

Is Addiction an Illness – Can it be Treated?

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Introduction

Problems of alcohol and drug dependence produce dramatic costs to society in terms of lost productivity, social disorder and of course health care utilization (1, 2). One recent study (3) estimated that alcohol abuse and dependence cost society approximately \$90 billion and that abuse of other drugs cost approximately \$67 billion each year. A recent study funded by the Robert Wood Johnson Foundation reported over 1/4 of all deaths in this country were associated in some way with alcohol, drug or tobacco use (4). Perhaps more subtle but no less significant is the fact that more than three fourths of all foster children in this country are the products of alcohol and/or drug dependent parents (5). In response to this threat to the general welfare, there has been renewed interest in the development and expansion of treatment programs as a method of dealing with these substance abuse problems. Yet, while some segments of the public are demanding greater availability and more financing for substance dependence treatments, there are those in government, insurance, managed care and the public who question the efficacy of these treatments, and whether they are "worth it" (6). As recently as 1997, the Wall Street Journal questioned the effectiveness and value of substance abuse treatment, saying "...the success rate of treatment programs is highly uncertain" (7).

The negative opinions about the effectiveness and value of substance abuse treatment appear to relate to core public perceptions about addiction and about what would be an "effective" addiction intervention, regardless of the type of intervention. The first perception is that drug addiction is primarily a "social problem" requiring a social-judicial remedy - rather than a "health problem" requiring prevention and treatment. This perception is quite understandable given the relative prominence of the social problems caused by drug and alcohol abuse. Crime, family disruption, loss of economic productivity and social decay are the most observable, dangerous and expensive effects of drugs on the social systems of our country. Thus, it is not surprising that many in the legislature and in the public at large expect law enforcement and interdiction efforts instead of public health efforts to correct the "drug problem."

Other important perceptions in this area involve the widespread skepticism about the advisability, effectiveness and value of treatments for addiction. For example, many individuals

believe that a medical or treatment-oriented approach to substance abuse conveys uncomfortable implicit messages. For example, some believe that to call addiction an illness suggests that the addicted person is not responsible for the addiction - nor the addiction-related problems; that they “can’t help themselves.” These are messages that many people find offensive and unfair. There is also the pervasive view that treatments are designed to help the drug user - but not designed to help society. Why should a society expend public resources to help individuals who may have produced many social problems? Finally, many in the public do not believe that treatment “works.” Specifically, many do not believe that any treatment can get addicted persons "off drugs and alcohol" and keep them off (See 7).

This is a view that is apparently shared by many physicians. Few medical schools have an adequate required course in addiction. It has been repeatedly documented over the past three decades that a majority of physicians do not screen for signs of alcohol or drug dependence during routine examinations (8, 9). Apparently there is the feeling that such screening efforts are wasted since in a 1997 survey, a majority of general practice physicians and nurses indicated that none of the currently available medical or health care interventions would be appropriate or effective in treating addiction (10).

It is well known that many persons who have received treatments have returned to alcohol and drug use. This "failure" of substance abuse treatments to reliably produce longstanding abstinence is seen as confirming the suspicions about treatment held by many Americans. Thus, treatment interventions that admittedly cannot cure the addiction and that may be seen as focusing only on helping an addicted individual – at great cost to society - are not widely popular. But are these perceptions true? Is there a role for addiction treatment in public policy aimed at reducing demand for drugs and reducing the social harms and costs associated with drug abuse? If treatments were considered a wise public investment, what treatments – behavioral interventions, medications or combinations – should be provided. Finally, is there evidence that these addiction treatments can be effective and valuable – not just to the affected patient – but to the society that would be expected to support those treatments?

In the text that follows we consider these questions from several perspectives. In **Part I** we ask whether there is evidence to suggest that addiction could be an illness:

- Is it possible to reliably diagnose “dependence” or “addiction” and to differentiate it from simple “drug use”
- Is there a predictable onset and course to the addictive disorders
- Is there evidence for genetic heritability in the susceptibility to addictive disorders; and
- Are there brain and physiological changes associated with the progression from drug use to addiction – and how long do these changes last.

Note: It is important to acknowledge at the outset that even substantial evidence in these areas will not prove that addiction is an illness. Such evidence will only suggest that the onset, course and presentation parameters seen in addiction are similar to those same parameters in other diseases. Moreover, it is also clear that even if we were able in some way to prove that addiction were an illness – it is an entirely separate but equally important question whether currently available medical interventions would be effective in addressing addiction problems.

Thus, in **Part II** of the paper, we examine the evidence basis for recently developed medications and medically oriented behavioral interventions. Here we address the question of whether there is evidence that medically oriented treatments for addiction could be effective and valuable to a society, relative to these other social policy alternatives - and whether incarceration and other forms of criminal justice interventions could be effectively combined with treatments.

In **Part III** of the paper we review the available research on specific treatment processes and treatment components that may be the “active ingredients” in effective drug abuse treatment. This review covers the past fifteen years and includes only data from clinical trials, treatment matching program studies, or health services studies where the patients were adults who were clearly alcohol or drug (excluding tobacco) dependent by contemporary criteria, where the treatment provided was a conventional form of rehabilitation (any setting or modality), and where there were measures of treatment processes and post-treatment outcome.

In **Part IV** of the paper we consider why it appears that addiction treatment is not as potent or effective as treatments for other medical disorders? To inform and frame this discussion we compare addiction treatments with treatments for three well-studied, chronic medical illnesses – adult onset hypertension, diabetes and asthma. The examination of this issue leads to particularly important conclusions regarding how addiction treatment is conceptualized by the public, how it is typically provided by treatment programs and how it has been evaluated by researchers. Here we suggest how addiction might be treated, insured and evaluated if it were considered a chronic illness.

PART 1

IS ADDICTION AN ILLNESS: HOW COULD YOU KNOW?

There has been much debate regarding the inappropriate "medicalization" of various conditions and problems (11). The public has grown skeptical of new "syndromes" and conditions that do not appear to conform to common sense diagnostic criteria for "true" medical illnesses; or of "conditions" that have no known treatments. For example, a recent New York Times editorial (12) suggests that to consider cigarette smoking a medical disorder "...shifts responsibility away from the individual...", helps doctors profit, and has "...little to do with improving the public health." In this context, many believe that "medicalization" of addiction is simply a way for physicians to declare more territory under their jurisdiction. Much of this skepticism is understandable when the term addiction has been applied to sex, gambling, work and even chocolate. Given this background it is reasonable to ask how any "condition" comes to be considered a "medical illness" (11). Here, we have tried to apply the same standards and methods that are currently used in the study of etiology, diagnosis and course of other disorders (e.g. diabetes, asthma, hypertension, etc.) to the study of drug dependence.

A) Advances in Diagnosing Drug Dependence - Perhaps the first question a physician might ask to determine whether a presenting "condition" is actually a medical disorder, is whether the supposed pathologic "illness" can be reliably differentiated from a non-pathologic state. This contrast has not always been clear in the area of alcohol and drug dependence, due in part to the fact that most adults have "used" alcohol and/or other drugs during their lives - sometimes heavily to the point of "abuse" - but rarely to the point where it could reasonably be called an "illness."

Further compounding this difficulty has been the lack of a laboratory test for "dependence" or even standardized definitions for the terms "addiction" and "dependence." The vagueness of these terms meant that diagnoses were often unreliable across different practitioners or different parts of the country. This situation has changed dramatically as a result of the concept of the dependence syndrome formulated by Edwards and Gross (13) and translated operationally through the Diagnostic and Statistical Manual of Mental Disorders, (the DSM) (14). In the current edition (fourth) of the DSM, "dependence" is defined as a pathologic condition that is manifest by a "...compulsive desire for the drug(or drugs) despite serious adverse consequences." (14).

There are seven specific diagnostic criteria that a practitioner must consider in making a DSM diagnosis of dependence and three or more of these must be satisfied for a valid diagnosis of dependence. Two of these criteria - tolerance and withdrawal - are considered evidence of neurological and behavioral adaptation to a drug. Tolerance is operationalized in the criteria through evidence that "... greater quantities must be used to produce the same effect..." (14). Withdrawal is evidenced by physical signs indicating "...a syndrome of unpleasant and often dangerous health condition developing hours to days following the cessation of the drug use..." (14). While tolerance and withdrawal had been cardinal features of drugs such as nicotine, alcohol, opioids, benzodiazepines and barbiturates for many years, there has been recent evidence for tolerance and withdrawal associated with tetrahydro cannabinol (THC) the most prominent active ingredient in marijuana (15, 16).

Additional DSM criteria inquire about whether a patient has "... reduced or eliminated previously pleasurable activities in order to concentrate on obtaining the substance..." and

whether the patient has "...used the substance instead of or while performing important responsibilities or functions..." (14). Answers to these seven diagnostic questions have been found to be more sensitive and specific than many laboratory tests used in diagnosing other illnesses such as prostate and breast cancers (17).

B) Genetic Factors in Drug Dependence - While many diseases are not genetically transmitted (e.g. Tuberculosis) and many heritable traits are not diseases (e.g. eye color), genetic transmission is one of the many criteria that a physician might use to decide whether a presenting "condition" is a medical illness. In this regard, Rounsaville and colleagues (18, 19) used standard diagnostic criteria to examine rates of alcoholism and drug dependence in the general population and among family members of diagnosed alcohol and drug dependent individuals. They found prevalence rates of approximately 11% for alcoholism and 6% for any type of other drug dependence in the general population. This compared with rates of 38% for alcoholism and 41% for drug dependence in family members of diagnosed alcohol or drug dependent individuals. In a separate study of siblings of diagnosed drug dependent individuals, 92% who tried a drug went on to meet diagnostic criteria for dependence (19). This compared with only an 18% rate of drug dependence among siblings of non-drug dependent individuals who tried the same drugs.

While these studies suggest that drug dependence "runs in families," many factors are known to operate in "familial transmission" and direct genetic heritability is only one of these. One of the best methods to estimate the level of genetic contribution within all the cultural and environmental variables that are operational in familial transmission is to examine the relative rates of a disorder in monozygotic and dizygotic twins. For example, heritability estimates (H^2) from twin studies of hypertension range from .25 - .50 depending upon the sample and the diagnostic criteria used (20 - 22). Similarly, twin studies of diabetes offer heritability estimates of approximately .80 for Type 1 (insulin dependent) (23) to about .30 - .55 for Type 2 (non insulin dependent) diabetes (24). Finally, twin studies of adult onset asthma have produced a somewhat broader range of heritability estimates, ranging from .36 to .70 (25, 26).

In the addiction field, four twin studies have been published over the past five years (27 - 30) and all found significantly higher rates of alcoholism and/or drug dependence among twins than among siblings and higher rates among monozygotic than dizygotic twin pairs. A recent twin study of heroin dependence produced a heritability estimate of .34 among males (28). Similar studies of alcohol dependence have produced heritability estimates of .55 to .65 among males (see 29, 31). Though there are still very few studies of heritability in the field of addiction and there is a need for studies of specific heritabilities by substance and by gender, the evidence accumulated over the past few years suggests significant contribution of genetic influence in approximately the same range as for chronic illnesses such as asthma and hypertension.

C) Comparing the Factors Associated with the Onset and Course of Illness in Drug Dependence and Other Illnesses - The evidence presented thus far suggests that drug dependence can be reliably and validly diagnosed and that there is evidence of genetic (as well as familial) transmission associated with contracting the illness. However, since the use of these substances is, at least initially, a voluntary action, behavioral control or "will power" is obviously a very important factor in the onset of these addictive disorders. At some level, and particularly in the case of dependence on illegal substances, the addicted individual is "at fault" for initiating the behaviors that later combine with the social, environmental and genetic factors to produce the dependence disorder. Though an addicted person may have been genetically predisposed to contract the illness and may have been raised in an environment that contained known risk factors, it remains a fact that this individual's behavioral choices played a prominent role in the onset and course of the disorder. Doesn't this voluntary initiation of the "disease process" set drug dependence apart, etiologically, from other medical illnesses?

In fact, there are many illness where "voluntary choice" contributes significantly to initiate and sustain a disease process - especially when these voluntary behaviors interact with genetic and cultural factors. For example, there is clear evidence, at least among males, that "salt sensitivity" is genetically transmitted (heritability estimate is .74) (32, 33) and salt sensitivity is a known risk factor for the eventual development of at least one form of hypertension. However, not all of those who inherit salt sensitivity go on to develop hypertension. This is because the use of salt is much more likely to be determined by familial

salt use patterns, cultural factors and individual choice. Similarly, factors such as obesity, stress level, and exercise are the joint product of familial, cultural, environmental and personal choice factors (30 - 32). Thus, while a diabetic, hypertensive or asthmatic patient may have been genetically predisposed to contract a disorder; and may have been raised in an environment that contained known risk factors such as poor parenting, poor diet, smoking and high stress, it is also true that behavioral choices such as the ingestion of high sugar and/or high cholesterol foods, smoking and failure to exercise, also played a role in the onset and severity of their disorder.

There is another aspect to the issue of voluntary choice as a contributor to the initiation of a disease process. This is the role of involuntary components embedded within seemingly volitional choices. For example, although the choice to try a drug the first time appears to be completely voluntary, it can be influenced by uncontrolled cultural, economic and ecological factors such as peer pressure, price, and especially availability, that are not completely determined by individual choice. For example, none of our grandmothers had the choice to use "crack" cocaine, ecstasy, GHB or LSD. In contrast, many children today are regularly offered these choices with substantial external pressures.

Further, it is clear that only a small minority of those who make the bad choice to use alcohol or another drug go on to develop addiction. Is this merely evidence that some people are "weak willed" while others "come to their senses?" In fact, the effects of the initial sampling of a drug are also influenced by genetic heritability and in turn are likely to modify the course of continued use in an involuntary manner. Those whose initial physiological response to alcohol or other drugs is extremely pleasurable may be more likely to repeat the drug-taking, than those whose involuntary, physiological reaction is neutral or even negative. Work by Schuckit and colleagues with sons of alcohol dependent fathers has shown that these sons are born with more tolerance to alcohol's effects than sons of non alcohol dependent fathers and that this effect is highly influenced by direct genetic transmission (heritability estimate is .67) (34, 35). Thus the positive effects of alcohol that may be experienced at relatively low doses by most individuals may only be experienced at higher doses by sons of alcohol dependent fathers. In turn, the negative, "hangover" effects of alcohol that may be felt by sons of normal fathers may not be experienced at the same level by sons of alcohol dependent fathers.

In contrast, an example of inherited “super-sensitivity” to alcohol has been shown in a large proportion of Chinese and Japanese individuals who experience an involuntary skin “flushing” response to alcohol. This effect has been traced to the presence of an aldehyde dehydrogenase gene that controls a central part of alcohol metabolism (36 - 38). Individuals who are homozygous for this allele (approximately 35% of Chinese population), have an especially unpleasant reaction to alcohol. This negative reaction reduces the appeal of alcohol to the point where there have been no alcoholics found with this genotype (36).

For those who do not have an initially negative reaction to their first drug administration, continued repetition of "voluntary" drug taking begins to change - often imperceptibly - into “involuntary” drug taking, ultimately to the point where the behavior is driven by a compulsive craving for the drug. In the text that follows we explore the physiological and molecular bases for these changes.

D) Pathophysiology Associated with Drug Dependence - The evidence presented thus far suggests that drug dependence has many of the elements of onset and presentation that are exhibited by other illnesses. However, it is a separate question whether there is a predictable pattern of pathophysiological changes such as those generally seen in the course of other medical illnesses. How does the voluntary choice to use alcohol or another drug ultimately become an involuntary compulsion? In fact, the acute effects of alcohol and many other drugs have been well characterized for many years. But even a complete understanding of these acute effects is inadequate to address fundamental questions regarding the mechanisms by which repeated doses of alcohol and other drugs produce paradoxically increasing tolerance to the effects of those drugs concurrent with decreasing volitional ability to forego the drug. As suggested by Koob and Bloom (39), the challenge is to find an internally consistent sequence by which molecular events modify cellular events, and in turn produce profound and lasting changes in cognitions, motivation and behavior.

Research in the neurochemical, neuroendocrine and cellular changes associated with drug dependence has led literally to volumes of remarkable findings over the past decade. These advances have been summarized in recent special issues of Science (40) and Lancet (41) and in two volumes produced by the Institute of Medicine of the National Academy of Sciences (42,

43). Here we will summarize just three areas of investigation that have produced clinically relevant information leading to medications to treat drug dependence.

There is now clear evidence that most addictive drugs have well specified effects on the brain circuitry that is involved in the control of motivated and learned behaviors. This evidence originated from studies in animals (42 - 44), and with recent developments in brain imaging techniques, has been confirmed in humans (45, 46). Anatomically, the brain circuitry principally involved in most of the actions of the major addictive drugs is the ventral tegmental area connecting the limbic cortex through the midbrain, to the nucleus accumbens (39, 47). Neurochemically, all of the major drugs of abuse (alcohol, opiates, cocaine, nicotine) have significant effects on the dopamine system - although through different mechanisms. For example, cocaine increases synaptic dopamine by blocking re-uptake into the pre-synaptic neuron; amphetamine produces increased presynaptic release of dopamine, while opiates and alcohol disinhibit dopamine neurons thereby producing increased firing rates (39 - 44).

Opiates and alcohol also have a direct effect on the endogenous opioid system (39 - 44). This finding has led directly to the development and wide clinical use of four effective medications (see below). Evidence is also emerging that the GABA system plays a central role in alcohol dependence and again, this has led to the development of an effective medication to treat alcohol dependence (See below). Finally, recent work on the stress response system suggests the possibility that lasting changes in neurochemical and neuroendocrine function may occur with the development of cocaine and/or opiate dependence (48, 49).

Significantly, the ventral tegmental area and the dopamine system are part of what have been called "survival circuitry" that accounts for some of our most basic behaviors including feeding, flight or fight responses in dangerous situations and sexual behavior. These brain areas have also been associated with the feelings of euphoria produced by naturally occurring reinforcers such as food, sleep and sex (50, 51). In experiments, animals who receive mild electrical stimulation of the dopamine system contingent upon a lever press response, will rapidly learn to press that lever tens of thousands of times, ignoring normal needs for water, food or rest, in order to maintain the stimulation of that system (43). Cocaine, opiates and several other dependence producing drugs stimulate this reward circuitry in a supernormal manner (47)

producing extremely powerful reward sensations. It is not hard to understand how addictive drugs can produce immediate and profound desire for their readministration. What is less clear is why simply preventing the administration of these drugs for some period of time (for example, by "detoxifying" the addict or locking them in jail) would not correct the situation, set the system back to normal and, like the child who burned his fingers, lead to a "sadder but wiser" individual who would be less (instead of more) likely to readminister those drugs.

Two explanations seem possible from the research done thus far. The most direct answer is that use of a drug at some dose, frequency and chronicity will reliably produce enduring and possibly permanent pathophysiological changes in the reward circuitry (43, 51, 52), in the "normal" levels of many neurochemicals (52 - 54) and to the stress response system (51, 52). It is not clear, just how much drug use is required to create these changes, how enduring the various effects are, or whether these effects will ever return to "normal." Physical signs of withdrawal generally last several days, motivational symptoms of withdrawal and cognitive impairment may last several months (43) and the learned aspects of tolerance to the drug may never return to normal (45, 46, 55). For example, Volkow found impairments in the dopamine system (reduced D2 binding) of abstinent former cocaine users for as long as three months after their last cocaine use (52, 53). In addition, her research team found reduced glucose metabolism in dopamine projection areas during cocaine abstinence (54), and the degree of metabolism reduction correlated with the long-term reductions in radioligand binding (53). Another human imaging study found decreased uptake of radiolabeled DOPA into the striatum of cocaine users tested one week after their last cocaine dose, indicating decreased dopamine synthesis at this early time point (56). Still other studies have documented areas of poor cortical blood flow ("patchy defects") and reduced prefrontal metabolism (57) in abstinent cocaine abusers (58, 59). Work investigating the stress response system suggests sustained changes in the stress response system following the development of opiate or cocaine dependence (48, 49). Taken together, these studies suggest that the neurochemical and possibly the neuroendocrine systems of abstinent but formerly drug dependent patients, are functioning irregularly and at a reduced level for a very long time.

A second explanation for the enduring pathology seen among drug dependent persons and their tendency to become re-addicted lies in the integration of the reward circuitry with the motivational, emotional and memory centers that are co-located within the limbic system. Connections among these "survival circuits" are apparently designed to give prominence and emotional significance to the normal biological events that usually precede arousal of those circuits (food, danger, sex). These circuits are also intimately involved in the control of emotion, motivation and "biologically significant memories" (50, 51). Importantly, these interconnected regions allow the organism not only to experience the pleasure of rewards, but also to learn the signals for them and to respond in an anticipatory manner.

This pairing of a person (drug using friend), place (corner bar), thing (paycheck), or even an emotional state (anger, depression) with drug use, including the supernormal activation of the reward circuits, leads to rapid and entrenched learning or "conditioning" to the point where these cues or signals acquire some of the properties of the drug itself. Thus, previously drug dependent individuals who have been abstinent for even long periods of time, may encounter a person, place or thing that has been previously associated with their drug use, producing significant physiological reactions. In the case of cocaine, these reactions include palpitations and other signs of sympathetic arousal such as ear-ringing, chest-tightness, light-headedness, a cocaine 'taste' in the back of the throat (55). In the case of heroin, this reaction includes pilo-erection, stomach cramps, fever and withdrawal-like symptoms (60). Importantly, and regardless of the particular drug, these responses are usually accompanied by profound desire or craving for that drug (55, 60). Ingrained through learning, the confluence of the physiological, emotional and craving symptoms combine to produce the "loss of control" that has been considered a hallmark of drug dependence (14). For example, Childress, O'Brien and their colleagues have shown the profound neurostimulation effects of cues that had been previously associated with use of drugs - even among stably abstinent former users (61). Using positron emission tomography (PET) they compared regional cerebral blood flow in limbic and control brain regions of 14 detoxified male cocaine users and 6 cocaine-naive controls during exposure to neutral videos and to videos of cocaine-related scenes. During the cocaine video, former cocaine dependent subjects experienced increased craving and showed a pattern of limbic (amygdala and anterior cingulate) increases and basal ganglia decreases in regional cerebral

blood flow. This pattern did not occur in cocaine-naive controls, nor among cocaine dependent patients in response to the neutral video or even to a different drug video (55). These findings indicate that even rather artificial video scenes of cocaine-related stimuli, presented in the sterile and remote context of a PET laboratory, produced excitation of brain reward regions that mimicked the effects of the drug itself.

It is likely that both the direct and sustained physiological changes produced by the drugs themselves and the acquired effects produced by conditioned cues are involved in the ultimate explanation of the continued vulnerability to relapse even among motivated, abstinent, former drug dependent individuals (See 48). At the same time, there is much left to explain here. As Childress has noted (55), all individuals have reward circuitry and most people have had their reward circuitry associated with natural reinforcers such as food, sex, sleep, and even some drug or alcohol use. Why don't all people use natural rewards compulsively? What distinguishes the brain function of those who use alcohol and other drugs but do not become addicted, from those who use similar amounts or at similar frequencies but do become dependent? Considered in combination with the heritability data from twin studies discussed above and data on congenital preference for alcohol and other drugs in specially bred strains of rats and mice it may be that alcohol, nicotine and other drugs have especially excitatory effects on particular "types" of individuals - or that the excitation of this circuitry is simply a parametric function of amount, duration, interval and frequency of drug administration - or both. These answers are not clear at this time and much more work needs to be done to identify the learned and innate aspects of vulnerability to drugs.

PART II

ARE THERE EFFECTIVE MEDICAL TREATMENTS FOR ADDICTION?

Regardless of whether the etiology and course of addictive disorders are similar to those seen in other chronic diseases - the question of most import is whether these supposed diseases will actually respond to medications and other forms of medical treatment. To address this, we

review the efficacy and effectiveness of treatment approaches for drug dependence compared against the untreated course of drug dependence; and continuing our comparison with other forms of chronic medical illness, we consider whether and in what ways, the effectiveness of drug dependence treatment compares with the effectiveness of treatments for other chronic diseases such as hypertension, asthma and diabetes.

A) Standards for Evaluating the Effectiveness of Drug dependence Treatments -

For the patient and particularly for the many treatment stakeholders in society, "effectiveness" of any medical treatment will be measured only in part by that treatment's initial effects on the presenting or primary symptoms. In fact, most treatments - especially those for chronic conditions and public health problems - are also evaluated in terms of their extended effects on the "disease related" problems that have limited personal function in the patient, that may have been costly to the health care system and/or may have become a public health concern to society (62). These considerations also apply in the evaluation of treatments for addictive disorders. Typically, the immediate goal of reducing alcohol and drug use is necessary, but rarely sufficient, for the achievement of the longer term goals of improved personal health and social function. Thus, from the both patient's and society's perspectives, a truly "effective" treatment is one that not only provides lasting reduction of substance use, but also significantly improves personal and social functioning, particularly in areas of special public health and public safety concern. Again, these broad and diverse expectations of treatment are not peculiar to the addiction field. To quote Stewart and Ware in their recent text on outcome evaluation in general medical care (62):

"...Since the 1970s however, the emphasis in America on what patient outcomes to measure to determine health status has been shifting... to the assessment of functioning, or the ability of the patients to perform the daily activities of their lives, how they feel, and their own personal evaluation of their health in general" (Ref. 62, p. 157).

Given that these issues are important in the treatment of drug dependence, not only to patients but also to society; addiction treatment outcomes have been measured on at least three domains (63):

1) Reduction of alcohol and drug use - the foremost goal of drug dependence treatments, measured objectively by urinalysis for drug screening and breathalyzer readings of blood alcohol content.

2) Improvement in personal health, and social function - measures such as general health status inventories, psychological symptom inventories, family function measures and simple measures of days worked and dollars earned can be reliably and validly collected directly from the patient via confidential self report and/or from medical/psychiatric evaluations and employment records.

3) Reduction in public health and public safety threats - threats to public health come from behaviors that spread infectious diseases and can be measured using standard laboratory tests for AIDS, STD's, TB and hepatitis. The commission of personal and property crimes can also be measured from public arrest and conviction records although these measures typically underestimate the extent of the criminal and dangerous behaviors actually performed (64).

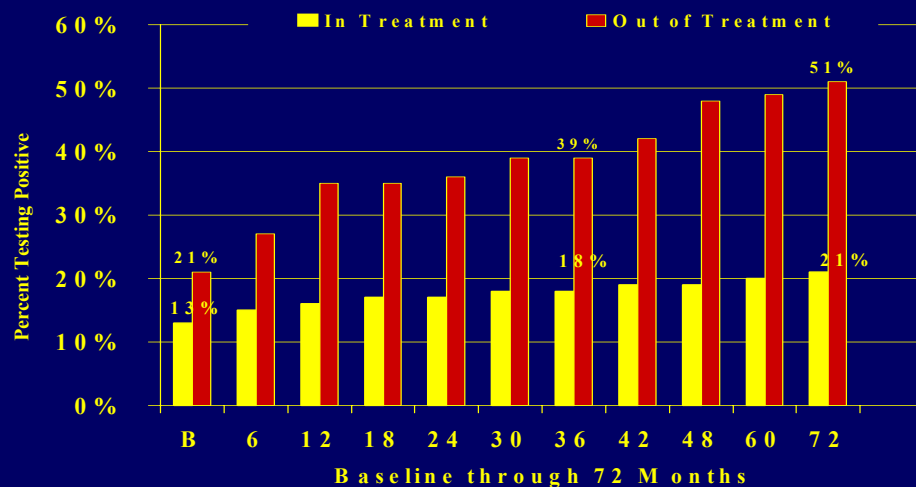
In our view, the first two domains are quite consistent with the "primary and secondary measures of effectiveness" typically used by the Food and Drug Administration to evaluate new drug or device applications in controlled clinical trials (65) and as indicated above, quite consistent with the mainstream of thought regarding the evaluation of other forms of health care (63). The final outcome dimension we believe is more specific to the treatment of drug dependence since it acknowledges the significant public health and public safety concerns associated with drug addiction. In the text that follows, we use these three domains to evaluate the published reports of drug dependence treatments with special emphasis upon medically oriented treatments.

B) Do treated Patients Show Better Outcomes Than Untreated Patients? While it is not ethically possible to deny available treatment to those whose condition appears to require it, there are situations where treatments have not been applied to substance dependent persons and these situations offer some indication of what happens to substance use, personal function and

the public health and safety problems of addicted individuals in the absence of treatment. Four recent studies provide information pertinent to this question.

Intravenous Drug Users - Metzger et al. (66) have examined the drug use, needle sharing practices and HIV infection rates of two large samples of opiate addicted patients in the Philadelphia area. Earlier studies of untreated intravenous drug users had shown reductions in drug injection rates and in needle sharing rates even from HIV testing alone (67 - 69). However, in all of these studies, one third to one half of intravenous drug users showed no reductions in behaviors known to increase risk for the spread of infectious disease. Thus Metzger and colleagues (66) attempted to assess the effects of a medically oriented treatment for opiate dependence (methadone) in reducing HIV risk behaviors and the actual rates of HIV infection in two groups of heroin dependent individuals. The "In-Treatment" group was comprised of 152 patients randomly selected at admission to a large methadone maintenance program. These In-Treatment subjects were asked to refer their heroin using friends from the same neighborhoods who had been out of all substance dependence treatments for at least one year. This resulted in a group of 103 "Out of Treatment" heroin dependent individuals who were matched on age, race, gender, neighborhood and many other relevant background and social factors that are associated with drug use.

Table 1
HIV Infection Rates Over Time



Both groups of patients were interviewed and tested for HIV status (90% contact rates at each interview) every six months over the next six years. Sero-positive rates are displayed for both groups in Table 1 above. As can be seen, at the initial assessment point, 13% of the In-Treatment sample and 21% of the Out-of-Treatment sample tested positive for HIV infection. By the six year point 51% of the Out-of-Treatment group, but only 21% of the In-Treatment group tested HIV positive (66). It is important to note that without the un-treated comparison group, data from the methadone group might have lead to a conclusion that treatment "did not work." That is, drug use had not been reduced to zero and there was still needle sharing in the treated group, but these risky behaviors were far less prevalent and less severe than seen among the matched group of untreated individuals.

Though the difference between the groups was quite remarkable, these data do not prove that treatment was the causal agent responsible for the different infection rates. It is possible and even likely, that the "out of treatment" subjects may have lacked the motivation for treatment found among the treated subjects, and this lack of desire for personal change, rather than the effects of the treatment itself, may have produced the status differences seen. For this reason, it is necessary to equate level of motivation, at least at the start of treatment, in order to make any valid judgment regarding the effectiveness of drug dependence treatment .

Waiting List Patients - An ongoing study of male veterans who applied for cocaine abuse treatment at the Philadelphia VA Medical Center helps to shed light on the relative outcomes of treated vs. untreated patients who were approximately equal in their initial motivation for treatment. In this four-week study of waiting list patients by Urschel and his colleagues (See 70), sixty-eight cocaine dependent individuals were contacted at the time of their application for inpatient substance abuse treatment. Due to the unavailability of treatment beds, these individuals were put on a waiting list for treatment. These individuals were followed each week of their waiting period and asked questions regarding their drug use and health status, by independent evaluators. The question of interest was whether the cocaine use and the related problems would change without treatment in this group of individuals who were all at least initially motivated to change.

Results indicated that over the following four weeks only 16% of the group received any treatment related services (typically detoxification and/or temporary housing at a community shelter), and this small subgroup did show some reductions in their alcohol and other drug use, but no improvements in their health and social function. Among those who received no treatment services at all, 57% reported increased severity of medical problems and 81% reported worse employment and support problems over the four-week waiting period. Thus, there was little evidence from these data that the drug use or the related health problems showed significant improvement without treatment, despite the fact that they were clearly motivated for change.

Unmotivated individuals - Another way to separate the effectiveness of drug dependence treatment from the direct effects of motivation would be to compare treated and untreated substance dependent individuals who were not initially interested in treatment. Such a study was recently performed by Booth and associates (71) among intravenous drug users seeking HIV testing and AIDS services as part of a multi-site AIDS initiative involving 4,000 subjects recruited from fifteen cities. In each city that participated in the study, out-of-treatment injection drug users were offered an opportunity to participate in drug abuse treatment as a part of AIDS risk reduction services. In all cities, subjects were randomly assigned to either a "standard" HIV counseling and testing intervention or to an "enhanced" intervention consisting of the standard intervention plus one to three sessions of motivational counseling from a health educator. At six-month follow-up, those who were randomly assigned to the enhanced intervention showed half the rates of drug injection (20% vs. 45%); four times the rates of abstinence (confirmed by urinalysis) and significantly lower arrest rates (14% vs. 24%) than those randomly assigned to receive just HIV counseling and testing (71).

This study is significant for several reasons. First, the very modest public health efforts to reduce needle sharing and drug use through HIV counseling and testing were associated with significant reductions in these target behaviors - even among those who were not initially motivated to receive these interventions. Second, more extended but still modest efforts at referring patients into more formal treatment at seven of the study sites, were associated with broader and more sustained improvements not only in the target problems but in other areas such

as abstinence, needle sharing and arrests. In turn, this finding suggests that treatment entry is not simply a matter of pre-conceived desire for change that would have occurred anyway - or the rates of treatment entry among these randomly assigned groups would have been approximately equal. Studies of other diseases show that even brief advice from physicians and other health care workers can affect the "motivation for treatment" among patients and the longer term course of their health (72. 73). This is the very foundation of "primary care medicine" and as Booth et al. suggest this also pertains even for seriously and chronically addicted individuals (71). Appointments for a health care service of any type may set the occasion for brief screening and health counseling that can have important and lasting benefits not only for the addicted patient, but also for the broader public health.

The costs of untreated addiction: an example from prenatal care. A final study comparing the effects of drug abuse treatment to no treatment was performed by Svikis et al. (74) among one of the most problematic and costly subgroups of substance dependent individuals - pregnant women. The dangers of drug use during pregnancy are extreme both for the mother and the child (75 - 77). Moreover, the costs associated with even the acute care of neonates born to addicted women can be extreme (78). Thus the Svikis et al. study was designed to test the effects of standard drug dependence treatment combined with a standard program of pre-natal and peri-natal care on the health status and costs of the mothers and their children. As in the Booth et al. study, the effects of drug abuse treatment were assessed among individuals who did not originally apply for treatment. All subjects in the study had simply applied for pre-natal care services and were found to be cocaine-positive on a routine drug screen. Two groups of pregnant women were compared: the first 100 women admitted to the combined drug dependence treatment-plus-pre-natal care program; and 46 comparison women drawn from the same geographic catchment area and matched for race, mental status, insurance coverage and parity with the treated women - but who were identified during the year prior to the opening of the experimental treatment program. Drug dependence treatment consisted of one week of non-hospital, residential care focused on stabilizing the women and engendering commitment for continued treatment, delivered in the context of their prenatal care. This was followed by twice-weekly addiction counseling that was also coordinated with the scheduled prenatal care visits.

Weight, Gestational Age & Costs

• 46 Control Women

2534 gms

34 wks

\$46,700

• 100 Treated Women

***2939 gms**

***39 wks**

\$14,500

Results were quite striking and three of the major findings are presented in Table 2 above. With regard to the primary measure of drug use, 37% of the treated patients had evidence of drug use (urinalysis) at the time of child birth. Again, considered in the absence of a comparison group these data could lead to the conclusion that the treatment had failed. However, 63% of the untreated women had cocaine positive urine tests at delivery. The treated women kept twice the number of appointments as the untreated women (8 vs. 4); the average birthweight was higher (2934 gms. vs. 2539 gms.); and the gestational age of the baby was over one month higher at delivery (39 wks. vs. 34 wks.). Following the deliveries, 10% of the babies in the treated group required treatment in the neonatal intensive care unit at an average length of stay of 7 days; as compared with 26% of the babies in the untreated group at an average length of stay of 39 days. The total costs of care for the mother and the baby in the treated group averaged approximately \$14,500, including the costs for the drug abuse treatment. This was dramatically lower than the average costs of over \$46,700 for the women and babies in the group that received pre-natal care but no treatment for drug dependence. The authors point out that these average cost calculations were quite conservative since they did not include costs such as criminal and family court costs, child and family services, continued health care costs for mother and child, etc. Nonetheless, the data present striking evidence that drug dependence treatment can be cost

effective in this severely affected population. The data also suggest that drug dependence treatment can be combined effectively with traditional perinatal medical care with mutual benefit.

C) Are Drug dependence Disorders Responsive to Medications - If physicians are expected to play a role in the treatment of drug dependence, it is reasonable to ask whether there are effective medications available. Perhaps the best known and studied of medications in the treatment of drug dependence are those used in the treatment of smoking cessation such as nicotine gum, nicotine skin patch and bupropion (Zyban). All of these medications were developed under FDA guidelines, researched in randomized clinical trials over the past twenty years and many have now reached the over-the-counter market. There is no doubt that these medications plus an educated physician population have made an important contribution in the larger public health efforts to reduce cigarette consumption.

A review of the evidence regarding the development of medications for the treatment of alcohol, cocaine and opiate addiction suggests many commonalities (See 40 – 43, 79, 80). These medications have also been developing in the same manner - albeit more slowly due in part to the lack of a large commercial market - but the identification, development, testing of new drugs concurrent with necessary physician education practices have been major efforts in both the National Institutes on addictive disorders (NIDA, NIAAA) for the past five years (see 43). These efforts have brought several existing medications to federal and state approval (e.g. LAAM, buprenorphine), identified important new uses for existing medications (e.g. naltrexone in alcohol treatment), and developed some promising new medications (e.g. buprenorphine, acamprosate). At the same time, there has been frustration in the development of an effective medication for cocaine addiction. Below we review briefly, several of the most prominent medications now available and some of the work in progress.

Medications for the Treatment of Opioid Addiction - Agonists, partial agonists and antagonists are the three primary types of medications available for the treatment of opioid dependence, all acting directly upon the opiate receptors - particularly mu-receptors (43). Agonist medications are prescribed acutely as part of an opioid detoxification protocol (gradually reducing doses to minimize discomfort as the patient becomes acclimated to lower and finally

zero doses of opiate); or chronically in a "maintenance" regimen (gradually increasing doses of long acting, pharmaceutical opiates to maximize the patient's tolerance and reduce or eliminate the effects of lower potency "street" opiates). Methadone has been an approved agonist medication for both the acute detoxification and the long term maintenance treatment of opiate dependence for more than 25 years. The long acting form of methadone (48 - 72 hour duration), Levo Alpha Acetyl Methadol (LAAM) has recently received FDA approval and has been accepted by 16 states for prescription - but only at methadone maintenance programs (81). Double blind, placebo controlled trials have shown methadone to be effective in detoxifying opiate dependent patients safely and comfortably in both inpatient and outpatient settings (82 - 85). As a maintenance medication, methadone's oral route of administration, slow onset of action and long half life have been very effective in reducing opiate use, crime and the spread of infectious diseases through needle sharing (e.g. AIDS, hepatitis, Tuberculosis) for the past three decades. Recently, the effectiveness of methadone was supported by a National Institutes of Health consensus conference where evidence for methadone's effectiveness was reaffirmed by a panel of impartial physicians and scientists (86).

Partial agonist medications such as buprenorphine have also been developed over the past several years and have been widely used in Europe (See 87). Buprenorphine is administered sub-lingually and has an effective duration of action of approximately 24 - 36 hours. Like methadone, buprenorphine significantly reduces craving for opiates and is currently being reviewed by the FDA. Large scale, double-blind, placebo controlled trials with buprenorphine have shown reductions in opiate use that are comparable to those seen with methadone (88). The partial agonist actions of buprenorphine may have some advantages over methadone since it produces few or no withdrawal symptoms upon discontinuation of its use (87).

Opioid receptor antagonists such as naltrexone have also been used for more than 20 years in the treatment of opiate dependence (See 89). Naltrexone is an orally administered opiate antagonist that blocks actions of externally administered opiates such as heroin through competitive binding for 48 to 72 hours (90 - 92). Like methadone and buprenorphine naltrexone is a maintenance medication, designed as an "insurance policy" in situations where the patient is expected to be confronted with relapse situations. Opiate antagonists produce neither euphoria

nor dysphoria when prescribed to abstinent opiate addicts, but as is true with so many maintenance medications in all other areas of medicine, compliance has been generally poor with most field studies showing retention rates of less than 20% after one month of treatment. Perhaps for this reason, several studies have combined this antagonist medication with social or criminal justice sanctions to increase compliance and sustain the benefits from the medication. For example, naltrexone is routinely used in the monitored treatment of physicians, lawyers, nurses and other professionals (93) where the loss of license to practice is contingent upon maintenance of abstinence. In a recent controlled trial with opiate dependent federal probationers Cornish and colleagues showed that naltrexone added to standard probation produced 70% less opiate use and 50% less re-incarceration rates than standard probation alone (94). Like the Svikis study with pregnant cocaine dependent women, the Cornish study also showed that drug dependence treatments could be combined with other medical or social interventions with the potential for great cost savings (94).

Antagonist Medications in the treatment of Alcohol Dependence - Naltrexone (marketed under the trade name - Revia™) has been found to be effective in the treatment of alcohol dependence (95, 96) Naltrexone at 50 mg./day has been approved by the FDA for use with alcohol dependent patients since independent studies have shown it to be a safe, effective pharmacological adjunct for reducing heavy alcohol among alcohol dependent patients. Its mechanism of action appears to be the blocking of at least some of the "high" produced by alcohol through competitive binding with mu opiate receptors (95, 96).

More recently, European researchers have found encouraging results using acamprosate to block craving and return to alcohol abuse. While acamprosate acts on different receptor systems than naltrexone, the clinical results are remarkably similar (97). Alcohol dependent patients who take acamprosate have shown 30% greater post-treatment abstinence rates at six month follow-up than those randomly assigned to placebo. Further, those who have returned to drinking while receiving acamprosate report less heavy (greater than five drinks per day) alcohol use than those in the placebo group who returned to drinking (97). While both of these medications can be used for extended periods, in practice they are generally prescribed for about

one to three months as part of a more general rehabilitation program that includes behavioral change strategies (See 79).

Medications in the Treatment of Stimulant Dependence - Over the past ten years there have been many medications tried in the treatment of cocaine and other stimulant dependence. While this literature is quite large, it has been disappointing (for recent review see 80). At this writing, there is no convincing evidence that any of the various types of cocaine blocking agents are truly effective for even brief periods of time or for even a significant minority of affected patients. Research continues in this important area and there have been indications of a potentially successful "vaccine" that may be able to immediately metabolize and inactivate active metabolites of cocaine (See 98). This promising work is currently being tested in animal models and clinical trials will not be scheduled for several years. It must be admitted that at present there are no medications available that aid in cocaine rehabilitation.

Medications in the Treatment of Co-Morbid Psychiatric Conditions - While we have briefly reviewed the still young literature on medications used to reduce or block the use of alcohol and other drugs, there is a large and important literature examining the use of medications to reduce psychiatric problems among addicted individuals (99 - 101). This is an important area for physician involvement. Psychiatric disorders such as depression, anxiety, phobia and others are prominent among nicotine, alcohol, opiate, cocaine and benzodiazepine dependent individuals. There is abundant evidence that addicted individuals with concurrent psychiatric problems are more likely to drop out of standard drug dependence treatments, more likely to perform poorly during those treatments and more likely to relapse early following those treatments (102 - 104) Finally, there is increasing evidence that the prescription of appropriate anti-depressant medications can alter that prognosis for these "psychiatrically more severe" individuals (99 - 101)

In summary, there are medications currently available for use by physicians in the treatment of nicotine, alcohol, and opioid dependence; and for the treatment of co-morbid psychiatric disorders associated with all forms of substance dependence. These have been tested in multiple trials and have been shown to be effective. At the same time there are still relatively few patients who receive - or practitioners who prescribe - these medications and, as in the

treatment of other medical illnesses, managed care companies have been slow to authorize maintenance medications (42, 43, 80). Because of this there is a need for additional studies of the appropriate use of these medications in "real world" treatment of drug dependence disorders.

D) Is Drug Dependence Responsive to Brief Physician Interventions ?

One of the most interesting and potentially important developments over the past decade has been the research in physician administered brief interventions as part of office-based primary care (105 – 111). The interventions follow the identification of “at risk” drinking or drug use through any number of simple screening instruments. Once the problem has been identified the physician begins a non-challenging discourse with the patient designed to get the patient to accept that there is a problem and that the patient has the ability to correct the problem. Problem acceptance (ie. that the patient is drinking too much) by a patient can be difficult but direct assessment of the problem and simple feedback of normal behaviors (e.g. simple charts showing normal levels of drinking by age and gender) can be much more helpful than scolding or confrontation (112). Patient behavioral change is accomplished through negotiation of some behavioral goals that are agreed upon by contracting with patient (105 - 107). These brief (usually 10 to 20 minutes of physician time in the office) have typically been accompanied by brief booklets or self-help manuals and regular follow-up, usually over the phone. In many ways, these brief interventions for problematic alcohol and drug use are similar to the types of interventions used in the office-based, primary care management of other chronic illnesses.

Clinical research in office-based settings has shown these approaches to be both effective and cost saving (108 - 111). For example, a study of office-based brief interventions by Kristenson in Sweden showed sustained reductions in alcohol use (verified by liver function tests) and healthcare utilization (108). A second study performed by the Medical Research Council in England with 47 general practitioners found more significant reductions in alcohol use in the intervention group than in the randomly assigned control (no intervention) group, twelve months following the intervention (109). A World Health Organization study of brief interventions in ten countries also studied brief interventions in both physician offices and in general clinic settings (110). When the total sample was analyzed, there were approximately equal reductions in alcohol use among both the control group (who had simply had their alcohol

use identified and reported to them) and the brief intervention group. However, when data from just the physician offices was analyzed there was a significant effect of the brief intervention. Brief interventions were also studied in 17 community physician office practices by Fleming and colleagues (111). In that study “at risk drinkers” were screened and offered two, 10-15 minute interventions by the physician, or simply provided a health booklet. Risk was defined as the self-reported drinking of more than 13 or 10 drinks in the past week for men and women, respectively. At both six and twelve month follow-up the intervention group was drinking on fewer days, drinking significantly less, reporting fewer binge drinking episodes (greater than 4 or 5 more drinks per occasion for women and men, respectively) and hospitalized for fewer days – than the control group. A follow-up study of costs and benefits (113) showed 5:1 savings per dollar invested in the intervention. Most of the savings came from reduced hospital days and emergency room visits as well as avoided crime and motor vehicle accidents (113).

Several points are relevant here. First, these interventions do require training (about one and one-half hours for the physician and the same for an office nurse) (113). The training is designed to help physicians avoid confrontation and to develop constructive methods of engaging the patient into the behavioral change that will be required. Second, these interventions require some form of screening for alcohol and drug problems but there are many patient-administered screening instruments available. Third, while these interventions have been studied in the context of alcohol treatment, these behavioral change initiation skills would be broadly useful in the treatment of most other forms of chronic illness. Finally, while the results reported here have been broadly replicated, it is likely that these brief forms of intervention are more appropriate for, and accepted by individuals with lower levels of problem severity. Further, these brief interventions have not been studied in populations of drug abusers. It therefore remains a question whether these minimal types of interventions would be effective for patients with more serious alcohol and particularly, drug abuse problems.

E) Treatment Adherence in Drug dependence and Other Chronic Diseases? -

There is no reliable "cure" for drug dependence. For reasons cited above, persons dependent upon nicotine, alcohol, opiates, cocaine, barbiturates or marijuana who attempt to reduce their use are likely to have problems in maintaining "controlled use." Among those who become

addicted, studies of treatment response have uniformly shown that those patients who comply with the recommended regimen of education, counseling and medication that characterizes most contemporary forms of drug dependence treatment, have the most favorable outcomes during and following treatment (114 - 118). Despite this, most of those who start any type of treatment drop out prior to completion and/or to ignore advice to continue medications or in aftercare or AA participation following formal treatment. Even those who do comply with treatment fully have problems sustaining abstinence, with one year follow-up studies indicating that only 40 - 60% of treated patients are able to remain completely abstinent throughout that time period, although an additional 15 - 30% do not resume dependent use or develop problems associated with drug use (118 - 120 also see below).

It is quite discouraging to many in the treatment field that so many drug and alcohol dependent patients fail to comply with the recommended course of treatment and that so many of those who complete treatment subsequently resume substance use. Recent reviews of the treatment literature have indicated that factors such as low socioeconomic class, co-morbid psychiatric conditions and lack of family or social supports for continuing abstinence are among the most important variables associated with lack of treatment compliance in this field, and with relapse following treatment (121). As indicated above there are now several medications that have demonstrated effectiveness in the treatment of alcohol and opiate dependence. However, for these medications to be effective, they must be taken on a regular basis and lack of patient compliance has severely limited the potential impact of these medications (122). Ongoing clinical research in this area is focused upon the development of longer acting or depot forms of these medications, as well as behavioral strategies to increase patient compliance (122).

As suggested previously, hypertension, diabetes and asthma are also chronic disorders, requiring continuing care for most, if not all of a patient's life. At the same time, these disorders are not necessarily unremitting or unalterably lethal, as long as the treatment regimen of medication, diet and behavioral change are followed. This last point requires emphasis. Treatments for these medical disorders are heavily dependent upon behavioral change and medication compliance to achieve their potential effectiveness. In a review of over 70 outcome studies of treatments for these disorders patient compliance with the recommended medical regimen was the most significant

determinant of treatment outcome (123, 124). However, studies have shown that less than 50% of Type 2, insulin dependent, adult diabetics fully comply with their medication schedule (e.g. 125), and less than 30% of hypertensive or asthmatic patients comply with their medication regimens (e.g. 126, 127). The problem is even worse for the behavioral and diet changes that are so important for the maintenance of short term gains in these chronic disorders. Again, a review of recent studies in the fields of adult onset diabetes, hypertension and asthma indicates that less than 30% of patients in treatment for these disorders comply with the recommended diet and/or behavioral changes that are designed to reduce risk factors for reoccurrence of the disorders (e.g. 128, 129). Across all three of these chronic medical illnesses, compliance is poorest among patients with low socioeconomic status, low family and social supports or significant psychiatric co-morbidity (check these) as is summarized in Table 3 below.

Factors Associated with Relapse in Hypertension, Diabetes & Asthma

- #1 - Lack of adherence to medication, diet, or behavior change**
- #2 - Low socioeconomic status**
- #3 - Low family supports**
- #4 - Psychiatric co-morbidity**

Sources: National Center Health Stats; Harrison, 13th Ed. (more than 30 published studies)

F) Relapse Rate in Drug dependence and Other Chronic Diseases? - This review of medication and behavioral compliance in the treatment of other chronic medical illnesses suggests important parallels with the treatment of drug dependence. As in the field of drug dependence treatment, lack of patient compliance with the treatment regimen is a major contributor to the reoccurrence of these disorders and to the development of more serious and more expensive "disease related" conditions. For

example, outcome studies indicate that 30 - 60% of insulin dependent, adult, diabetic patients, and approximately 50 - 80% of adult hypertensive and asthmatic patients suffer reoccurrences of their symptoms each year to the point that they require at least, restabilization of their medication and/or additional medical interventions to re-establish symptom remission (125 - 129). Many of these reoccurrences also result in more serious additional health complications. For example, limb amputations and blindness are common results of treatment non response among diabetics (130, 131). Stroke and cardiac disease are common problems associated with exacerbation of hypertension (132, 133). These reoccurrence or relapse rates are summarized f in Table 4 below.

⋮
Relapse* Rates for Chronic Medical Disorders

<u>Hypertension</u>	50 – 60%
<u>Diabetes</u>	30 - 50%
<u>Asthma</u>	60 – 80%

* Relapse = Retreated w/in 12 months, in ER or Hospital

PART III

WHAT ARE THE “ACTIVE INGREDIENTS” IN ADDICTION TREATMENT?

What components contribute to treatment effectiveness?

A) The Detoxification-Stabilization Phase of Treatment

Medical detoxification has been the initial and acute stage of virtually all forms of addiction treatment. However, the term “detoxification” has been used to describe both treatments of a true withdrawal syndrome (i.e., neuroadaptation) as well as simply the stabilization of acute physiological and emotional symptoms associated with the cessation of drug use that might not produce a bona fide withdrawal syndrome. “True detoxification” is required only for certain types of drug dependence, most notably nicotine, alcohol, opiate, barbiturate, and benzodiazepines. In each of these cases (particularly barbiturate use) persistent use of a substance at gradually escalating doses and for escalating time periods produces neuroadaptation or “tolerance” to the drug – to the point where greater amounts of the drug are typically required to produce euphoria –and importantly – eliminate withdrawal symptoms. Withdrawal symptoms reflect the “rebound” of a physiological system that has been perturbed by drug use for a substantial period of time. These symptoms can include headaches, bone pain, fever, chills, watery eyes, runny nose, diarrhea and profound emotional upset. Opiate drugs in particular can produce these symptoms and while they are profoundly uncomfortable, they are rarely life threatening. Importantly, alcohol, barbiturates and benzodiazepines will also produce many of the previously described symptoms – but also seizures and cardiac irregularities – that can be life threatening depending upon the history and general health of the user.

It is also true that virtually all drug use – including caffeine, amphetamine, cocaine and hallucinogens – will produce acute periods (1 – 3 days typically) of physiological and emotional instability following abrupt discontinuation of regular use. While uncomfortable, this instability will almost always subside without formal medical attention. Thus, at least in the United States, few patients are admitted to a hospital or even to residential care for the acute treatment of the instability produced by these drugs. Although cocaine "withdrawal" has been

recognized in the *Diagnostic and Statistical Manual*, Fourth Edition (DSM IV, See 14), there is continued debate regarding the treatment and even the existence of a bona fide withdrawal syndrome following cocaine use (134, 135). At the same time, there is clear agreement that patients who have used cocaine or crack continuously over sustained periods, suffer two to five day periods of measurable physiological and psychiatric instability (136, 137). For this reason, cocaine “stabilization” is included in this review along with formal detoxification.

Goals of Detoxification - Stabilization

Patients and Treatment Settings - The detoxification and stabilization phase of treatment is designed for patients who have been actively abusing alcohol or street drugs, or both, and who are suffering physiological or emotional instability, or both. In cases of severe withdrawal potential or extreme physiological or emotional instability, detoxification-stabilization helps to prevent serious medical consequences of abrupt withdrawal, to reduce the physiological and emotional signs of instability, and to motivate necessary behavioral change strategies that will be the focus of rehabilitation. This stage of treatment may take place in inpatient settings, either a hospital or a non-hospital, residential setting, or in outpatient settings, such as in a hospital-based clinic or a residential or social setting.

Treatment Elements and Methods - Medications are available for both physiological withdrawal signs and for the temporary relief of acute medical problems associated with physiological instability (e.g., sleep medications, antidiarrheal medications, vitamins, and nutritional supplements). Motivational counseling is widely used to address shame and ambivalence, as well as to increase adherence with recommendations for continued rehabilitation.

Duration - Regardless of the setting, stabilization of acute problems is typically completed within 2 to 10 days, with the average being 3 to 5 days (138). True detoxification is necessary only for cases of severe alcohol, opiate, benzodiazepine, or barbiturate use, although many cocaine-dependent and other drug-dependent patients suffer from significant physiological and emotional instability that precludes immediate participation in rehabilitation. The duration of the detoxification-stabilization process depends on the presence and severity of the patient's

dependence symptoms as well as concurrent medical and psychiatric problems. Treatments longer than 5 days are unusual and typically are due to conjoint medical or psychiatric problems or physiological dependence upon some forms of sedatives (e.g., alprazolam).

Effective Components of the Detoxification – Stabilization Stage of Treatment

Setting of Care: Medical or Nonmedical and Inpatient or Outpatient - Debate regarding the appropriate setting of care in which to detoxify alcohol-dependent patients has been substantial. Since the mid-1970s, medical settings such as residential treatment facilities or even outpatient treatment centers have conducted detoxification or stabilization treatments for alcohol, opiates, and more recently, cocaine. Although studies have not systematically compared social settings with medical settings for detoxification from alcohol dependence, there are reports of favorable outcomes in both.

In the presence of significant physiological signs of alcohol, opiate, benzodiazepine, or barbiturate withdrawal however, the standard treatment includes medical supervision in either a hospital or an outpatient medical clinic (138). Although research is not extensive, medical settings are generally viewed as being more appropriate for detoxifications involving medical problems (particularly those with a history of seizures) and psychiatric problems (particularly for individuals with depression and at risk of suicide) and also when patients have concurrent cocaine dependence.

Alcohol Detoxification. Within the framework of medically supervised alcohol detoxification, the relative effectiveness and costs of inpatient versus outpatient alcohol detoxification have been examined (139, 140). In a study by Hayashida et al. (139), chronic alcohol-dependent patients without histories of serious psychiatric or medical complications were randomly assigned to receive medically supervised alcohol withdrawal in either an inpatient or a day-hospital setting. On two of the outcome domains considered important for detoxification treatments (safe elimination of withdrawal signs and engagement in ongoing rehabilitation), the inpatient group showed significantly better performance, but the re-addiction rates were less than 12 percent for both groups. Despite this statistically significant advantage

for the inpatient setting, it was 10 times more costly than outpatient detoxification in an outpatient setting.

There may be some advantage to inpatient detoxification when a patient does not have the social or personal supports necessary to comply with the outpatient attendance requirements. However, despite somewhat lower retention rates for outpatient than for inpatient alcohol detoxification (139, 140), outpatient detoxification may be more acceptable to a wider range of drinkers who wish to avoid the stigma of treatment in a designated detoxification (140).

Opiate Detoxification. Available evidence suggests that opiate detoxification can be accomplished with many medications including clonidine, lofexidine, buprenorphine and of course methadone. Recently there has been reports of rapid (24 hours or less) opiate detoxification under general sedation (141). There are at least four reports in the literature showing the “efficacy” of this method, but there are also some elevated dangers associated with this modality as applied in general practice (142). Apart from these relatively new procedures, a wealth of studies over the past ten years have shown that opiate detoxifications can generally be accomplished in outpatient settings under medical supervision with gradually reduced doses of methadone (143, 144). However, completion rates for treatment of opioid dependence may be higher in inpatient than in outpatient detoxification programs (145, 146).

Cocaine, Crack and Other Stimulant Stabilization. Few studies have examined the appropriate setting for the stabilization of physiological and psychiatric signs and symptoms associated with extended cocaine or crack use. The prevailing practice has been to attempt to stabilize all but the most severely affected patients through outpatient care. Patients who are in the acute stages of cocaine cessation and who are more severely affected (medically or psychiatrically) are placed into a hospital if they have significant cardiac problems or significant psychiatric symptomatology or are at least placed in inpatient social settings for the first 3 to 5 days of cocaine treatment (136 - 138).

The available literature is replete with accounts of early dropouts during the first 2 to 3 weeks of outpatient cocaine treatment (147 - 149), with attrition rates ranging from a low of 27 percent to a high of 47 percent in the first few weeks of care. As discussed below, it is

reasonable to conclude that the patients with the most severe medical and psychiatric problems are most susceptible to drop out of treatment early.

Length of Stay and Criteria for Completion

Alcohol and Opiates. Several detoxification studies (139, 143) have measured detoxification as 3 consecutive days of abstinence from observable withdrawal signs or symptoms (opiate or alcohol), using standardized inventories of these physical measures. Using these criteria, the great majority of detoxifications can be accomplished in 3 to 5 days (138), and there is no evidence of greater effectiveness from extended stays.

In an early study by Cushman et al. (143), only 3 percent of 525 opiate-dependent patients who failed to provide an opiate-negative urine specimen following the outpatient detoxification (signifying at least 3 days of abstinence) were able to engage in the suggested abstinence-oriented rehabilitation program following detoxification. One hundred percent of these patients were re-addicted to opiates at the 6-month follow-up.

Cocaine. A recent study of cocaine-dependent patients entering outpatient rehabilitation also offers some relevant information on the clinical importance of developing a criterion for successful completion. In a study of cocaine-dependent veterans, Alterman et al. (147) found that the single best predictor of engagement into the rehabilitation process, and ultimately program completion (elimination of cocaine use verified by urinalysis), was the presence or absence of cocaine metabolites in the urine sample submitted upon admission to the rehabilitation program, signifying recent cocaine use. Of those patients without cocaine metabolites present in their urine on admission, 79 percent engaged in and completed the outpatient treatment, whereas only 39 percent of those with a positive urine sample on admission engaged and completed the outpatient treatment.

Indicators of Effectiveness in the Detoxification – Stabilization Stage

The therapeutic goals of detoxification and stabilization are focused primarily on the amelioration and stabilization of the acute medical, psychiatric, or substance use symptoms that

were out of control and thus responsible for preventing the patient from entering directly into rehabilitation. Thus, the goal of detoxification-stabilization is removal of the physiological and emotional instability that has impeded direct entry to rehabilitative treatment – as well as motivating the patient to recognize the severity of the drug use, to accept that there is a problem that s/he must and can address, and to engage the patient in continued rehabilitative care, almost always in an outpatient setting. The acute, detoxification/stabilization stage cannot be considered complete treatment – only preparation for continued treatment. Research over the past 20 years in most countries has concluded definitively that detoxification is associated with lasting improvements only when there is continued rehabilitative treatment (1). Thus, detoxification can be said to have succeeded if shortly after discharge (i.e., 2 – 3 weeks) the patient has:

- shown significant reductions in physiological and emotional instability (at least to levels appropriate for outpatient rehabilitation admission),
- has not had serious medical or psychiatric complications, and
- has been integrated into and engaged in an appropriate ongoing rehabilitation program.

B) The Rehabilitation – Relapse Prevention Phase of Treatment

Patients and Treatment Settings - Rehabilitation is appropriate for patients who are no longer suffering from the acute physiological or emotional effects of recent substance use and who need behavioral change strategies to regain control of their urges to use substances. Rehabilitation may be initiated in a residential setting but sustained benefits require that it continue beyond that setting – since life in a controlled environment does not permit the patient to practice the skills necessary to prevent a relapse to substance use. Thus, most rehabilitation takes place in outpatient clinics or social settings. A practical goal of this stage of treatment is to prevent a return to active substance use that would require re-detoxification/stabilization; to assist the patient in developing control over urges to use alcohol or drugs, or both, usually

through sustaining total abstinence from all drugs and alcohol; and to assist the patient in regaining or attaining improved personal health and social function, both as a secondary part of the rehabilitation function and because these improvements in lifestyle are important for maintaining sustained control over substance use.

Treatment Elements and Methods - Professional opinions vary widely regarding the underlying reasons for the loss of control over alcohol and/or drug use typically seen in treated patients. For example, genetic predispositions, acquired metabolic abnormalities, learned, negative behavioral patterns, deeply ingrained feelings of low self-worth, self-medication of underlying psychiatric or physical medical problems, character flaws, and lack of family and community support for positive function have all been suggested as mechanisms. Thus, there is an equally wide range of treatment strategies and treatments that can be used to correct or ameliorate these underlying problems and to provide continuing support for the targeted patient changes.

Strategies have included such diverse elements as psychotropic medications to relieve “underlying psychiatric problems”; medications to relieve alcohol and drug cravings; acupuncture to correct acquired metabolic imbalances; educational seminars, films, and group sessions to correct false impressions about alcohol and drug use; group and individual counseling and therapy sessions to provide insight, guidance, and support for behavioral changes; and peer help groups (e.g., Alcoholics Anonymous [AA] and Narcotics Anonymous [NA]) to provide continued support for the behavioral changes thought to be important for sustaining improvement.

Duration - Typically, residential rehabilitation treatments range from 30 to 90 days; outpatient, abstinence-oriented forms of treatment range from 30 to 120 days; therapeutic community modalities typically range from 6 months to 1 year; and methadone maintenance can have an indefinite time period.

Many of the more intensive forms of outpatient treatment (intensive outpatient and day hospital) begin with full or half-day sessions five or more times per week for approximately 1 month. As the rehabilitation progresses, the intensity of the treatment reduces to shorter-

duration sessions of 1 to 2 hours delivered twice per week and tapering to once per week. The final part of outpatient treatment is typically called "continuing care" or "aftercare," with biweekly to monthly group support meetings continuing (in association with parallel activities in self-help groups) for as long as 2 years.

Maintenance Medications - Although the majority of rehabilitation treatment programs in the United States are abstinence-oriented, a significant number of rehabilitation programs maintain patients on a medication that is designed to block the effects of the abused drugs (e.g., acamprostate, disulfiram or naltrexone to block alcohol abuse), thus preventing the re-emergence of drug use. In the case of opiates and nicotine, many patients are "maintained" on a medication that is designed to override the effects of the abused drugs in what may seem a paradoxical way - through the development of greater physiological tolerance to the same class of drugs. While more tolerance is typically developed during the course of medication with these maintenance drugs, the tolerance is to a safer, more potent, and longer-acting medication from within the class of abused drugs. For example, nicotine patch provides significant doses of nicotine, elevating tolerance to nicotine but preventing withdrawal that abstinence would induce and obviating the need for cigarettes to provide the nicotine. In the same way, methadone, LAAM and buprenorphine produce more opioid tolerance in an opioid abuser – but again, no worries about withdrawal and no need for heroin.

Maintenance forms of treatment are always controversial since many in the public and even those in the treatment field believe that medications are just another form of "drug," and that all drug usage should be eliminated. However, if one takes a broader, medical perspective on this form of rehabilitative care, these medication maintenance approaches are quite similar to current strategies for ameliorating the physiological or emotional problems in individuals with other chronic medical conditions, such as long-term maintenance on antidepressant, antipsychotic, or other psychotropic medications for psychiatric patients; maintenance on beta-blockers and other normotensive agents for patients with hypertension; antiasthmatics for asthma sufferers; and insulin for diabetics. A substantial amount of research has shown that these medications can be very effective in the rehabilitation of several forms of addiction (144, 150, 151).

Defining Outcomes - All forms of rehabilitation oriented treatments for addiction have the same four goals, regardless of the specific setting, modality, philosophy, or methods of rehabilitation. These are to:

1. maintain the physiological and emotional improvements that were initiated during detoxification-stabilization phase, preventing need for re-detoxification,
2. enhance and sustain reductions in alcohol and drug use (most rehabilitation programs suggest a goal of complete abstinence),
3. teach, model and encourage behaviors that lead to improved personal health, improved social function, and reduced threats to public health and public safety, and
4. teach and motivate behavioral and lifestyle changes that are incompatible with substance abuse.

It is important to note the purposely broad perspective on measuring effectiveness as was discussed in Part 1. Specifically, for any form of substance abuse rehabilitation intervention to be worthwhile to society, **there must be lasting improvements in those problems that led to the treatment admission and that are important to the patient and to society.** This definition purposely emphasizes improvements that have an enduring or lasting quality (152 - 155). Because these disorders are chronic and relapsing, a "cure" for substance use disorders is not now achievable in most cases. Nonetheless, there are many illnesses that cannot be cured and yet there are "effective treatments" for these illnesses that arrest and contain symptoms and permit improved function. The definition also emphasizes those improvements that are important to society. For the many parts of society affected by substance abuse, the effectiveness of treatment will be measured by the extended effects of treatment on the addiction-related problems that have become public health and public safety concerns. Given this framework, it can be seen that achievement of the primary goal of reducing alcohol and drug use is necessary, but not always sufficient, to improve the addiction-related problems that are typically so prominent among individuals seeking treatment. Furthermore, without additional

improvements in these associated problems, addiction treatment may not be worthwhile either to the patient who undergoes it or to the society that supports it (152 - 155).

C) Effective Components in the Rehabilitation – Relapse Prevention Stage of Treatment

Using the above framework for defining outcome, we now summarize briefly, some of the many studies that have investigated treatment processes and treatment components in order to determine the “active ingredients” of the rehabilitation stage of treatment, and who appears to benefit most from these ingredients. Until only recently patient factors had been more thoroughly studied than treatment process factors with regard to their role in treatment outcome. With the development of new medications and behavioral interventions there are now many studies devoted to the exploration of treatment “ingredients” or elements and their role in post-treatment outcome. Below, we review several of the more prominent factors.

1) Medications - Great progress has been made over the past ten years in the development of new medications and in the application of existing medications for the treatment of particular conditions associated with substance dependence and for particular types of substance dependent patients. This progress has been summarized above in Part II.

2) Setting of Treatment - There have now been many studies investigating differences in outcome between various forms of inpatient and outpatient rehabilitation. For example, studies by McCrady et al. (156) and Alterman et al. (157) randomly assigned alcohol dependent patients to an equal length (28 - 30 days) of either inpatient or day-hospital rehabilitation, where the treatment elements were also designed to be similar. Both studies showed very similar findings. Patients in both the inpatient and outpatient arms of both these studies showed substantial and significant reductions in alcohol use, as well as improvements in many other areas of personal health and social function - suggesting that both settings of care were able to produce substantial benefits. At the same time, a wide range of outcome measures collected at six month follow-up in both studies, showed essentially no statistically significant or clinically important differences

between the two settings of care - suggesting that the setting of care might not be an important contributor to outcome.

Other reviews of the literature on inpatient and outpatient alcohol rehabilitation by Miller and Hester (158) and Holder et al., (159) also concluded that across a range of study designs and patient populations there are few significant advantages provided by inpatient care over outpatient care in the rehabilitation of alcohol dependence, despite the substantial difference in costs. In contrast, a widely cited study by Walsh et al. (160) did find a significant difference in outcome favoring an inpatient program. However, this difference was shown among employed alcohol dependent patients who were assigned to either an inpatient program plus Alcoholics Anonymous (AA) or to AA meetings only (rather than to formal outpatient treatment). One recent review of the alcohol inpatient-outpatient literature did conclude that in studies that found an advantage to inpatient care over outpatient treatment, outpatients did not receive inpatient detoxification and the studies tended to not have social stability inclusion criteria or to require randomization (161). This review points to the need to consider “real world” factors when evaluating the effectiveness of different treatment settings.

In the field of cocaine dependence treatment, there have also been several studies examining the role of treatment setting. Again, while there have typically been high attrition rates (e.g. 148), there is still evidence indicating that outpatient treatments for cocaine dependence can be effective, even for patients with relatively limited social resources. For example, Alterman and his colleagues followed up a prior comparison study of inpatient and day-hospital treatment of alcohol dependence (156) with an identical examination comparing the effectiveness of four weeks of intensive, highly structured day hospital treatment (27 hours weekly) with that of inpatient treatment (48 hours weekly) for cocaine dependence. The subjects were primarily inner city, male African Americans treated at a Veterans Administration Medical Center. The inpatient treatment completion rate of 89% was significantly higher than the day-hospital completion rate of 54%. However, at seven months post treatment entry self reported outcomes indicated considerable improvements for both groups in drug and alcohol use, family/social, legal, employment, and psychiatric problems. The finding of reduced self reported cocaine use was supported by urine screening results. Both self report and urine data indicated

50-60% abstinence for both groups at the follow-up assessment. The comparability of both treatment settings was also evident in 12 month outcomes in both randomized and self-selecting patients (162).

There have been at least two attempts to formalize clinical decision processes regarding who should, and should not be assigned to inpatient and outpatient settings of care (Cleveland Criteria; American Association of Addiction Medicine Criteria). McKay et al. (97) failed to show evidence for the predictive validity of the Cleveland placement criteria at least when applied to the assignment of alcohol and drug dependent patients to day hospital or inpatient care. That is, patients who met the Cleveland criteria for inpatient treatment did not have worse outcomes than those who met criteria for day hospital only when both groups received day hospital treatment. If the Cleveland Criteria had been valid, those who "needed inpatient treatment" but did not receive it should have had poorer outcomes than those who were appropriately "matched" to day hospital. In a similar study evaluating the psychosocial predictors from the American Association of Addiction Medicine (ASAM) criteria, McKay et al. (163) did find at least partial support for the predictive validity of these placement variables. That is, among patients who "needed inpatient treatment" as defined by the psychosocial elements of the ASAM criteria, those who were randomly assigned to outpatient care did show somewhat worse abstinence rates and generally poorer social outcomes than those who were randomly assigned to inpatient rehabilitation. The retrospective nature of this study made it impossible to complete a full evaluation of these criteria.

The most recent versions of the ASAM criteria have attempted to make very fine grained decisions regarding placements to levels of care defined by the amount and quality of medical supervision and monitoring. Research is needed to determine the predictive validity of these finer distinctions and whether placements to settings and modalities with "more medical supervision" actually receive more medical contact or services than placements that are not expected to receive such services.

3) Length of Treatment/Compliance with Treatment - Perhaps the most robust and pervasive indicator of favorable post treatment outcome in all forms of substance abuse rehabilitation has been length of stay in treatment. Virtually all studies of rehabilitation have

shown that patients who stay in treatment longer and/or attend more treatment sessions, have better post treatment outcomes (164 - 168). Specifically, several studies have suggested that outpatient treatments of less than 90 days are more likely to result in early return to drug use and generally poorer response than treatments of longer duration (164, 167, 168).

Though length of stay is a very robust, positive predictor of treatment outcome, the nature of this relationship is still ambiguous. Clearly, one possibility is that patients who enter treatment gradually acquire new motivation, skills, attitudes, knowledge, and supports over the course of their stay in treatment; that those who stay longer acquire more of these favorable attributes and qualities; and that the gradual acquisition of these qualities or services is the reason for the favorable outcomes. An equally plausible possibility is that "better motivated and better adjusted patients" come into treatment ready and able to change; that the decisions they made to "change their lives" were made in advance of their admission and because of this greater motivation and "treatment readiness" they are likely to stay longer in treatment and to do more of what is recommended. These two interpretations of the same facts have very different implications for treatment practice. If treatment gradually produces positive changes over time, it is obviously clinically sound practice to retain patients longer - perhaps even through coercion - and to provide them with more services during treatment. On the other hand, if well motivated, high functioning, compliant patients enter treatment with the requisite skills and supports necessary to do well, then efforts to provide more services or to coerce patients into longer stays may not add to the effectiveness of more streamlined and less expensive rehabilitation efforts.

4) Participation in AA/NA - AA is of course recognized as a self-help or mutual support organization and not a formal treatment. For this reason, and because of the anonymous quality of the group, much less research has been done to evaluate this important part of substance abuse rehabilitation (169, 170). While there has always been consensual agreement on the value of AA and other peer support forms of treatment, new evidence has emerged over the past five years showing that patients who have an AA sponsor, or who have participated in the fellowship activities - have much better abstinence records than patients who have received rehabilitation treatments but have not continued in AA. McKay and his colleagues (171) found that

participation in post treatment self-help groups predicted better outcome among a group of cocaine or alcohol dependent veterans in a day hospital rehabilitation program. Timko et al., (172) found that more AA attendance was associated with better 1-year outcomes among previously untreated problem drinkers regardless of whether they received inpatient, outpatient, or no other treatment. Finally, a recent review of the literature on the impact of self-help programs concluded that greater participation was generally associated with better alcohol and psychosocial outcomes, although the magnitude of the effects tended to vary as a function of the quality of the study and whether patients were treated in inpatient or outpatient settings (173).

There has been less research in the use of self-help organizations among cocaine and/or opiate dependent patients. However, a recent study of cocaine patients participating in outpatient counseling and psychotherapy showed that while only 34% attended a cocaine anonymous (CA) meeting, 55% of those who did become abstinent as compared with only 38% of those who did not attend CA.

It is difficult to sort out the extent to which AA attendance is an active ingredient of successful treatment and/or the extent to which it is simply a marker for general treatment compliance and commitment to abstinence. In this regard, several investigators have studied the relationship of completing various 12-step processes during the course of rehabilitation, to relapse following treatment. Morgenstern and colleagues reported that patients who adopted more of the attitudinal and behavioral tenets of the 12-step model of rehabilitation such as admission of powerlessness, acceptance of a higher power, commitment to AA, and agreement that alcoholism is a disease, were no more (or less) likely to relapse following treatment than patients who had adopted very few of the 12-step tenets by the end of the rehabilitation treatment (174). At the same time, two general tenets found in all rehabilitation models-- greater commitment to abstinence and greater intention to avoid high risk situations-- did predict a lower likelihood of relapse (174). In another analysis from the same study, greater affiliation with AA following treatment predicted better outcomes. AA affiliation was in turn positively associated with self-efficacy, motivation, and coping efforts, which were themselves significant predictors of outcome (174). Thus, more research in this area is warranted to determine how participation in AA exerts its positive effects.

5) The therapist or counselor - Research also suggests that having access to regular drug/alcohol counseling can make an important contribution to the engagement and participation of the patient in treatment and to the post treatment outcome. One example of the role of the counselor and of individual counseling was shown in a study of methadone maintained patients, all within the same treatment program and all receiving the same methadone dose, who were randomly assigned to receive counseling or no counseling in addition to the methadone (175). Results showed that 68% of patients assigned to the no counseling condition failed to reduce drug use (confirmed by urinalysis) and 34% of these patients required at least one episode of emergency medical care. In contrast, no patient in the counseling groups required emergency medical care, 63% showed sustained elimination of opiate use and 41% showed sustained elimination of cocaine use over the six months of the trial.

A study by Fiorentine (176) as part of a larger "Target Cities" evaluation also showed the contribution of counseling in drug rehabilitation. Group counseling was the most common modality (averaging 9.5 sessions per month) followed by 12-step meetings (average 7.5 times per month) and individual counseling (average 4.7 times per month). Greater frequency of both group and individual counseling sessions were shown to decrease the likelihood of relapse over the subsequent six months. One important contribution of this study, given the above cautions regarding the role of simple length of stay in determining treatment outcome (See above), is that the relationships shown between more counseling and lower likelihood of relapse to cocaine use were seen even among patients who completed treatment - that is, having approximately the same tenure in the programs. Thus, it may be that beyond the simple effects of attending a program, more involvement with the counseling activities is important for improved outcome.

At least four studies of substance abuse treatment have documented between-therapist differences in patient outcomes. These differences have emerged both among professional psychotherapists with doctoral level training and among paraprofessional counselors. Luborsky et al. (177) found outcome differences in a variety of areas among nine professional therapists providing ancillary psychotherapy to methadone maintenance patients. McLellan et al. (178) found that assignment to one of five methadone maintenance counselors resulted in significant differences in treatment progress over the following six months. Specifically, patients

transferred to one counselor achieved significant reductions in illicit drug use, unemployment, and arrests while concurrently reducing their average methadone dose. In contrast, patients transferred to another counselor evidenced increased unemployment and illicit drug use while their average methadone dose went up. In a study of two different interventions for problem drinkers, Miller, Taylor, and West (179) found significant differences between paraprofessional therapists in the percentage of their patients who improved by six month follow-up. These percentages varied from 25% for the least effective therapist to 100% for the most effective therapist. Finally, McCaul et al. (180) reported significant differences in post treatment drinking rates and several other outcomes among alcohol dependent patients assigned to different individual counselors within an alcohol treatment program.

There is much research that needs to be done in this area. Although it is relatively clear that therapists and counselors differ considerably in the extent to which they are able to help their patients achieve positive outcomes, it is less clear what distinguishes more effective from less effective therapists. In an experimental study of two different therapist styles, Miller, Benefield, and Tonigan (181) found that a client centered approach emphasizing reflective listening was more effective for problem drinkers than a directive, confrontational approach. In a review of the literature on therapist differences in substance abuse treatment, Najavits and Weiss (182) concluded, “The only consistent finding has been that therapists’ in-session interpersonal functioning is positively associated with greater effectiveness” (p. 683). Among indicators of interpersonal functioning were the ability to form a helping alliance (177), measures of the level of accurate empathy and a measure of “genuineness,” “concreteness” and “respect” (183).

It should be noted that there are a variety of certification programs for counselors (Committee on Addiction Rehabilitation (CARF) and Certified Addictions Counselor (CAC)) as well as other professions treating substance dependent patients (American Society of Addiction Medicine; American Academy of Psychiatrists in Addiction; recent added certification for psychologists through the American Psychological Association). These “added qualification certificates” are offered throughout the country, usually by professional organizations. Although the efforts of these professional organizations to bring needed training and proficiency to the treatment of addicted persons are commendable, we were unable to find any studies validating

whether patients treated by "certified" addictions counselors, physicians or psychologists have better outcomes than patients treated by non-certified individuals. This is an important gap in the existing literature and results from such studies would be quite important for the licensing efforts and health policy decisions of many states and health care organizations.

6) Community Reinforcement and Contingency Contracting - Azrin and colleagues initially developed the "Community Reinforcement Approach" (CRA) and tested it against other "standard" treatment interventions (184). CRA includes conjoint therapy, job finding training, counseling focused on alcohol-free social and recreational activities, monitored disulfiram, and an alcohol-free social club. The goal of CRA is to make abstinence more rewarding than continued use (185). In a study in which patients were randomly assigned to CRA or to a standard hospital treatment program, those getting CRA drank less, spent fewer days away from home, worked more days, and were institutionalized less over a 24 month follow-up(184).

A more recent set of studies by Higgins et al. (186 - 189) has used the CRA approach with cocaine dependent patients. Here, cocaine dependent patients seeking outpatient treatment were randomly assigned to receive either standard drug counseling and referral to AA, or a multi-component behavioral treatment integrating contingency managed counseling, community based incentives and family therapy comparable to the CRA model (189). The CRA model retained more patients in treatment, produced more abstinent patients and longer periods of abstinence, and produced greater improvements in personal function than the standard counseling approach. Following the overall findings, this group of investigators systematically "disassembled" the CRA model and examined the individual "ingredients" of family therapy (188), incentives (Higgins et al., 1994), and the contingency based counseling (186) as compared against groups who received comparable amounts of all components except the target ingredient. In each case, these systematic and controlled examinations indicated that these individual components made a significant contribution to the outcomes observed, thus proving their added value in the rehabilitation effort.

7) "Matching" Patients and Treatments – There have been a great number of research studies attempting to "match" particular "kinds" of patients with specific types, modalities or settings of treatment. The approach to patient-treatment "matching" that has received the

greatest attention from substance abuse treatment researchers involves attempting to identify the characteristics of individual patients that predict the best response to different forms of addiction treatments (e.g., cognitive-behavioral vs. 12-Step, or inpatient vs. outpatient) (169). In general, the majority of these "patient - to - treatment" matching studies have not shown robust or generalizable findings (See 190). Another approach to matching has been to assess patients' problem severity in a range of areas at intake and then "match" the specific and necessary services to the particular problems presented at the assessment. This has been called "problem - to - service" matching (191). This approach may have more practical application as it is consonant with the "individually tailored treatment" philosophy that has been espoused by most practitioners.

Substance abusers with comorbid psychiatric problems may be particularly good candidates for the "problem - to - service" matching approach; especially the addition of specialized psychiatric services for those most severely affected by psychiatric problems. For example, recent studies suggest that tricyclic antidepressants and the selective serotonergic medication fluoxetine may reduce both drinking and depression levels in alcoholics with major depression (192 - 194). Similarly, the anxiolytic buspirone may reduce drinking in alcoholics with a comorbid anxiety disorder (195). Highly structured relapse prevention interventions may also be more effective in decreasing cocaine use, as compared to less structured interventions, in cocaine abusers with comorbid depression (196).

Woody and colleagues have evaluated the value of individual psychotherapy when added to paraprofessional counseling services in the course of methadone maintenance treatment (197). In that study patients were randomly assigned to receive standard drug counseling alone (DC group) or drug counseling plus one of two forms of professional therapy: supportive-expressive psychotherapy (SE) or cognitive-behavioral psychotherapy (CB) over a six month period. Results showed that patients receiving psychotherapy showed greater reductions in drug use, more improvements in health and personal function and greater reductions in crime than those receiving counseling alone. Stratification of patients according to their levels of psychiatric symptoms at intake showed that the main psychotherapy effect was seen in those with greater than average levels of psychiatric symptoms. Specifically, patients with low symptom levels

made considerable gains with counseling alone and there were no differences between types of treatment. However, patients with more severe psychiatric problems showed few gains with counseling alone but substantial improvements with the addition of the professional psychotherapy.

Another type of substance abuser that can pose particular problems for outpatient treatment is the cocaine dependent patient who is unable to achieve remission from cocaine dependence early in outpatient treatment. Several randomized studies suggest that highly structured cognitive-behavioral treatment is particularly efficacious with such individuals. In two outpatient studies with cocaine abusers, those with more severe cocaine problems at intake had significantly better cocaine use outcomes if they received structured relapse prevention rather than interpersonal or clinical management treatments (Carroll et al., 104, 149). In a third study, cocaine dependent patients who continued to use cocaine during a four-week intensive outpatient treatment program (IOP) had much better cocaine use outcomes if they subsequently received aftercare that included a combination of group therapy and a structured relapse prevention protocol delivered through individual sessions rather than aftercare that consisted of group therapy alone (171).

McLellan and colleagues recently attempted to match “problems to services” in two inpatient and two outpatient private treatment programs (191). Patients in the study (N=130) were assessed with the ASI at intake and placed in a program that was acceptable to both the EAP referral source and the patient. At intake, patients were also randomized to either the standard or “matched” services conditions. In the standard condition, the treatment program received information from the intake ASI, and personnel were instructed to treat the patient in the “standard manner, as though there were no evaluation study ongoing.” The programs were instructed to not withhold any services from patients in the standard condition. Patients who were randomly assigned to the matched services condition were also placed in one of the four treatment programs and ASI information was forwarded to that program. However, the programs agreed to provide at least three individual sessions in the areas of employment, family/social relations, or psychiatric health delivered by a professionally trained staff person. In fact, matched patients received significantly more psychiatric and employment services than

standard patients, but not more family/social services or alcohol and drug services. Second, matched patients were more likely to complete treatment (93% vs. 81%), and showed more improvement in the areas of employment and psychiatric functioning than the standard patients. Third, while matched and standard patients had sizable and equivalent improvements on most measures of alcohol and drug use, matched patients were less likely to be retreated for substance abuse problems during the six month follow-up. These findings suggest that matching treatment services to adjunctive problems can improve outcomes in key areas and may also be cost-effective by reducing the need for subsequent treatment due to relapse.

Summary of Part III

In Part III of this paper we briefly reviewed the substance abuse treatment research literature to identify treatment process variables and treatment components that have been shown to be important in determining outcome from addiction rehabilitation efforts; and in this way to contribute to the discussion of what aspects of treatment are “worth it” to society. The major treatment variables or components are summarized in Table 5 below

Components of Effective Treatment

Treatment variables:

- Staying longer in treatment
- Reinforcement (financial incentives or vouchers) for attendance and abstinence
- Having an individual counselor or therapist;
- Specialized services for psychiatric, employment and family problems;
- Medications to:
 - Block drug craving and drug effects
 - Reduce psychiatric symptoms
- Participating in AA or NA following rehabilitation

In light of these findings, it was surprising that some of the treatment elements that are most widely provided in substance abuse treatment have not been associated with better outcome. For example, our review of the literature has shown little indication that any of the following lead to better or longer lasting outcomes following treatment:

- a) alcohol/drug education sessions
- b) general group therapy sessions - especially "confrontation" sessions
- c) acupuncture sessions
- d) patient relaxation techniques
- e) treatment program accreditation or professional certification criteria.

Holder and Miller (159) have also reviewed the available research on effectiveness of various treatment components in the alcohol rehabilitation field. These researchers also concluded that there are a number of therapeutic practices and procedures that remain prevalent in the field that have not yet shown indication of success.

In this regard it is important to note that "the absence of evidence" does not prove a treatment element is ineffective. Some of the treatment practices or conventions cited may actually have benefits for some patients or under some circumstances but we have found little support for these in the existing literature.

Part IV

WHY AREN'T ADDICTION TREATMENTS CONSIDERED AS EFFECTIVE AS TREATMENTS FOR OTHER ILLNESSES?

Implications for the Delivery and Evaluation of Addiction Treatment

In the previous parts of this paper we have examined the addiction treatment field from the perspective of its value to society. It would seem that our review would provide a relatively simple answer to what appears to be a direct question of cost and value. Yet it is not a direct question at all. We have tried to show that the reasonable expectations of a society regarding any form of intervention designed to “take care of the drug problem” must address many different issues all typically related to the “addiction related” problems that are so frightening and costly to society. Multiple perspectives on outcome are not typical in evaluations of medical illnesses. In the treatment of most chronic illnesses “effective” treatments are expected to reduce symptoms, increase function and prevent relapse – especially costly relapse. Thus, as a final perspective on the issue of the effectiveness and worth of addiction treatments, we now consider an evaluation of the effectiveness of addiction treatments using the criteria typical for evaluations of other chronic illnesses.

A Chronic Illness/Continuing Care Perspective: Implications for Treatment and Evaluation

There are no "cures" for any of the chronic medical illnesses reviewed here. Yet it is interesting that despite rather comparable rates of compliance and relapse across all of the disorders examined, there is no serious argument as to whether the treatments for diabetes, hypertension or asthma are "effective" or whether they should be supported by contemporary health insurance. However, this issue is very much in question with regard to treatments for drug dependence (see 7, 12). In this regard, it is interesting that the relatively high relapse rates among diabetic, hypertensive and asthmatic patients following cessation of their medications have been considered evidence of the effectiveness of those medications and of the need for compliance enhancement strategies. In contrast, relapses to drug and alcohol use following cessation of addiction treatments has often been considered evidence of treatment failure.

One major difference is that drug dependence treatments are not provided, evaluated or insured under the same assumptions that pertain to other chronic illnesses. Particularly important in this regard is that drug dependence treatments are rarely delivered under a continuing care model that would be appropriate for a chronic illness. Indeed, with the exception of methadone maintenance and AA/NA forms of treatment (parenthetically, among the most effective forms of treatment currently available) most contemporary treatments for drug dependence are acute care episodes. For example, it is common for a drug dependent individual to be admitted to a 30 to 90 day outpatient rehabilitation program, rarely accompanied by medical monitoring or medication. This period of treatment is typically followed by discharge with referral to "community sources." While the intentions and overall goals of addiction treatment might be conceptualized as ongoing by those in the treatment field, operationally addiction treatments are delivered in much the same way as one might treat a surgical patient following a joint replacement. Outcome evaluations are typically conducted six to twelve months following treatment discharge. A major (sometimes the exclusive) measure in all these evaluations is whether the patients had been continuously abstinent since leaving treatment.

Consider these goals and this treatment/evaluation strategy applied to a hypertension treatment regimen. Patients who meet diagnostic criteria for hypertension would be admitted to a 30 - 90 day outpatient "hypertension rehabilitation" program where they might receive medication, behavioral change therapy, dietary education, and an exercise regimen. Because of insurance limits and evaluation goals, the medication would be tapered during the last days of the treatment and the patients would be referred to community sources. The evaluation team would re-contact the patient six months later and determine whether the patient had been continuously normotensive throughout that post treatment period. Only those patients that met this criterion would be considered "successfully treated." Obviously, this hypothetical treatment management strategy and its associated outcome evaluation approach are absurd for any chronic illness - including drug dependence.

CONCLUSIONS

Although science has made great progress over the past several years, we cannot yet fully account for the physiological and psychological processes that transform controlled, voluntary "use"

of alcohol and/or other drugs into uncontrolled, involuntary “dependence” on these substances – and we cannot cure this condition once it has been contracted. But can we treat it “effectively” and would a societal investment in treatment provide an attractive return on the investment? The research reviewed here suggests the answer is clearly yes to both parts of the question. Both controlled clinical trials and large-scale field studies have shown statistically and clinically significant improvements in drug use and in the drug-related health and social problems, of treated individuals. Further, these improvements translate into substantial reductions in social problems and costs to society. Recent pharmaceutical research has produced effective medications for the treatment of alcohol, nicotine and opiate dependence, and has identified promising candidate medications that will provide even more assistance to physicians in treating these illnesses. Thus, we conclude that drug and alcohol dependence are treatable medical illnesses.

If this conclusion is true, then why does it seem so surprising to so many parts of society. The thesis of this paper is that there are two main reasons for this.

Addiction is a *Chronic Condition* – Much of society has the view that addiction to drugs or alcohol is simply the product of poor impulse control complicated by the physiological problems associated with dependence and withdrawal. This assumption leads to a view that these acquired habits and withdrawal symptoms ought to be correctable with some education, some severe consequences associated with use (to teach the user a lesson) and some period of brief stabilization to “get the drugs out of their system.” Our research is quite clear on these points, Education does not correct drug dependence – it is not simply a problem of lack of knowledge. Consequences for drug use appear to be important stimuli leading to drug abuse treatment entry. Indeed, over half of all treatment entrants in the United States are under some form of coercion (198). At the same time, very few addicted individuals are able to profit from a corrections-oriented approach by itself. Relapse rates are over 70% to all forms of criminal justice interventions. Finally, addiction is not simply a matter of becoming stabilized and getting the drugs out of one’s system. Relapse rates following detoxifications are approximately the same as those following incarceration (86, 94, 123, 153,199).

The evidence is compelling that, at the present state of medical knowledge, addiction is best considered as a chronic relapsing condition. I have chosen the word “condition” for those who do

not wish to call it an illness. It does not matter. Once considered a chronic condition it is no longer surprising that incarcerations, or brief stabilizations would not be effective. The research evidence is clear that for those with alcohol, cocaine, opiate or other drug dependence the best available treatments are those that are ongoing, able to address the multiple problems that are risks for relapse – such as medical and psychiatric symptoms and social instability - and are well integrated into society, thereby permitting ready access for monitoring purposes and to forestall relapse. Importantly, the research has shown that while motivation for treatment plays an important role in maintaining treatment participation – most substance abusing patients enter treatment with combinations of internal motivation and family, employment or legal pressure. These pressures can be combined with treatment interventions for the benefit of the patient and society.

Addiction Treatments Must Address the Concerns of Society While we have compared addiction to other chronic illnesses, there are many differences. One of the most prominent differences is the breadth of treatment focus. The major foci of most treatments for other chronic illnesses are symptom remission and return of function for the benefit of the patient. This has also been true for many addiction treatments – and it has left much of society with the view that the major goal of addiction treatment is to simply make the patient feel better – not something those who have suffered from the crime, lost productivity and embarrassment of addiction are eager to do. Our perspective is that addiction treatment providers must broaden their views of their responsibilities. To achieve the potential social value of addiction treatment it will be necessary for providers to focus on such socially important goals as:

- working with employers and social welfare agencies toward the goals of returning to – or initiating work
- working with criminal justice agencies and parole/probation officers toward the goals of keeping the patient from returning to drug-related crime and incarceration
- working with family agencies and the families themselves toward the goals of returning to – or initiating responsible parenting

These are the addiction-related conditions that most affect society. Reduction or elimination of these problems are the goals that society expects from any “effective” intervention. Our review has shown that addiction treatments can (but do not always) show evidence of being able to meet these societal expectations of effectiveness. With application of the treatment elements that have been shown to be effective under a continuing care model of treatment, our review suggests that addiction treatment can be an effective and valuable part of a social policy on drug abuse problems.

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