brain regions when drug free cocaine addicts experienced cue-induced craving (Volkow et al., 2006). Brain activation in response to drug related cues in the addicted brain has now been shown to occur very rapidly, even before the stimulus reaches conscious awareness (Childress et al., 2008).

The measurement of addiction (Addiction Severity Index)

In the early 1970s, it became obvious that the usual ways of measuring severity of substance abuse problems by recording the number of bags of heroin or ounces of absolute alcohol consumed daily by the patient were totally inadequate. Addiction is a disorder that impacts on all aspects of a patient's life and thus estimates of severity should consist of multiple components that will influence prognosis and selection of treatment. In 1975 Norman Krasnagor, then a behavioral psychologist at NIDA, organized a one-day meeting at the Conference Center in Reston, Virginia. At the symposium on measurement chaired by Joseph V. Brady, the concept of an index of severity of addiction based on multiple factors such as psychiatric disorders, legal and social problems was presented by one of us (CO'B).

The development of such an instrument became a major goal of the Penn/VA Center and when A. Thomas McLellan joined the faculty, he became the PI of this effort. The first paper describing the ASI was published in 1980 (McLellan et al., 1980) and the instrument has rapidly been adopted worldwide as both a research tool and, in many programs, a clinical tool. The ASI has seven dimensions: drugs, alcohol, family/social, employment/support, medical, legal and psychiatric. The ASI has been translated into 19 different languages and is used widely. It has been progressively improved (Version 6 has recently been completed) and a companion instrument called the Treatment Services Review (TSR) (McLellan et al., 1992) has been developed to score the different types of treatments provided to a given patient. It has been shown in a prospective, randomized study that if the needs of the patient as measured by the ASI are matched by specific treatments as measured by the TSR, the outcome is significantly better (McLellan et al., 1997).

Psychiatric severity

The psychiatric severity dimension of the ASI does not provide a specific psychiatric diagnosis; rather it measures the need for treatment irrespective of diagnostic category. Several studies using the ASI have shown that psychiatric severity is the most consistent and powerful predictor of outcome in treatment (McLellan et al., 1983). This is an important finding that has called attention to the need for substance abuse treatment programs to refrain from an exclusive focus on drug taking and provide treatment for psychiatric disorders with psychotherapy and psychoactive medication.

Treatment of opioid addiction

When the Center was founded in 1971, methadone was on the verge of becoming available for widespread use in the treatment of opiate addiction. The Penn/VA Center conducted early studies demonstrating synergy between methadone treatment and individual psychotherapy that was professionally delivered and guided by a treatment manual (Woody et al., 1983) (Woody et al., 1995). The Center also demonstrated that the "dose" of psychotherapy could influence benefits from methadone in a population of heroin addicts. Minimal counseling with methadone provided the least benefits; moderate levels of counseling with methadone provided significantly more benefits and high levels of counseling with psychotherapy and methadone provided the best treatment results of all. These findings fit with studies showing the high levels of comorbidity with substance abuse coexisting with other forms of psychiatric disorders. Subsequently the Penn/VA Center was involved in early studies of buprenorphine and of the combination of buprenorphine with naloxone, (Fudala et al., 1998) now an important tool in the armamentarium for the treatment of opioid addiction. Rather than being a competitor of methadone, buprenorphine should be considered a complement because it adds another option and with the revisions in laws allowing treatment of patients with buprenorphine in doctors' offices rather than requiring specialized methadone treatment programs, more patients are able to receive treatment with this partial agonist.

Early in the history of the search for new treatments for opiate addiction the concept of an opiate receptor antagonist was given high priority. It was hoped that finding a medication that would block receptors would provide an effective treatment for opiate addicts. The Center researchers initially conducted trials with cyclazocine, an opiate receptor antagonist available in the early 1970s. The major problem with cyclazocine was that it had some agonist effects that made it unpleasant for most patients to take. In 1974 naltrexone became available for clinical trials and it was utilized in several studies in the Penn/VA Center with a goal of trying to use naltrexone to decondition or extinguish drug-seeking behavior. It has few side-effects and very effectively blocks μ , κ and δ receptors. While the search for a

more effective antagonist has been successful, this type of medication has not been widely accepted by clinicians and patients. In retrospect naltrexone turns out to have been very effective for certain populations such as physicians, nurses, pharmacists and other “white collar” opiate addicts (O'Brien et al., 1986). It has also been reported to be helpful in those who have legal constraints and who would return to prison if they relapse – thus, they will show better compliance with medical taking (Cornish et al., 1997). The Cornish et al study in parolees demonstrated in a randomized controlled trial that naltrexone could cut the reincarceration rate of parolees in half compared to a control group. Currently the center is funded to lead a five site study of depot naltrexone to prevent relapse in recently released parolees with a history of opioid addiction.

Though not shown to be very useful for treating unselected patients in the U.S., more recent studies have shown that the U.S. findings with oral naltrexone do not necessarily apply to other countries. For example, naltrexone studies done by Center investigators in St. Petersburg, Russia have shown much higher levels of patient interest with higher rates of adherence, less relapse, and substantial reductions in HIV risk behavior (Krupitsky et al 2004; 2006). These positive findings were due in large part to the involvement of the Russian family members in supervising dosing.

Another exciting finding related to opiate receptor antagonists was a true translation from the animal laboratory to the clinic. The finding of endogenous opioid receptors and endogenous opioids caused major excitement in the 1970s and there was much speculation as to how this very important basic science finding could be turned into something clinically useful. At the 1979 Meeting of the College on Problems of Drug Dependence, Hal Altshuler reported that a subgroup of rhesus monkeys (10 of 22) avidly self-administered alcohol. The self-administration was blocked in a dose/response fashion by naloxone or naltrexone (Altshuler et al., 1980). This led to the hypothesis at the Penn/VA Center that endogenous opioids were involved in alcohol reward.

In 1983 permission was obtained from the FDA to study naltrexone in human alcoholics. It was first tested in open clinical trials and then later in a randomized, double-blind trial against placebo at the Philadelphia VA Medical Center (Volpicelli et al., 1990) (Volpicelli et al., 1992). Patients received either naltrexone or placebo for three months and all received intensive group therapy according to 12-step principles and traditions. It was found that when alcoholics receiving naltrexone “slipped” and took a drink of alcohol, their pleasure from alcohol was greatly reduced. In a 3-month trial conducted at the Day Treatment Center of the Philadelphia VA Medical Center, the alcoholics randomized to naltrexone had a significantly lower relapse rate compared to the alcoholics randomized to placebo. Thus, it appeared that blocking opiate receptors helped some alcoholics avoid relapsing to alcoholic drinking. This finding was later replicated by O'Malley and colleagues at Yale (O'Malley et al., 1992) and led the FDA to add alcoholism to the indications for naltrexone. Thus, a medication developed with a goal of treating opiate addiction became much more widely used to treat alcohol addiction.

We were intrigued by the fact that some alcoholics respond very well to naltrexone by reducing or eliminating alcohol drinking, but others show no benefit. Those who respond usually have a strong family history of alcoholism and high alcohol craving (Monterosso et al., 2001). Those with a positive family history of alcoholism show a significantly greater endorphin response to alcohol (Gianoulakis et al., 1996) and report greater stimulation from alcohol that is blocked by naltrexone (King et al., 1997). This suggests that genetic factors may play a role in naltrexone response. A logical place to look for candidate genes was in the endogenous opioid system. In a retrospective analysis of our clinical trial data, we found that patients carrying a variant of the gene for the μ opiate receptor (A118G) had a

significantly better response to naltrexone than placebo (Oslin et al., 2003). Recently this finding was replicated by a different group of researchers (Anton et al., 2008). Currently the Center is engaged in a prospective study of depot naltrexone in the treatment of alcoholism with patients genotyped in advanced and randomized so that equal numbers of the SNP under study and those with the standard allele are in medication and placebo groups. If our hypothesis is again supported by the data, we will have evidence for genomic data to be used in the selection of medication for this disorder (O'Brien, 2008).

Substance abuse treatment as HIV prevention

Center investigators conducted one of the first prospective studies showing that methadone maintenance reduces not only HIV risk behavior, but also infection by the virus (Metzger et al, 1994). This study was important not only because it found a protective effect of methadone maintenance on acquiring HIV infection, but also because it showed that intravenous drug users could be studied in HIV preventive trials. It was followed by the participation of Center investigators in the first clinical trial of a HIV preventive vaccine, by studies showing that treatment of non-injecting drug users reduces HIV risk behavior (Woody et al, 1993; Metzger et al 1994), and by studies in Brazil showing relationships between methods of cocaine use and HIV infection that were similar to what had been found in the U.S. (Pechansky et al, 1994).

Opioid addiction in prisoners

Investigators in the Center have long been concerned about the increase of the American prison population to over 2.2 million persons with a majority incarcerated for drug-related crimes. A significant number of these prisoners are addicted to opioids, both street heroin and prescription opioids. Our prior work with parolees suggested that naltrexone could be helpful if used on a wider scale. Most recently released prisoners are not treated with methadone or buprenorphine, despite these medications being highly effective. As a non-agonist, naltrexone is more acceptable to many probation and parole officials.

In 2006 a depot, the FDA approved a slow release, depot form of naltrexone and it is now in clinical use for alcoholism. This depot preparation greatly improves compliance, which is the major weakness of oral naltrexone. Ironically, depot naltrexone is still not approved for the purpose for which the oral form was originally intended: opiate addiction. Center investigators have recently been funded to lead a multi-site trial of depot naltrexone for recently released prisoners with a history of opioid addiction. It is hoped that this will add one more new medication to the armamentarium for opioid addiction.

Medications for cocaine addiction

An epidemic of cocaine abuse began in the United States in the 1980s. Psychosocial interventions provided some benefit, but it became clear that medications were needed to aid in the prevention of relapse. Over the past quarter century, medication researchers have been frustrated. At first, the anti-depressant desipramine seemed effective in increasing abstinence rates in patients who were using cocaine largely by the intranasal route (Gawin et al., 1989), but subsequent studies in crack addicts found no benefit for this medication in the reduction of cocaine use although depressive symptoms were ameliorated (Arndt et al., 1992). The Penn/VA group conducted independent studies (topiramate, amantadine, propranolol, modafinil) as well as collaborative studies with other NIDA investigators using a large number of different molecules, most already FDA approved for depression, seizures or muscle spasms. None has yet proved consistently effective in placebo-controlled trials. Our recent attention has been focused on modafinil, a medication approved for the treatment of narcolepsy. Animals chronically self-administering cocaine show glutamate depletion and

modafinil enhances glutamate (Dackis and O'Brien, 2003). The Penn/VA group first reported that modafinil reduced the high produced by intravenous cocaine in a human laboratory study (Dackis et al., 2003; Malcolm et al., 2006). This was subsequently confirmed by two independent groups (Hart et al., 2008; Malcolm et al., 2006). In clinical trials, modafinil was found effective in one double-blind trial and several others are in progress.

Treatment Research Institute

While there has been significant progress in the development of new and more effective treatments for addiction, relatively few of these advances have had an impact on care in the community. Tom McLellan was particularly frustrated by this failure in translation to the treatment community so with support from the Center, he founded the Treatment Research Institute (TRI) in 1991. Later a grant from the Pew Charitable Trust launched the TRI in earnest with the goal of bringing evidence-based treatment to therapists and patients throughout the country. The TRI has made numerous contributions in the confidential evaluation of treatment programs with the goal of pointing out weaknesses that can be fixed. TRI has conducted numerous training programs for clinicians at all levels and has consulted on the re-design and improvement of city and state programs in many locales. An important part of the work has involved the justice system where TRI researchers have applied the "gold standard" of randomized clinical trials to test the efficacy of rehabilitative procedures in, for example, drug courts (Marlowe et al., 2005). The impact of TRI can be measured by the number of programs that are now using evidence-based treatment methods and by the improved results that have benefited their patients.

Vision for the future

Since the early 1970s, the Penn/VA Center for Studies of Addiction has worked to learn more about the nature of addiction and to improve the results of treatment. This overview paper presents some of the accomplishments of the past 37 years. We hope to build on these accomplishments by developing more effective treatments, perhaps using pharmacogenetic knowledge to more precisely identify sub-categories of patients and target specific behavioral and pharmacological treatments more accurately. We also hope that there will be progress in the development of more effective prevention methodologies because prevention is by far the best way to address the nation's drug problems.

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