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STIMULANT ABUSE AND DEPENDENCE

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A review of the Central Nervous System (CNS) stimulants is timely given the recent, perhaps epidemic, surge of stimulant use in Asia among workers, reflected in the greater number of arrests, drug seizures and treatment entries in several Asian countries.[1] So far, prevalent use has been described among truck drivers, fishermen, farmers and construction workers in several Southeast Asian countries. The smoking of "shabu" (methamphetamine) in the Philippines outranks cannabis in popularity there, and accounts for more than 60% of the drug treatment admissions.[1a] Preparations abused range from clandestinely manufactured amphetamine "look-alike" tablets containing ephedrine and caffeine[2] to the pharmaceutical preparations of amphetamine and methamphetamine,[2] and even some use of cocaine and MDMA, popularly known as "Ecstasy" (an hallucinogenic derived from amphetamine), has been reported among the wealthy youth of some large Asian cities.

This report will review the epidemiology, patterns of use, pharmacological effects and neuropharmacological components of the abuse and dependence upon cocaine and amphetamine and amphetamine-related stimulants (e.g., methylphenidate, phenmetrazine) and will discuss the current treatments available for stimulant dependence.

EPIDEMICS OF STIMULANT ABUSE

Stimulant drugs have been compelling to human beings for centuries. Long before the amphetamines were introduced into Western medicine in 1936, Indians in the Andes mountains were chewing the leaves of the coca shrub, and in China, Ma-huang, the active ingredient of which is ephedrine, was being used. Currently, nearly 9 million kilograms of coca leaves are consumed annually by about 2 million of the inhabitants of the highlands of Peru.[4] The amount of ephedrine used in China is unknown, but much is supplied to other nations, and some finds its way to clandestine laboratories and is used to synthesize illicit amphetamine and methamphetamine.[3b]

The history of stimulant use by Western medicine begins with Sigmund Freud, who in the early 1880's obtained some cocaine from Merck to study its effects. Although narrowly

missing fame for the discovery of its local anesthetic properties, Freud became an advocate of its stimulant properties,[5] used it himself for a few years and tried it on others. When, by 1887, it became clear to Freud that individuals could become addicted to cocaine, he withdrew his earlier recommendations for its use in morphine withdrawal, wrote about the cocaine toxic psychosis, and implicated the use of hypodermic injection (then used subcutaneously) as a causative factor in the addiction. Some physicians accused Freud of unleashing "the third scourge of humanity," the other two being alcohol and morphine.[6]

Alles in Los Angeles synthesized amphetamine in 1927 and methamphetamine in 1929, while searching for a substitute for ephedrine, which was then difficult to obtain. As a result of his work, an amphetamine sulfate inhaler was introduced in 1931, and oral medication followed in 1935. Early reports recounted the dangers of addiction to these compounds.[4]

In the West, in the 1960's and 70's, historical descriptions of cocaine dependence were dismissed as moralistic and exaggerations, and in the 1970's and early 1980's, an epidemic of cocaine use and abuse exploded in the United States (U.S.) leading to widespread social concern and calls for treatment and research. By 1986, the National Institute on Drug Abuse estimated that 3 million people there abused cocaine regularly, more than five times the number addicted to heroin.[6a] Between 1976 and 1986 there were increases of more than 15 fold in emergency room visits attributed to cocaine abuse, cocaine-related deaths, and admissions to public treatment programs for cocaine. By 1986, almost 15% of the U.S. population had tried cocaine, with nearly 40% in the age range of 25 - 30 years.[6a] By 1990, prevalence of cocaine use had decreased dramatically, attesting to the epidemic surge and decline[7] influenced in part by widespread public education.

But stimulant epidemics in the West had occurred before. In the 1890's, cocaine use in Europe and the U.S. surged and was temporarily considered safe; it abated as severe problems of abuse became well known. This pattern was repeated in the U.S. and Europe in the 1920's. And in the early 1950's and 1960's, the same cycle occurred in the U.S., but with other stimulants: amphetamine and methamphetamine.[6a,6b,147] Increasing controls on amphetamines resulted in clandestine manufacture of methamphetamines in the U.S. in the 1970's.[147] Again, in the mid 1980's methamphetamine abuse indicators increased dramatically in metropolitan areas in California and Seattle, Washington.[147] Reports in 1990 of increasing methamphetamine abuse in California[164] and Hawaii[165] signaled an increase in use there and described an alternate method of administration, new to the U. S.: smoking and inhaling the vapors of methamphetamine HCl, marketed as "ice." A 1996 study documented a surge after 1992 in amphetamine-related consultation/liaison workups at the University of California, San Diego, Medical Center, reflecting an epidemic surge in use in the wider community.[147] Suicide attempts and trauma and burn cases were overrepresented.[147]

Epidemics of drug abuse reenact a cyclical pattern that involves rediscovery of old knowledge.[7,11] Population groups forget lessons about stimulants painfully learned by their ancestors and ignore lessons of history and historical research writings on the drugs. Thus, a country or a continent is ripe for an epidemic of use. It is probable that cultural change and social stress are relevant prior variables or, at least, drug use taps such forces and factors as well as generating consequences. As memories fade and the epidemic subsides, cultural resistance to a drug is reduced, and the society becomes susceptible to epidemic resurgence. The transient illusion of safety has repeatedly enabled serious clinicians and scientists to forget history. Thus, Gawin and Ellinwood were able to write in the *New England Journal of Medicine* in 1988, "We thus find ourselves in the fifth, and largest epidemic of stimulant abuse," referring to the current cocaine epidemic in the U.S. now in its 15th year.[8]

Ephedrine, which occurs naturally in various plants, was used in China (as Ma-huang) for at least 5000 years before being introduced into Western medicine in 1924.[8a] Accounts of epidemics of stimulant abuse in China have not appeared in Western literature. Ephedrine's central actions are less pronounced than the manufactured amphetamine derived from it. And yet, ephedrine, caffeine and phenylpropanolamine which themselves may be abused, but have lower abuse potential, often appear as stimulants in over-the-counter preparations sold in the East and the West, and are often used as adulterants in illicitly manufactured "pep or energy pills." Their effects and toxicity are reviewed elsewhere.[3]

Epidemics of amphetamine abuse in the East and the West occurred after their use on both sides during World War II. During that war, the German, Japanese and Allied forces distributed amphetamines to increase the "war effort." Bell and Trethowan noted that "more than 72 million energy tablets were supplied to service personnel in Great Britain and much the same quantity to the United States armed forces."[8b] The British noted increasing oral amphetamine dependence after the war,[6b,6c] the Swedish experienced an epidemic of phenmetrazine abuse;[9] and in the U.S., several stimulant epidemics occurred.[6a,6b,10,10a,10c,10d,10e,10f] Amphetamines were available in Japan on a non-prescription basis, and by 1954, when controls were placed on the drug there, there were estimated to be more than 200,000 amphetamine addicts in Japan.[10b] Most of these individuals were abusing methamphetamine intravenously, but in a low-dose maintenance pattern (described below). Another methamphetamine epidemic in Japan occurred in the 1970 - 1985 period.[166]

A brief discussion of the post-war epidemic[10,11,12,13,13a] is instructive. After World War II, the Japanese war defeat led to widespread disaffection with traditional roles, customs and social controls centering on the family. Disillusionment and a multitude of Japanese teenagers discovering Western ways contributed to the problem. Gangs purchased large quantities of American and Japanese amphetamines (used by soldiers of both sides during the war and a standard part of survival kits) which were both plentiful and cheap and marketed them. Postwar Japanese manufacturers probably diverted large supplies through these channels. Soldiers and students, followed shortly by night workers,

prostitutes and delinquents in the entertainment areas, used it orally and intravenously. Although there was drunkenness, opioids and marijuana were rarely used, but amphetamine was particularly suited to the Japanese achievement-oriented society. Delinquency, particularly crimes of violence, increased sharply concurrently with the amphetamine epidemic, but subsequent studies and events "showed that although delinquency and drugs were linked, delinquency rates followed an independent course, even after the amphetamine epidemic was over."[12] Amphetamine psychosis became prevalent, and by 1954, when controls were placed on the drug, it was estimated that 1% of the population of Japan and 5% of the 15 - 25 age group were addicts.[13] Perhaps because Japan was then a more authoritarian society, still emphasizing family reverence, "they were able to stem this epidemic (and an incipient heroin problem during the early 1960's) by mobilizing a broadly based social response centered on effective use of the criminal law and an education effort based in large measure on nation pride."[14] The broad discretionary powers of the Japanese police, prosecuting attorneys, and judges resulted in many compulsory hospitalizations. Legislation aimed at the sources of supply, the ability of police to work in the community, the expanding economy, increased employment, and social attitudes and cultural support inimical to drug abuse, all played a significant role in eliminating the problem.[7]

STRUCTURE-ACTIVITY RELATIONSHIPS

Amphetamines and cocaine are Central Nervous System (CNS) psychomotor stimulants which are sympathomimetic amines. Cocaine is an ester of benzoic acid. Amphetamine is beta-phenylisopropylamine. The basic skeleton of amphetamine is a phenylisopropylamine arrangement crucial to its pharmacological properties. Any type of substitution on the phenyl ring, or lengthening the number of carbons between the phenyl ring and the nitrogen, will abolish or radically alter the nature of its CNS effects.[14a]

The phenylisopropylamines can somewhat arbitrarily be divided into those compounds with substituents on the ethylamine portion, which act as CNS stimulants (and often are used as anorexics) and those with methoxyl substituents on the phenyl ring, which are largely hallucinogens or psychedelics (e.g., mescaline). Methoxyl groups drastically alter the spectrum of activity. The addition of methoxyl groups on the phenyl ring greatly enhance psychotogenic/hallucinogenic propensity of amphetamine, render the molecule psychotomimetic, and largely abolish the effects on norepinephrine.[14a,14b,14c,14d]

Some amphetamine congeners have little potential for reinforcement (thus, for abuser dependence), including fenfluramine (Pondimin), a depressant; phenylpropanolamine; mazindol (Mazanor, Sanorex), a reuptake inhibitor; diethylpropion (Tenuate), less severe CNS and CV effects; pemoline (Cylert) with fewer sympathomimetic effects.[4] All are used medically as anorexics or for Attention Deficit Hyperactivity Disorder (ADHD) in children and adults.

The cathinone-related agents, structurally related to amphetamine are the active ingredients in fresh leaves of the khat shrub (Catha edulis), chewed for its stimulant properties in some Middle Eastern countries.[14c,14d] On the other hand, the Kratom plant (Mitragyna speciosa), chewed by workers in Thailand and Malaysia for its alleged "stimulant effects," and used as a remedy for diarrhea and opium craving, appears primarily to be an analgesic/antitussive, not antagonized by nalorphine, and not related to any known analgesic.[15] The only study (of mitragynine) on antifatigue effects was done in 1932. Although the leaf contains over 40 indole alkaloids and flavonoids, only mitragynine has been studied recently (1972). In the South Seas, it is added to lime and betel and chewed as a betel quid.[15]

CLINICAL CHARACTERISTICS OF STIMULANT ABUSE AND DEPENDENCE

Patterns of Use

Stimulant users begin by experimenting with drugs obtained by prescription, from friends, or through illicit means. Teenagers usually try it out of "curiosity" or seeking "kicks and thrills" or because of peer pressure, attracted to the euphoric feeling and sense of increased pleasure.[7] Adults more often experiment with stimulants for "circumstantial" reasons, for example: to study for an exam; to reduce fatigue in time-limited exertions, for example among construction workers, over-tired businessmen, military personnel on extended missions, and long-distance truck drivers; for weight reduction; and to eliminate fatigue or boredom, e.g. housewives, fishermen. An experimental or circumstantial pattern of use[14] consists of low oral doses for very limited time periods. This pattern is usually benign, although untoward effects involving bad judgment or impaired discrimination and post-stimulant depression can occur.

By far the greatest hazard is the propensity by a so far unknown number of people to escalate their use of stimulants by increasing the dose or the duration of consumption, by using stimulants in a wider variety of situations, and by the use of other drugs to treat the side-effects of stimulant abuse.[6b,8,16] Most experimental users of stimulants, however, do not progress to dependence, yet some will begin to use regularly in a low-dose maintenance pattern of abuse or dependence,[6b,128] characterized by sustained use, orally, intranasally, by smoking, or, quite rarely, intravenously (as in the case of the post-war Japanese epidemic). Use is daily, initially in the therapeutic range, but gradually dosage increases as tolerance develops. Toxic effects, particularly violence and paranoid stimulant psychosis, are common at higher dosages.

Finally, some users graduate to a high dose cyclical pattern[6b,8,10c,10e,128] of binges and "crashes" and often (but not always) use is intravenous, or in the case of cocaine, it may be smoked in its freebase form ("crack" is freebase cocaine prepared with sodium bicarbonate which crackles when heated and smoked).[95] Whether smokers of

methamphetamine ("Shabu" in the Philippines) evolve into a high-dose cyclical pattern is unstudied. This pattern provides users with a profoundly reinforcing and dramatic experience, called a "rush" or "flash" by intravenous users, which is dose-dependent[17] and which the brain equates with drive states such as hunger, thirst, and sex. This results in a degree of dependence which is more severe and refractory than with low-dose maintenance use. Blood levels achieved are extremely high, toxic effects are rapid and severe, and withdrawal effects equally profound, resulting in short "runs" of use, of hours to a few days, punctuated by severe toxicity. Normal social functioning is impossible, and high-dose abusers display severely disturbed behavior, violence, psychosis, and a severe degree of dependence. There are cycles of unproductive, frenzied activity, stereotypy and psychosis alternating with exhaustion, extended sleep, and a period of dysphoric lethargy, despondency, and sometimes despair thereafter.[8,8b,10e,151] Abusers often administer other drugs, for example, sedatives, alcohol, marijuana or heroin, to combat the toxicity. The abuser stops use and "crashes" when supplies are exhausted or toxic effects become too great, but then after several hours to a few days, the withdrawal and abstinence syndrome begin (see below), characterized predominantly by craving, prompting resumption of high-dose use.

Who graduates to the high-dose cyclical pattern of use? Individuals with genetic predispositions to chemical dependence and individuals with pre-existing severe characterologic disorders (e.g., antisocial or borderline personality disorder) are prime candidates. Other Axis I (DMS-IV) major psychiatric disorders may predispose. Drug abuse fads and peer pressure may tempt some low-dose users to begin to try other routes of administration, different compounds (cocaine or MDMA), or higher doses. Thus, progressing from using the drug orally or intranasally to intravenous stimulant abuse or to cocaine freebase smoking[95] is generally sufficient to induce (and almost guarantees) a high-dose cyclical pattern of use. Demographic variables, intelligence or education/social position confer no resistance.

Given the parameters that define drug abuse susceptibility, the degree of stimulant exposure may be the most important determinant of progression, since large doses and rapid routes of administration result in high plasma concentrations, producing euphoria and reward so extreme that it is often compared to orgasm. Stimulant euphoria becomes an acquired drive state,[160] which once experienced, shifts the pattern of use toward high-dose binges, and since there is such a rapid decline in the effects of the rush, there is a compelling desire to recreate the experience by readministering the stimulant. Thus, *stimulant use drives its own use*, and the pulses of euphoria create vivid long-term memories, which become a source of subsequent craving for stimulants.[8, 148]

Abusers can often abstain temporarily until such memories are evoked (generally by conditioned cues), and after several days of abstinence, abusers resume use. *Thus, absence of daily use in a stimulant user may not indicate moderate use. If binge use is present, it generally indicates severe abuse and dependence.* This is in marked contrast to the necessity for daily use in alcohol or opioid-dependent individuals and must be appreciated to understand patterns of stimulant dependence.

Animal models are instructive.[8,18,19,20,21,22] Compulsive, rapidly escalating self-administration of stimulants occurs in all animals given unlimited access to these agents; death follows within 14 days, usually from cardiopulmonary collapse.[23-25] If access to stimulants is limited, animals can be kept alive and healthy, but they adjust their self-administration to maximize the effect of the stimulant; monkeys will press a lever thousands of times for a single dose of stimulant and will do 2 - 16 times more work to receive an injection of cocaine than for the closely related drugs methamphetamine and amphetamine. Monkeys will choose cocaine over any other drug, over food and over the opportunity to socialize with another monkey. Thus, sex, nourishment, sleep, safety, survival, money, morality, loved ones and responsibility become immaterial.[8] In rats, the fatality rate associated with continuous cocaine self-administration is 90%, in contrast to a 36% rate with heroin. Animals allowed to self-administer stimulants display a dramatic schedule of bursts of administration indicating a loss of control.[148] Monkeys will choose cocaine, even though they receive an electric shock; thus punishment (and presumably adverse effects) is not an effective deterrent. In similar self-administration experiments, monkeys are allowed to become addicted to a drug. The supply is then turned off and the number of lever presses are counted before the monkey gives up in an effort to estimate the addictive liability of the drug and the amount of work he will exert to receive it. On the average, monkeys will press the lever approximately 50 times before they will give up after the supply of barbiturate is turned off, 500 times after the supply of heroin is turned off, but they will press the lever approximately 12,000 times in an attempt to receive more cocaine. Clearly stimulants are powerful reinforcers--more powerful in these experiments than heroin or barbiturates.

Pharmacological Properties.

The CNS stimulants exhibit a wide variability of individual response in animals and humans, which is to some degree under genetic control.[26] The D isomer of amphetamine is three to four times as potent as the L isomer in producing CNS excitory effects; they are equivalent in peripheral system effects. The central nervous system stimulants, for the most part, are indirect-acting sympathomimetic drugs, which produce heightened adrenergenic and dopaminergic activity. The exceptions are the amphetamine-derived psychotomimetic drugs, e.g., MDA, MDMA, mescaline, which presumably exert hallucinogenic/psychotomimetic actions by direct receptor interaction, rather than through an intermediate neurotransmitter.[14a]

Amphetamine, the most common member of the stimulant group, has powerful cardiovascular, CNS stimulant, hyperthermic and appetite-suppressing actions. Cocaine has, in addition, a powerful local anesthetic effect and vasoconstrictive effect. In fact, "tissue strangulation" due to the vasoconstrictive actions and resultant tissue hypoxia account for many of cocaine's toxic effects.

Dosage, hence blood level, is the most critical determinant of stimulant effects, but the subjective effects reflect not only the dose and route of administration of the drug, but also the user's metabolism, psychology, previous drug experience and his environment. Minimal doses (perhaps 2.5 to 15 mg of *d*-amphetamine) of CNS stimulants produce a "relaxed" alertness, energetic vitality, and confident assertiveness. Appetite and fatigue disappear, and the individual cannot sleep.

Larger doses (e.g. 20 to 50 mg amphetamine), intensify these effects, and the alertness is replaced by a "driven" feeling. Dysphoric feelings become mixed with euphoria. Thoughts are rapid, and emotions become more labile and intense. Impulsivity increases, and, as in hypomania, confidence and ordering of priorities may be inappropriate. These effects combined with sometimes rapid talkativeness, intrusiveness, and inappropriately personal topics of conversation frequently make individuals seem tiresome to others.

Even higher doses produce cycles of unproductive, frenzied activity, stereotypy, or psychosis alternating with exhaustion, extended sleep, and a period of dysphoric lethargy thereafter. It is interesting to note that both rats and monkeys given free access to CNS stimulants in intravenous self-administration experiments tend to evolve a similar cyclical pattern of use.[27,28,29,148]

Experienced cocaine users describe the euphoria produced by cocaine in the same terms as amphetamine addicts describing the "speed high." Under laboratory conditions, experienced cocaine users cannot distinguish between 16 mg of cocaine and 10 mg of dextroamphetamine given intravenously.[30]

Performance of simple mental tasks is improved at low doses, and although more work may be accomplished, the number of errors is not necessarily decreased. Like amphetamines, cocaine reduces the sense of fatigue and restores to baseline the decrement in performance which results from sleep depravation.[30] However, there is no evidence that cocaine improves mental or physical performance in rested individuals.[30b] The improvement in performance impaired by fatigue may also be due to alteration of unfavorable attitudes toward the task. As little as 64 mg of cocaine interferes with the learning of new tasks. Physical performance in athletes is improved acutely by amphetamines, yet these effects are not invariable and may be reversed by overdosage and repeated usage.[4]

Depression of appetite and weight loss in obese humans treated with amphetamine is almost entirely due to reduced food intake and only in small measure due to increased metabolism. Increased physical activity may also contribute to the loss of weight. Although in dogs the anorectic effect is powerful and may lead to starvation with small daily amphetamine dosages, the effect in man is much smaller, and tolerance to the appetite suppressant effect develops rapidly with both amphetamine and cocaine. By suppressing appetite, high doses of amphetamine may foster ketosis; and, since amphetamine is excreted much more rapidly in acidic urine, some of the apparent tolerance may be due to more rapid elimination of the drug.[4]

Amphetamine raises systolic and diastolic blood pressure and reflexly slows the heart at low doses. Cardiac output is not changed, nor is cerebral blood flow.[16] Amphetamine generally has a contractile effect on smooth muscles, stimulates the medulary respiratory center and lessens the degree of central nervous system depression caused by various sedative-hypnotic drugs.[4]

Stimulants are deceptively addicting drugs. Although most recreational users of cocaine report that they can "take it or leave it" and imply that they have control over its use, in fact, most so-called "recreational users" do not abstain when it is made available to them.[39] For many people, stimulants are capable of exerting tremendous control over behavior. Cocaine is probably the most reinforcing drug known,[18,19] followed by amphetamines.

By far, the *most important effect* of the stimulants in producing repeated use and abuse and dependence is their powerful *ability to produce biochemical reinforcement* in the CNS, a reward that is subcortical (limbic; hypothalamic), immediately reinforcing, and eludes conscious control.[30a,31]

Stimulants produce a *neurochemical magnification of the pleasure* experienced in most activities.[8] *Stimulants reinforce their own use*; probably by their combined powerful actions on dopamine reward centers (see below) and their stimulant actions; by contrast, opioids, although also rewarding, through sedation, inhibit their continued use. Thus, in rats, the fatality rate associated with continuous cocaine self-administration is 90%, but is only 50% with heroin.[19]

Neuropharmacology

Drug abuse involves ancestral or prehistoric parts of the brain comprising instincts for survival such as hunger, thirst, and sex, as well as life-threatening fears involving neural pathways (locus coeruleus = flight or fight response) activated during withdrawal.[148]

The mechanisms of stimulant reinforcement implicate the dopamine-rich nucleus accumbens for amphetamines, the pre-frontal areas of the brain for cocaine and amphetamines, and the ventral tegmentum which sends dopamine fibers to the nucleus accumbens for the opioids. Intact mesolimbic and mesocortical dopaminergic reward pathways are required to produce reward and addiction in animals; severing these pathways reverses addiction in experimental animals.[18,30a,31, 148,157]

For many people, both drugs are capable of exerting tremendous, powerful control over behavior, implicating brain reward circuits. Probably multiple brain reward systems exist, but the ventral tegamental-nucleus accumbens dopaminergic reward system is the best understood, and much data has been accumulated that the positive rewarding effects (as differentiated or distinct from the physical dependence producing effects) of abused drugs are mediated through this brain system.[18,30a,31] There are at least five dopamine-receptor subtypes so far identified; which perpetuate dependence await discovery.[151] The

psychomotor stimulants, opioids, barbiturates, alcohol, marijuana, nicotine and phencyclidine all can facilitate brain stimulation reward and can serve as reinforcers in animal experiments.[31,157]

Drugs of abuse either enhance brain stimulation or lower thresholds for reinforcement. Abused stimulants have multiple effects on multiple neurotransmitter systems. All effect dopaminergic, noradrenergic, serotonergic and cholinergic systems.[16,33,148,157] The local anesthetic effects of cocaine are important, too, as is generalized reduced cerebral metabolism produced by cocaine administration demonstrated on PET scans,[34] and procaine and cocaine produce subcortical (limbic) seizure activity and the phenomenon of "kindling," or reduced subcortical seizure threshold[34a,35,35a] (discussed below).

Exactly what combination of systems produce stimulant euphoria is unknown. Stimulants increase dopamine concentration in the synaptic cleft, which increases neurotransmission in brain reward systems, yet cocaine and amphetamine have multiple actions on multiple neurotransmitters, e.g., dopamine systems modulate endogenous opioid system activity and the converse; serotonin, GABA, and enkephalins are inhibitory to the dopamine and ventral tegamental systems.[16,33,148,157]

In animals, the local anesthetic effects of procaine, lidocaine and cocaine, acting centrally, induce subcortical (or limbic) spindle, seizure, and after-discharge activity, and a process known as "kindling" (the phenomenon of reduced subcortical seizure threshold) may, over time, lower the threshold for these types of seizures.[35,127] Electrically kindled animals display heightened responses to stress.[127] This mechanism has been invoked to explain stimulant craving and the reported phenomenon of "reverse tolerance,"[17] where abusers assert that they become "more sensitive" to the effects of cocaine, as for example, when lower doses reactivate the paranoid syndrome,[34a,35a,127] earlier in the binge than before. Sensitization to increased locomotor activity, stereotypy, and dyskinesias is a robust and consistent finding in animals.[35a]

Although the effects of amphetamine and cocaine are similar, their mechanisms of action are probably not the same.[31a] It used to be said that amphetamine worked by releasing stored catecholamine neurotransmitters and that cocaine worked by blocking the reuptake of norepinephrine and dopamine. Nowadays we know that both drugs have both actions to some degree (although the blockade of reuptake seems more important for cocaine), and as research in neuroendocrinology progresses, the neurochemical processes actually responsible for the psychological effects will be better elucidated.

The acute physiological effects of tachycardia, hypertension, vasoconstriction, mydriasis, diaphoresis and tremor are best explained by acutely potentiated central (at the locus coeruleus) and peripheral norepinephrine neurotransmission.[4] Amphetamine releases norepinephrine and dopamine from newly synthesized, versus stored, pools of catecholamines.[16] Cocaine blocks the reuptake of norepinephrine and dopamine as well as facilitating its release peripherally and centrally.[33] It activates postsynaptic receptors as well as inhibitory presynaptic alpha-2 receptors on norepinephrine neurons. Cocaine

increases beta cell (postsynaptic receptor) populations--especially pronounced with chronic administration.[33]

The acute physiological effects of euphoria and reward (nucleus accumbens), anorexia (lateral hypothalamus), stereotyped behavior, hyperactivity, sexual excitement and spontaneous ejaculation without genital stimulation (amygdala) are best explained by presynaptic influences on dopamine receptors.

Chronic use produces a functional reduction in dopamine activity (hypofunction), coupled with a compensatory supersensitivity of auto-receptor receptors over time, and compromised or dampened dopamine function.[36] There is not an actual decrease in dopamine per se. This may be perceived as the anhedonia, dysphoria and craving associated with the abstinence syndrome.[37,38] Dopamine is no doubt involved in the cocaine toxic psychosis. Amphetamine does cause dopamine depletion--from cell loss through destruction from 6-hydroxydopamine, a metabolite.[36] Depletion of dopamine stores has not been supported by evidence. Some hypothesize that the relative dopaminergic hypofunction depletion is experienced as craving and that the supersensitivity of dopamine inhibitory auto-receptors on the neuron could decrease or dampen neurotransmission and reward pathways, causing decreased sensitivity to reward, explaining the anhedonia of withdrawal.[30b,31a,37,36] Ellinwood has shown much the same thing in animal models with amphetamine.[16] To summarize, repeated stimulant use perturbs the equilibrium of the norepinephrine, dopamine and serotonin neurotransmitter systems (and perhaps other systems as well).

The *neural substrates of complex higher-order "feelings"* which users report after using stimulants such as confidence, calm, elation and self-admiration, are the result of complex neural systems and *not due to a single mechanism.* Some cocaine users report that using "relaxes" them--an effect which is counter-intuitive to what we as clinicians would expect from stimulant pharmacology.[39]

Stimulants produce a *neurochemical magnification of the pleasure* experienced in most (pleasureful) activities. Although magnifying pleasure, they do not distort it at low doses as do the psychedelic drugs, e.g. MDMA or MDA. Because early experiences are accompanied by increased productivity, energy and enthusiasm, the use seems benign at first, and users readily repeat the use. It is in these early phases that operant conditioning of the drug habit occurs (see Extinction, below). At higher doses the pharmacologic euphoria predominates and users pursue this euphoria to the exclusions of other activities and other forms of (less intense) reward.

Cocaine, as well as amphetamines, are particularly potent in producing conditioned responses in animals, expressed in the idea that "people will do anything for cocaine." Conditioned cues evoke vivid memories of aspects of the stimulant use, especially the euphoria. Stimulant using dreams occur, especially during withdrawal phase. The conditioned cues are not affected by withdrawal/ pharmacotherapy/or 28-day inpatient or residential treatment programs. Extinguishing the link through desensitization between

conditioned cues ("triggers"), euphoria and reward is critical in treatment during the extinction phase, described below.

Tolerance

Stimulant users describe a tolerance which appears to a pharmacodynamic tolerance, an apparent tachyphylaxis, rather than metabolic tolerance. Tolerance develops to some effects (euphoria, anorexia, cardiovascular and respiratory effects, hyperthermia, elevated urinary excretions of catecholamines, convulsive dose, and lethality)[17,30a,30b,41,42,43] and not to others (sleeplessness, increased locomotor activity, stereotyped behavior).[17,40] An acute tole-ance, consistent with recreational user's reports, develops to cocaine and amphetamines after a single dose, and disappears quickly, sometimes after a night's sleep, and may lead to higher doses being taken subsequently.[42,43] Such tolerance probably reflects depletion of neurotransmitter levels released by both drugs, although other mechanisms may be factors.

Humans continue to self-administer doses of cocaine which they've become tolerant to (and which have stopped producing subjective or cardiovascular effects) and call those doses placebo, since they're getting minimal feedback from their bodies.[30,42] Yet they're still getting biochemical reward, presumably from the dopamine systems, causing them to continue to self-administer.

Endocrine Abnormalities in the Abstinence Syndrome

Cocaine perturbs immunologic and neuroendocrine functioning in male and female cocaine abusers and affects modulation of stress and sexual behavior.[151] Luteinizing hormone is secreted and corticotropin is released enhancing pleasure and sexual interest and reducing concern.[151]

Prolactin is complexly regulated.[36] Dopamine inhibits prolactin release, and both dopamine and norepinephrine stimulate growth hormone release. Serotonergic neurons release prolactin. Depending upon where one looks in the abstinence phase, decreased or increased prolactin levels can occur among stimulant abusers. In one sample of chronic cocaine users tested after 4 - 10 days of abstinence, 35% had below normal prolactin levels, 20% had increased plasma growth hormone levels, and 42% had abnormal dexamethasone suppression of cortisol.[44] Eighty percent displayed one or more abnormal neuroendocrine levels. Other researchers reported increased prolactin levels associated with sexual dysfunction in 7 out of 10 cocaine abusers measured on the 2nd to the 28th day of abstinence.[45] Unexplained breast development (gynecomastia), glactorrhea, amenorrhea, and sexual dysfunction may signal increased prolactinemia from cocaine withdrawal. Glactorrhea and decreased libido may be corrected with bromocriptine 0.625 mg, twice a day.[45]

Abstinence Syndrome

Controversy exists whether the stimulant abstinence syndrome (a reversal of the neuroadaptation which has theoretically occurred) is truly a withdrawal syndrome, since, it is argued, reinstatement of the drug (or another drug in the same pharmacological class) does not reverse it. Whether the symptoms identified by abusers in studies of outpatient treatment[38] after stimulant discontinuation represent the reversal of neuroadaptation or are simply the result of sleep deprivation, overstimulation, and classical conditioning (exposure to envoronmental cues) is unsolved.[116,162]

For many years, stimulants were thought to be only "psychologically addicting" and not to produce physical dependence. Recent descriptive and biochemical studies have bolstered current clinical consensus[8,38,46,47,16] that chronic stimulant use produces a *neuroadaptive state* in the CNS of physical dependence, and an abstinence syndrome characterized by physical craving, anhedonia, lethargy and dysphoria, which begins, not immediately as in opioid withdrawal, but after several days of relative freedom from craving. Thus, the user's craving is the most obvious component of the emerging physical withdrawal. Not all studies have identified symptoms of cocaine withdrawal, especially when questioning users in hospitalized settings,[116,162] yet all studies have identified drug craving. Kosten[132] contrasts opioid and cocaine craving and discusses instruments for measuring craving.

These abstinence or withdrawal symptoms are often thought of as characterizing "psychological dependence," but actually result from physical, psychopharmacological alterations in brain function--*neuroadaptation*--a hypofunction of dopamine reward circuits at least, and probably involve other neurochemical systems.[38,47]

While it is not of the same degree or character as the abstinence syndrome of opioid or sedative-hypnotic dependence, interviews with abusers in outpatient treatment programs[38] have described a regular three-phase sequence of symptoms which occurs following cessation of chronic stimulant abuse: the "crash," rather like the "hangover" of alcohol;[47] the phase of "withdrawal," which does not begin immediately as with opioids; and the phase of "extinction."[8,38,48,39]

The Crash

Symptoms of the "crash" begin immediately following a binge, when the user ceases his use of stimulants after supplies are exhausted. This phase lasts for a day to one week. For several hours after stopping use, the user is confused and anorexic, agitated, increasingly dysphoric and depressed, and initial insomnia and craving is replaced by an increasing need for sleep which overtakes him. Suicidal symptoms may develop. During this phase, many users will use drugs such as marijuana, alcohol, opioids (commonly heroin) or benzodiazepines to blot out the dysphoria and induce sleep. The user may sleep on and off for several days (hypersomnolence), awakening hungry (hyperphagia), and then sleep again. Mood returns to normal after hypersomnolence, but some residual

dysphoria may linger. During the early hours of the crash, stimulant craving is quite high, but as the hours progress, in contrast to opioid withdrawal, craving diminishes and can be quite low for several days. Clinical management consists of observation and protection from self-harm and resumption of use.

Withdrawal

The withdrawal symptoms from stimulants are the opposite of the acute intoxication effects. The phase of "withdrawal" begins with several days of near normal affective feelings and low cocaine craving, in contrast to opioid or alcohol withdrawal cravings which begin after hours. Soon thereafter, fluctuating feelings of dysphoria, irritability, depression, decreased energy (anergia), lessened ability to experience pleasure (anhedonia), coupled with high cocaine craving triggered by environmental cues, ensue. Withdrawal symptoms, which are mildest after the crash, intensify over several days and fluctuate in cyclical bursts. The withdrawal phase, in fluctuating intensity, can last more than 10 weeks after cocaine is stopped, should continued abstinence be possible. The symptoms are neither severe enough nor consistent enough to meet criteria for major affective disorder. Nevertheless, memories of euphoria contrast vividly with the anhedonia of withdrawal and induce strong drug craving and unrelenting cycles of binges and transient abstinence. The anhedonia and dysphoria may wax and wane in attenuated form for 6 - 9 months.[8,16]

Gawin and Kleber[38,47] hypothesize that the neurochemical foundation of "crash" symptoms is probably acute depletion of catecholamine neurotransmitters; that of "withdrawal," dopamine auto-receptor supersensitivity and hypofunction of reward circuits. Intermittent or so-called recreational users who infrequently use low doses seldom experience the symptoms of the withdrawal state, except for brief post-use dysphoria. Animal studies demonstrate similar behavioral depression on withdrawal.

Extinction

The final phase of indefinite duration--most important from a treatment perspective--called "extinction" follows. Neurochemical circuits have normalized, and the user is left with a profound habit. Stimulants have been shown to instill stronger conditioning than any other drug or reward (e.g. food or sex), producing automatic drug-seeking derived from vivid memories conditioned during euphoric episodes during acute intoxication, during low-dose as well as high-dose use.[8,25,160] The phase of extinction is a normal affective state which is punctuated by episodic cravings for cocaine, which can wax and wane indefinitely, usually triggered by conditioned cues (secondary reinforcers). Circumstances (moods, people, locations, salary disbursements, days of the week) and objects (money, paraphernalia, pills or white powders) comprise these cues, which are "triggers" to resumption of use.[8,16] It is during this phase that the reversal of the

conditioned response to the drug occurs (extinction), if users consistently remain abstinent. This requires participation in structured treatment programs.

In contrast to withdrawal syndromes from sedative-hypnotics or opioids, when craving for the drugs is continuous, the *craving for stimulants is discontinuous,* greatest at the end of the "run" and at the beginning of the "crash" and then diminishing markedly, but re-emerging at some point (after days) during withdrawal, stimulating further stimulant use. Thus, high-dose users indulge in a recurrent pattern of cyclical binges, rather than daily use.[8,38,17] For example, the common syndrome of weekend cocaine use fits nicely into almost methodical cycles of 6 - 36 hours of cocaine use, 1 - 2 days of crash, 1 - 2 days of normalization, then 1 - 2 days of resisting cocaine, then repeated cocaine abuse. It is during the withdrawal phase, when craving is high, that users most frequently relapse or leave treatment.

Thus, the withdrawal phase is a time to focus on the control of craving until these symptoms lift, whether through compensatory pharmacotherapy, confrontation about the denial associated with leaving treatment, or elimination of access to stimulants by prolonged hospitalization, or even desensitization with provoked cravings. Thus, treatment intervention should be intensive (typically 4 evenings per week) during the first 10 - 11 weeks after cessation of use and less intensive treatment (twice per week) should continue well beyond 10 weeks, during the active extinction phase--a time when cognitive/behavioral relapse prevention techniques are appropriate (see below).

Because severity of withdrawal symptoms depend on extent and intensity of use, low-dose maintenance or recreational (experimental) users may not experience severe withdrawal symptoms, but when treating these users, a subliminal craving response should not be overlooked as a component of precipitants for resuming use.

Toxicity: Medical and Psychiatric

The paranoid toxic psychosis characteristic of stimulant abuse, and the organic brain syndrome, still controversial, are the most important toxic effects, clinically, and are distinct from abstinence or withdrawal phenomena (discussed above).

High-dose users of stimulants (by any route of administration) commonly report a hypervigilance and hyperarousal, resulting in a suspicious, paranoid state with ideas of reference and eventual paranoid psychosis resembling an acute schizophreniform illness[34a,35a,51-56,71] (in a clear sensorium). This is usually accompanied by various levels of stereotypy, and well-formed delusions and loss of insight can occur. It may occur among low-dose maintenance, or even experimental users, with use of only moderate doses over several days.

The toxic stimulant psychosis can be produced experimentally among almost all subjects not predisposed to psychotic conditions by gradually increasing the oral dose over a short

time, in one study 5 - 10 mg per hour and another up to 50 mg per hour of racemic amphetamine.[17,49,50] Thus "normal" individuals (not "pre-psychotic") are not immune. Neuroleptics do abort the paranoid psychotic symptomatology but may increase craving, anergia and anhedonia, presumably due to their dopamine blocking effects. They are rarely needed, since the psychosis disappears so rapidly (more quickly from cocaine than from amphetamine), usually within 48 - 72 hours after cessation of use. Most users note that after once experiencing this paranoid state, it later occurs at lower doses and more quickly after resumption of use. This may be due to "kindling," i.e., the phenomenon described above of reduced subcortical seizure threshold induced by the repeated use of stimulants and/or the altered dopamine activity in the central nervous system.[35a] Sleep deprivation alone does not account for the psychosis, and it is not a withdrawal psychosis, but a toxic psychosis. Ellinwood has compared some milder aspects of the syndrome to temporal lobe epilepsy.[53] Stimulants probably do not produce a chronic psychotic state except in individuals predisposed.

Tactile hallucinations, or formications ("coke bugs"), are rarely reported, but unformed auditory hallucinations are more frequent, and hyperacuity is common, depending upon dose. Attention may become disrupted and thinking disorganized, leading to a syndrome resembling a hypomanic state or even delirium state, but when delirium is seen in the hospital in a stimulant abuser, sedative-hypnotic withdrawal delirium must be ruled out. Abusers' use of sedative-hypnotics to reduce the stimulant hyperarousal can make individuals panicky, confused and impulsively violent.[7,8,17] Dopamine-induced stereotyped behaviors such as picking, pacing, bathing, cleaning, doodling, dismantling mechanical objects, or other repetitive activities also occur.[7,8,17] Stuporous or comatose patients should immediately receive intravenous naloxone, a parenteral opioid antagonist, to rule out an opioid overdose emergency, which is treatable.

A mild, depressive-like syndrome (sometimes severe) does occur as part of the abstinence syndrome, and some abusers present acutely suicidal. Whether depression can persist in individuals without primary affective disorder is unstudied.

Chronic high-dose users on admission to treatment often display an organic brain syndrome, including slowed reaction time, impaired short term memory, and coordination difficulties, which persist from several days to several weeks after cessation of use, and are unrelated to depression.[39,57] The repeated administration of high doses of stimulants in laboratory animals produces decreases in dopamine (and serotonin) concentrations in the brain--and even neuronal degeneration, cell loss, and changes in cerebral vasculature (in monkeys treated with amphetamine for one year) perhaps by the formation of toxic metabolites of e.g., dopamine.[3a,8,31a,37,30b] Subtle irreversible changes in humans, such as vulnerability to mood dysfunction or decreased capacity to experience pleasure might be possible, although this is, so far, unproven in humans.[3a,8,32] Anecdotal reports occasionally describe high-dose stimulant users who report anhedonia, anergia and craving for stimulants that do not remit even with 10 years of abstinence, yet most user's anhedonic and anergic symptoms disappear over time.[8] The possibility exists that some

stimulant users may be relapsing to compensate for a stimulant-induced neuro-toxic deficit.[8]

Toxic effects also may be produced by the adulterants in the stimulants, principally the "-caine's," and the over-the-counter stimulants such as phenylpropanolamine, ephedrine, pseudoephedrine and caffeine.[3] Furthermore, heavy metal and organic contaminants in methamphetamine produced in clandestine laboratories which are synthesis by-products and reagent residuals (sometimes from process errors in production) may cause adverse reactions and neurotoxicity, including two documented cases of lead poisoning.[3a,3b,3c] There is still controversy over whether abuse of MDMA produces irreversible CNS (serotonin) neurotoxicity among users.[59-62]

"Tissue strangulation" from vasoconstriction (and resultant hypoxia) is important with cocaine, as is the elevated blood pressure and the perturbations in neurochemistry with all the stimulants in producing organic brain phenomena, perfusion defects and disorders of cerebral blood flow,[151] microvascular damage throughout the body, and fatalities.

Most fatalities occur among individuals who inject stimulants or smoke cocaine in its freebase form, although deaths can occur with "snorting."[63] Deaths from "body packing," where smugglers conceal large amounts of cocaine in containers in their stomach, intestinal tract or vagina can occur when the container bursts and large amounts are quickly absorbed. Death involving stimulants generally occurs from respiratory arrest, cardiac arrhythmia or cardiovascular collapse, and hyperpyrexia, systemic acidosis, cardiovascular shock, and convulsions may occur.[64] There may be hypertensive encephalopathy and cerebrovascular accidents following subdural and/or subarachnoid hemorrhage. Death from amphetamines is usually preceded by convulsions and shock; cocaine overdose is more frequently characterized by convulsions and cardiac arrhythmias. Treatment consists of emergency treatment of the airway, respiration and circulation. Intravenous diazepam generally controls the seizures. Beta-blockers are appropriate for the stimulant-induced hypertensive crisis, and hypothermia may be useful. Aggressive urinary acidification promotes the excretion of stimulants, but may upset the acid-base balance, which must be monitored closely.[64,65]

Rhinitis caused by the reactive hyperemia of the nasal mucosa is the rule among intranasal cocaine abusers, and some display erosions, mucosal sloughing, and not uncommonly, perforation of the septum or sinuses. Intravenous stimulant users risk blood-borne infections, including Hepatitis B and C, and HIV, as well as local effects around the injection site. Chronic freebase cocaine smoking produces bronchitis and, in some users, a chronic impairment of pulmonary gas (CO_2) exchange which persists even after long, drug-free intervals.[66,99] Increased catecholamines can sensitize the myocardium and increase the risk of arrhythmias, and cocaine high-dose use sometimes causes chronic arrhythmias (sometimes persisting after long abstinence), myocardial degeneration and scarring, congestive heart failure, silent ischemia and infarction.[16,32,33]

Stimulants have a reputation among users as aphrodisiacs, and "sexual stimulation" is sometimes a potent motivation for repeated use, yet reported increases in sexual appetite and activity occur only among subgroups of users;[17,6b,8b,39,51,52,67,68,69] others report the opposite. The increase in sexual desires is in part explained by the effects of stimulants on the dopamine tracts in the amygdala. Users often experience decreased abilities to perform due to the sympathomimetic effects of stimulants and reduced ability to sustain concentration. Occasionally, users describe opposite performance effects. Male cocaine users sometimes report enjoying the local anesthetic effect on the mucous membranes of the penis which delays orgasm. Some individuals engage in a wider variety of sexual activities when intoxicated, and for some, the anticipation of the sexual enhancement becomes a major motivation to take cocaine, and anticipation of sexual activity, and their partners are often triggers (conditioned cues) to resume use.

The occurrence of violence among groups of stimulant users is well documented.[51,10a,69,70,74,75,128] Connell indicated that hostile or aggressive behavior occurred in 22% of amphetamine dependent subjects.[51] Ellinwood studied 13 persons who committed homicide while intoxicated with amphetamine, and found that the paranoid thinking, panic, emotional lability, and lowered impulse control associated with amphetamine abuse contributed to the events leading to the homicidal act.[70] Two surveys of adult and juvenile prison populations have indicated many inmates committed their crimes while intoxicated with stimulants;[13a,76] other studies have not confirmed these findings.[16,128] The prevalence of sociopathy among drug abusers and alcoholics is a confounding variable. Amphetamine greatly enhances the aggression of opioid withdrawal in animal studies[16,72,73] which may have implications for mixed substance abusers, and animal studies[16] and one study in humans[77] indicated amphetamine *alone* increased aggressiveness.

We must keep in mind that stimulants can *decrease* aggressive behavior in some aggressive and hyperactive people, because of their "paradoxical" effect with, for example, individuals with ADHD, adult type.[78] Clearly, many factors are involved in the association between aggression, violence and stimulants, including the pervasive paranoia among users due to both amphetamine psychosis and the illegal activity in which many stimulant users are involved.

An additional factor may be the human analogy to "aggregate toxicity" observed in rats. In studies where groups of rats were administered sub-lethal doses of stimulants, many more died when caged together than when caged alone as a result of heightened aggressiveness brought on by their exposure to amphetamines. When caged alone, higher doses may be given without being lethal.[6b,39]

It may be the phenomenon of aggregate toxicity of which we are seeing on a human scale, particularly where abusers live together or in close proximity, for example, in "flash houses," housing amphetamine users in the U.S. in the '60's and '70's,[74,79] the "crack (cocaine) houses" of the 1980's and 1990's, or among fishermen on boats where stimulant and opioid use is prevalent.

Cocaine and Pregnancy

Significant literature, reviewed by Gold,[32] has developed as a result of clinical experience with "cocaine babies" from pregnant addicts in the U.S. Placental abruption occurs in approximately 1% of pregnancies among cocaine mothers, and is a significant cause of maternal morbidity and fetal mortality. Spontaneous abortion is also prevalent. Even at doses non-toxic to the mother, there are significant effects on the fetus, e.g., intrauterine hypoxia, cardiac rhythm abnormalities, fetal cerebral infarction, growth retardation, birth defects and fetal death. The nervous system irritability seen among cocaine-exposed infants is so common that it is known as "Jittery Baby Syndrome." Cocaine babies who survive are likely to display visual impairment, symptoms of stroke, or mental retardation.

Comorbid Psychiatric Disorders: "Dual Diagnosis"

Intoxication, toxic phenomena, and the stimulant withdrawal syndrome produce psychiatric syndromes, many of which, at first, are indistinguishable from non-organic psychiatric syndromes; e.g., organic mood disorder in amphetamine withdrawal may appear the same as a major depressive disorder; stimulant-induced paranoia may mimic paranoid schizophrenia or a paranoid mania. Because both addictive and psychiatric disorders often first appear in the 20 to 30 year old age bracket, there may be no way to tell which is primary (came first) and which is secondary (came after), especially in retrospective appraisal. Both the drug dependence and the psychiatric disorder often first appear concurrently in patients. In all drug abusers (including alcoholics), the chance for psychiatric syndromes occurring together with the chemical dependence is high, but having a second, *co-occurring addiction* (usually alcoholism or opioid dependence) is by far the *most common second diagnosis* among stimulant abusers.[85]

Substance abuse, co-occurring with a major psychiatric disorder (including severe Axis II personality disorder) is commonly referred to as a "dual diagnosis." The association between current substance abuse and a wide variety of psychiatric disorders has been documented in surveys of patients[80,81,82,87] and in non-clinical populations.[83,84] It is prevalent and difficult to treat effectively.[146]

Among alcoholic patients in treatment settings, coexisting (comorbid) psychiatric disorders most commonly are (in order) major depression, antisocial personality disorder (ASPD), dependence on other drugs, and anxiety disorders.[82,81,85] High rates of alcoholism are found among schizophrenic and manic patients in psychiatric treatment settings.[86] Similar patterns of comorbidity are found in opioid patients in treatment settings: major depression, ASPD, alcoholism and current phobias and anxiety disorders.[85] Similar to alcoholics in non-clinical settings, opioid patients not in treatment showed substantially lower rates of major depression than in treatment settings, suggesting that the discomfort reflected in the depressive symptoms drives some (alcohol and opioid) abusers into treatment.[85]

Although similar studies of amphetamine abusers are absent, because of the recent cocaine epidemic in the U.S., cocaine abusers have been increasingly studied,[85,87] and only research will determine whether results may be generalized to stimulant abusers in other countries. Although the overall rates for psychiatric disorders among cocaine abusers seeking treatment (50% have at least one current psychiatric disorder; 75 - 85%, at least one lifetime diagnosis) are similar to rates among alcoholics or opioid addicts, the prominence of particular types of disorders differ.

Among cocaine users seeking treatment, rates for current clinical depression remain high (30 - 40%), but most of the cases appear to be a more chronic, mild form of the disorder. There are significantly higher lifetime rates (10 - 23%) for bipolar spectrum disorder (mania, hypomania, cyclothymia) reported in cocaine abusers than among opioid-dependent patients or alcoholics in treatment. Anxiety disorders (predominantly phobias) are somewhat lower (3 - 15% current; 20% lifetime), and rates for alcoholism (30% current; 60% lifetime) are substantial. Psychotic disorders (other than cocaine psychosis) are rare in cocaine treatment settings. Some authors suggest that ADHD, unresolved into adulthood may predispose some individuals to cocaine (or other stimulant) dependence. There is a relatively lower prevalence of ASPD but higher rates of other personality disorders, compared to alcohol and opioid addicts. Treatment-seeking cocaine-dependent patients do not display patterns of psychopathology different from those not in treatment, except higher rates of ADHD among those in treatment.

There is evidence that comorbid Axis I disorder (DSM-IV) or personality disorder (Axis II) negatively affects treatment outcome.[146] For example, one study[85] of lower socioeconomic class, unemployed cocaine addicts in an inner-city urban outpatient treatment program reported rates of Axis I psychopathology similar to those of the population base, yet rates of personality disorder were considerable. There was a lot of overlapping of syndromes, with personality features of affective lability, cognitive rigidity, restricted problem-solving repertoire, impaired perspective-taking ability, impulsivity, paranoid ideation, all which could easily negatively affect participation in treatment groups, but all which may be amenable to focused intervention in treatment. To effectively treat such patients, clinicians must be able to set firm and consistent limits, assist patients in managing risk factors for impulsivity, behavioral acting out, and negative mood states. Furthermore, Sloan and Rowe found that among 665 veterans applying for substance abuse treatment, having had a history of psychiatric treatment was associated with "higher rates of homelessness, disconnection from social support systems, unemployment and vocational disability, and treatment chronicity; a narrower definition [of psychiatric disorder] selected for even greater impairment."[146]

Effective treatment of the comorbid (co-occurring) psychiatric condition will rarely stop the progress of the stimulant abuse or dependence patterns (even with low-dose maintenance users) once conditioning of the habit occurs, unless there is concurrent, intensive outpatient chemical dependency treatment for several months. Once conditioned, these habits of chemical dependency tend to have a "life of their own,"[144] and treatment of accompanying conditions, whether they are seen as primary or

secondary, are not sufficient, and do not supplant additional involvement in traditional chemical dependency treatment.

Abuse of Other Drugs and Co-Occurring Addiction

Stimulant use may become a way of life, and be so totally absorbing that the high-dose user reduces or abandons normal societal obligations. Even low-dose maintenance users may be plagued by toxic effects, yet unable to stop for long periods, and may begin to treat these toxic effects with opioids or sedative-hypnotics, alcohol or cannabis. Although some multiple drug abusers have a long history of abuse of other drugs prior to their involvement with stimulants, other stimulant users have been only recreational users of alcohol or marijuana, and are "taken by surprise" by their emerging stimulant addiction, since it is the first drug that they have "lost control over."

Another group of patients have opioid addiction histories. Before treatment admission, these patients have abused both stimulants and an opioid, typically heroin or methadone. Some are on methadone-maintenance programs. A few patients in this group have been free from opioids for months or years until escalating to high-dose stimulant use, when they begin treating stimulant over-stimulation or withdrawal reactions with opioids with which they are familiar.

A third group of stimulant users consists of alcoholics who begin using a stimulant and find that it allows them to function better and consume more alcohol.* They may be dually dependent upon entering treatment. A few individuals in this group, too, have been free from alcohol for varying periods of time before being introduced to amphetamine or cocaine.

A fourth group of patients reports using alcohol or marijuana only occasionally in a controlled, social pattern between bouts of stimulant excess; during stimulant-abusing periods, however, these patients drink alcohol or smoke marijuana in excess to "mellow out or come down" from stimulants. They exhibit no alcohol withdrawal symptoms upon admission, and whether they will eventually develop alcohol or marijuana dependence is unknown, but likely.

Finally, we see multiple-substance abusers for whom amphetamine or cocaine is simply one more drug of abuse in a long line of drug dependencies. Often these individuals are abusing alcohol and several drugs in addition to stimulants when admitted and tend to have more psychiatrically-disturbed character disorders.[39,89]

Stimulant abusers often concomitantly abuse various other drugs in order to modulate the hyperactivity, stereotypy, dysphoria or toxic paranoia associated with chronic high-dose use, and many enter treatment facilities dually-addicted to two or more drugs.

* Cocaine and alcohol in combination result in a metabolite, cocaethylene, that may reduce withdrawal effects and lengthen euphoria.[151]

Nevertheless, considering the severity and uniformity of the toxic effects of stimulants, it is surprising that a full 10 to 30% of abusers admitted to U.S. hospital-based treatment programs report the abuse of no other drug except cocaine.[39] Others generally report the abuse of marijuana, alcohol, opioids or sedative-hypnotics in some combination to ameliorate the toxic effects.

Numerous intravenous abusers in the United States are involved with "speedballing," that is the concomitant administration of intravenous heroin along with the intravenous cocaine. The antipsychotic and sedative effects of opioids diminish the paranoid and dysphoria. Sedative-hypnotics, alcohol and marijuana may be used either concurrently or sequentially to diminish the hyperactivity or, in high-dose cyclical use, during early phases of the crash, to reduce dysphoria, and to induce sleep. Increasingly, due to the fear of contracting HIV from intravenous use, some users also "snort" or smoke heroin for the same purpose. Stimulant abusers are at high risk to develop opioid dependence after their experimentation reveals that opioids relieve toxic effects. Stimulant abusing subgroups and communities (e.g., Asian fishermen, truck drivers) are ripe to become heroin using communities.

Since abrupt withdrawal from stimulants can proceed without complications (other than occasional suicidal ideation and depression) and is otherwise not life-threatening, withdrawal from the other drugs can proceed concurrently. Should cocaine abusers be dependent upon both opioids and sedative-hypnotics, stabilization (on methadone for the opioid physical dependence, and on benzodiazapines for sedative-hypnotic dependence) should be instituted and sedative withdrawal completed prior to the withdrawal from the opioids. Once sedative doses have decreased to normal therapeutic ranges, opioid withdrawal can resume, while maintaining the sedatives at a reasonable level to reduce the symptoms of opioid withdrawal.

TREATMENT APPROACHES TO PATIENTS WITH STIMULANT DEPENDENCE

Failure to diagnose chemical dependency when drug abusing patients present for another medical or psychiatric problem is a common occurrence. In the United States, physicians correctly identify only about 25% - 50% of alcoholics who present for medical care, and 25% of all patients hospitalized for a medical or surgical treatment have a significant problem with alcohol. Approximately 50% of seriously disturbed hospitalized psychiatric patients test positive for illicit drug use or alcohol when screened upon admission, and among seriously disturbed psychiatric patients who return to the hospital for a second or third treatment within twelve months, the prevalence of chemical dependency is even higher. Thus, with any medical or psychiatric patient it is appropriate to **keep a high index of suspicion** for chemical dependency. Obviously, if you don't think about the possibility, you will fail to make the diagnosis. One should always ask about chemical use and dependence, perform a urine toxicology if possible, and try to get collateral information from the spouse, family, friends, roommates, or employers.

The first step and most important part of treatment is to obtain a comprehensive assessment of the patient, which may not be fully completed during the first contact or interview but may require several additional contacts after the initiation of secure abstinence is achieved. During the initial consultation in either a medical or psychiatric setting one must evaluate the patient's physical findings, get laboratory tests, especially a urine toxicology, take a history of life problems, especially those associated directly and indirectly with drug abuse, assess the intensity and duration of drug use, and establish a diagnosis using all available resources, including collateral informants, e.g., the spouse.

The initial assessment should include a good drug history: the extent or intensity of drug use revealed in questions about the frequency and estimated amount of use over a specified interval, typically the past 30 days, past seven days, past 24 hours, and time and amount of last use. These are the most common intervals designated, since they provide information necessary to describe recent using habits and to prescribe detoxification medication. Concurrent abuse/dependence upon several classes of drugs (polydrug dependence or abuse), is common among stimulant abusers, and the extent of use of those drugs over the same intervals must be determined.

The extent or intensity of drug use alone (how much he has used), does not define a dependency syndrome. It is more important to ask how often his use has caused him pain.[144] Diagnosing chemical dependency of any sort is best achieved by asking about life problems in areas of physical and psychological health, family, employment, social life, legal matters, and trying to relate those problems to the history of current drug use.[144] Collateral information gathered from contact with family members and close friends (and from employers, should the patient grant permission) can be extremely helpful. Simple questionnaires such as the CAGE or MAST, over 90% sensitive when used in assessing alcoholism, are not commonly used to diagnose stimulant dependence.[152] The Addiction Severity Index (ASI), which helps to grade substance disorders can be useful for research and treatment but requires trained interviewers.[159] Physical and laboratory examination is rarely helpful in making the diagnosis (except in alcoholism when the GGTP, SGOT and MCV taken together are sometimes useful laboratory markers);[152] however, urine toxicology for drugs of abuse and an assessment of blood alcohol level can be confirmatory. Loss of control is the *sine qua non* of dependency, and denial is a universal aspect of the syndrome. Preoccupation with acquisition of the drug, a pattern of relapse over time, and use despite adverse consequences complete the syndrome. These criteria have been verified in field trials as reliable for diagnosis of dependency.[148,161]

If there are physical medical problems, those must be assessed and treatment begun, and their relation to current drug abuse determined. Past and current support systems which could be mobilized as part of treatment during early abstinence should be reviewed and called into service to help achieve initial abstinence. Discussions about previous periods of abstinence or near abstinence and how those were achieved and maintained, and what caused resumption of use can provide valuable insight into what supports should constitute the current treatment plan. The individual's level of motivation for treatment

and abstinence, in fact whether total abstinence is really a goal and for how long, and why he is coming for treatment *now*--the precipitating event--should be addressed.

Because stimulant abusers appear to have elevated levels of concurrent psychopathology, and because prompt and proper treatment can be crucial to retention in treatment and to the maintenance of abstinence, the current and past history of DSM IV, Axis I and Axis II psychiatric disorders should be an integral part of the comprehensive assessment. A history of previous psychiatric treatments can be obtained promptly, and the full workup of the current psychiatric situation can be most productive and accurate after a few days of abstinence. Naturally, diagnosis of delirium, psychosis, dangerousness to self or others, and estimation of the likelihood of resumption of drug use must occur during the first interview. The extent of residual organic brain impairment is best assessed by psychometric measures two or more months after abstinence, after time has stabilized measurable impairment.

During the initial contact, the goal is to enhance the patient's motivation to try to achieve and maintain abstinence and to get the help he needs, but it is helpful to remember that the patient, himself, not the clinician, is responsible for choosing to become abstinent; you can only raise his motivation to get appropriate treatment. When problems due to the chemical dependency are severe and when dangerous adverse outcomes are likely, great leverage must be brought to bear during the initial contact--usually involving family or close friends--to get the reluctant patient to accept the immediate treatment that he so desperately needs. Intervention involving close friends or family members rehearsed with a trained intervention coach can be productive if done properly,[162] but may not result in total compliance. In less severe cases or in extremely recalcitrant and resistant patients, in an effort to convince the patient to accept help and treatment, it can be appropriate to work with him for six to twelve months, at each appointment attempting to treat medical or psychiatric problems, while continually endeavoring to show the relationship of his many problems to his drug use in an effort to confront and break through his denial about the need for formal treatment. Explaining that these problems are made worse and more difficult (if not impossible) to treat without abstinence sometimes can be an effective motivator. Physicians may suggest that they cannot treat a medical, surgical, or psychiatric problem adequately until the patient stops. This sometimes is a source of initial motivation.[144]

Once the diagnosis of dependency is made, it must be communicated directly to the patient and family along with a reasonable treatment plan. It is particularly useful to focus on the **patient's area of concern** about his drug dependence or its manifest consequences and then to establish the patient's *actual* goals--which may well be different from the clinician's. This will help reconcile and establish realistic goals and time frames for both patient and physician. One should also meet with the patient's family, to establish and communicate the details of a concrete plan for treatment, although the patient may be unable to accept that plan immediately. Explore all available and practical avenues for treatment and determine and highlight the patient's and family's resistances to treatment. Always schedule a follow-up appointment and aggressively pursue the patient

(or his family, with permission, and in an emergency, without permission) if he cancels or doesn't show.

The problem for the patients is not in their "**cutting down**" on their drug use but in **stopping and remaining drug free**. The agreed upon goal for treatment ideally should be abstinence from all drugs. The first issue is how to help the addict to achieve two or three months of abstinence from all drugs so that he can begin to feel successful, family supports can begin to be mobilized and repaired, ongoing psychiatric assessments can be made, the individual's denial can be addressed, and relapse prevention techniques can be taught and practiced.

Confronting Users' Denial

Denial about the extent of the problem or about the amount of treatment needed is a universal feature of a chemical dependency diagnosis. Most patients are in denial about the extent of their chemical problem and tend to minimize the seriousness of their involvement with drugs--many have been aggressively denying the problem for years. Thus, one must utilize continued confrontation and not expect a single, isolated episode of confrontation to evoke compliance with treatment recommendations. Patients simply may deny that they have problems with drugs or alcohol, or they may deny that their medical problems or work and family difficulties are related to their drug use, or they may admit to both of these ideas but continue to maintain that they can control their drug use without help. In other instances, they may be open to accepting some help but be in denial about how much help they truly need.

In the United States, although the average length of time between first use of cocaine and coming to treatment is between 2 - 6 years for intranasal cocaine users, the progression is much more rapid with intravenous and freebase users--these users generally enter treatment 6 months to 2 years after their first use of stimulants by these more addictive (reinforcing) routes of administration. Similar rapid progression and treatment entry would be expected among intravenous amphetamine abusers, or perhaps methamphetamine "smokers."[164,165]

Generally, alcoholics have experienced many years of attempting to control their use ("drying out" and then starting again) before they enter treatment. Because of the rapid progression of toxic effects and the large sums of money spent on cocaine, cocaine abusers generally seek treatment sooner than alcoholics--often because they have run out of money and have large debts--without the understanding that they can no longer use cocaine in a controlled way. Thus, their denial of their addiction is more like that seen among early alcoholics who have never sought treatment before. They often believe that after a period of abstinence, they can return to the controlled, recreational use. Therefore, in the early phases of treatment, working with the stimulant user's denial about controlling use is paramount. Often after a week or two of abstinence, they are feeling better, and they assert their belief that they can use in a more controlled way--can "snort"

cocaine, but not return to freebasing or intravenous use, or can "deal" (sell drugs) but not use. It is the persistence of such false beliefs coupled with the intense physiological craving during the early weeks of stimulant abstinence which results in the high rate of slips and relapses after outpatient or even inpatient treatment.

Treatment Intervention

First, the patient must decide that his stimulant use is a problem,[140] which often means he must experience and admit to toxic effects, loss of control over intake, previously failed efforts to remain abstinent, interference with work or home, or be under pressure from family, friends, employer or the legal system, a process commonly referred to as "hitting bottom."* Then he must be helped to give up all use of stimulants (and other drugs and alcohol)--a difficult task during which the clinician encounters resistance, ambivalence and relapses. Total abstinence from all drugs and alcohol should be the agreed upon treatment goal. The often-voiced wish that the user can learn to "control my use" never works for long and can be a dangerous period of denial.

High-dose stimulant abusers usually become willing to discontinue their use following a binge (after severe toxicity) during the crash period (4 hours to 6 days), and effective treatment must be instituted during that short "window of opportunity." Intervention with the user, preferably involving the family, can break through the user's denial that he is addicted and needs treatment. Although some are then able to stop using, few can continue their resolve in the face of physical withdrawal cravings (which are rationalized in all sorts of ways) and occur during the first 10 weeks or so of abstinence (see Abstinence Syndrome). Practically all stimulant dependent persons need formal treatment.

Treatment of stimulant dependence involves:

- detoxification and the initiation of secure abstinence;
- the management of withdrawal cravings;
- stabilization of supportive, abstinent environment;
- structured long term outpatient treatment;
- progressively increased structure for lapses;
- extinction of conditioned cues;
- relapse prevention techniques;
- urine toxicology;
- self help groups;
- family involvement.

Secure abstinence must usually be initiated with inpatient treatment or non-hospital based confinement, followed by a structured, 4 or 5-day a week, day or evening "partial

* As Vaillant[144] says, "'Hitting bottom'...is not arriving on skid row. Rather,...[it] signals that the message 'I have truly lost control of my use of alcohol' has penetrated the alcoholic's system of denial." p.191

hospital" (outpatient) program for at least 1 - 2 months, which represents the intensity of structure necessary to achieve continued abstinence during the approximately 10 week stimulant withdrawal, when cravings are very intense and "triggers" are numerous. Some abusers are able to begin abstinence without confinement by participating in such an outpatient treatment program, if their home and work environments are drug-free and supportive of abstinence. Patients who are unable to maintain abstinence with outpatient programming require the next higher level of care temporarily until, with a review of the assessment and treatment plan, a more secure plan for outpatient abstinence is achieved. Exploring the precipitants for stimulant use and the environmental cues ("triggers") which exacerbate stimulant craving is important, and therapy based on Marlatt's relapse prevention strategies[90,91] (described below) are appropriate in the early months of treatment after secure abstinence is achieved and denial addressed.

Pharmacological intervention of the type described below (especially in patients who have received treatment but have relapsed) appears to improve retention or engagement in some outpatient programs.[134] Pharmacotherapy alone is never enough--it must be coupled with self-help program involvement and structured outpatient drug treatment. In most patients, traditional psychological and psychopharmacological treatments are only adjunctive and ameliorate stimulant use only for a few weeks or months. Pharmacotherapeutic intervention, though experimental, may be useful to diminish craving and alleviate other withdrawal symptoms even in patients without other Axis I psychiatric diagnoses.

Pharmacotherapeutic Approaches to Treatment

There is an accumulating body of treatment research attempting to define an effective pharmacotherapeutic intervention for cocaine-dependent populations.[18,148,150,151] This work either attempts to find an effective blocker for the reinforcing or rewarding actions of stimulants, or to find a craving-reducing drug, which would also enhance affective tone and diminish the anergia and anhedonia of stimulant withdrawal. Then treatment could begin to focus on extinction of conditioned response (the drug habit) in a more benign neurophysiological environment in the abuser.

It is well known that stimulant craving is very high during the first few months after ceasing drug use, and that the dysphoria, anhedonia and anergia of withdrawal are very unpleasant to users and promote leaving treatment and relapsing. In our inner-city, lower socio-economic bracket, unemployed sample of cocaine abusers (many of whom concurrently abuse other drugs and alcohol) hospitalized for an average length of stay of 15 - 20 days, a full 8 - 10% leave inpatient treatment before completing it. Another 2 - 5% use while on a eight to ten hour therapeutic pass from the hospital, but are retained in treatment. In outpatient day or evening intensive programs (4 - 5 days per week), a full 25 - 50% relapse, but sometimes only briefly, and then re-enter the program. Many patients do not choose to enter the outpatient program, thus ensuring their rapid relapse at some later point. It is estimated that over a 6 - 12 month period, probably less than 25%

are able to maintain drug abstinence defined as no more than 2 relapses for less than 2 weeks during that period; however, when abusers remain in treatment three months or longer, 60 - 80% reduce their drug use significantly. Thus, pharmacotherapeutic interventions that are low in side-effects, but efficacious, decrease craving, and promote abstinence and retention in treatment would be greatly welcomed by patients and treatment staff.

Antidepressants, Anticonvulsants and Stimulants

Several studies reported that cocaine abusers do less well than alcoholics in established treatments;[111] and animal data has established the powerful reinforcing ability of cocaine.[18,20,160] Knowledge of the withdrawal syndrome among cocaine users led researchers to try to reverse patients' neuroadaptation to cocaine, theoretically linked to relapse, initially with the use of desipramine and lithium carbonate.[93]

Tricyclic antidepressants, which reversed this neuroadaptation in animal studies,[111] were first used to treat the symptoms of cocaine withdrawal in the 1970's. These preliminary reports were for the most part open trials, and they demonstrated both positive and negative results.[93,111,113,135,150]

Gawin and Kleber[93a] reported the first double blind study utilizing desipramine, lithium carbonate or placebo, following 72 outpatients for only 6 weeks. They concluded that desipramine was better than placebo or lithium carbonate in reducing craving for cocaine and obtaining abstinence in both depressed patients and normals. In their study, desipramine was substantially better than placebo during weeks 4 - 6, but was no better until about day 17, and 59% of subjects were able to maintain abstinence for 3 - 4 consecutive weeks. They also demonstrated considerable placebo effect. Although their initial report[93] about lithium carbonate was encouraging, their double blind replication[93a] indicated that lithium was no better than placebo in reducing cravings among patients unselected for psychiatric diagnosis; however in some patients with bipolar spectrum disorder (mania, hypomania, cyclothymia), who appear to self-medicate the depressive cycles, lithium pharmacotherapy may reduce relapse. A six month follow-up[113] of 43 of the original 72 patients in that study found that "the ability to abstain from cocaine use during the [six week] clinical trial was the strongest predicator of continued abstinence during the [six month] follow-up," rather than the pharmacotherapy. Unfortunately, when similar outpatient studies were done with desipramine in a 12-week treatment trial with methadone-maintained subjects, results were less promising.[114,115] There have been other negative studies of desipramine as well.[116,120,135] This variability of findings in these random assignment, placebo controlled studies of pharmacotherapy for early abstinence has generated some controversy about the design of such studies and the reasons for varying results (critiqued by Meyer[111]).

The inconsistency of pharmacotherapeutic effect is reflected in both patients' and treaters' ambivalence toward the efficacy of medications during stimulant recovery. Drug abusers

are often reluctant to take prescribed, psychotropic medications anyway, during early recovery, a time they see as being "abstinent from all drugs."

Resnick and Resnick[67] suggested that the MAO inhibitor, phenelzine may be more useful than the tricyclic antidepressants, because it has an earlier onset of action. Their open trial with 16 patients initially indicated good results. There has been no follow-up, nor double-blinded studies. Using MAO inhibitors is risky, because of the possibility that the patient could develop a severe hypertensive crisis if stimulants were used on top of the MAOI; and in addition, MAOI's may stimulate the auto-oxidation of released dopamine to the more toxic 6-hydroxydopamine.[67,111a,111b]

Based on the efficacy of methadone maintenance among opioid addicts, Kleber[111a] tried a similar approach for cocaine abusers: a long-acting stimulant with few side-effects, methylphenidate. While initial trials of methylphenidate twice a day to treat the cocaine abstinence syndrome suggested that the drug diminished cravings acutely in addicts, the drug decreased craving for only 3 or 4 days and then required increasing doses as tolerance built. It did not block cocaine craving and may have evoked desire for resumption of use by week two.

Methylphenidate and other stimulants have been useful, however, for treating stimulant abusers with the added diagnosis of ADHD, Adult Type.[100,131,145] Although these patients are rare, they sometimes use stimulants in small doses daily, in a self-medicating fashion, rather than in a binge-like fashion and discontinue their use with a combination of appropriate stimulant drug therapy and traditional substance abuse treatment, but rarely without formal chemical dependency treatment. Again, there are no controlled studies.

The anticonvulsants (e.g. carbamazepine, valproic acid) have been recommended to treat stimulant craving, because in animal studies, carbamazepine decreases the development of cocaine-kindled, sub-cortical seizures, although it does not affect the development of cocaine stereotypy, and increases brain dopamine concentration.[117,118,119,141] In open trails, Halikas and co-workers found that carbamazepine reduced cocaine craving and improved cocaine abstinence rates among methadone-maintained cocaine abusers[118,119] and in drug-free subjects,[141] and some subjects reported a "blockade" effect,[141] as yet unconfirmed by other studies. Double-blind studies are in progress.

In a placebo-controlled, double-blind study, levodopa and carbidopa together did not reduce abstinence symptoms after abstinence from cocaine.[87,151]

Dopamine Agonists

Concurrent studies have attempted to use dopamine agonists to reduce cocaine craving more quickly than antidepressants. Initial studies by Tennant and Sagherian[121] with amantadine were promising, although recent studies have not supported its utility in decreasing cocaine craving;[122] however, studies of bromocriptine have suggested that it

decreases craving[112,114,116,123,124,125] within hours, however modestly.[137] Patients experience immediate relief, but when the drug is discontinued, usually after about 10 days, patients can experience reinstatement of their symptoms, and prolactin levels rebound. Bromocriptine gives more rapid results than the tricyclics or carbamazepine, which require at least two weeks to become effective;[121a,121b] thus, bromocriptine seems most useful as antidepressants or anticonvulsants are being concurrently begun.

Because bromocriptine works quickly, it is also useful in patients who are threatening to leave treatment early due to withdrawal craving. Patients often do not recognize or will not tell hospital personnel about the severe craving when they are insisting upon leaving a hospital-based treatment, during the first week or two. Thus, administering bromocriptine and asking them to wait for an hour or two, as it takes effect, to make their decision, often leads to a reduction in craving and enlists their continued cooperation to remain in treatment.

The use of a newly marketed dopamine agonist, pergolide, increased length of stay in cocaine-dependent inpatients, and may have decreased craving for cocaine.[142] A placebo-controlled study with the indirect dopamine agonist, mazindol, was not effective in reducing cocaine craving.[138] The use of both amantadine and bromocriptine among cocaine-dependent, methadone-maintained patients increased the time they remained in the programs in the studies.

Chronic amphetamine and cocaine abusers develop deficiencies of B complex and C vitamins, tyrosine and tryptophan.[16,37] Based on these deficiencies, treatment programs often administer multi-vitamins with tyrosine and tryptophan, the amino acid precursors to norepinephrine, dopamine and serotonin, in order to reduce the symptoms of the crash and withdrawal phases and replete the deficiencies more quickly. The advantage is that these substances are safe, and if they work, they may work quickly. Open label studies suggest improvement; double blind studies provide little evidence.[168]

Experimental Drugs: Buprenorphine, Flupenthixol, and Naltrexone

Initial work in rhesus monkeys by Mello and Mendelson[109] confirmed that daily administration of buprenorphine*, a mixed opioid agonist/antagonist[143,129,149] significantly suppressed cocaine self-administration for 30 days, but did not produce a generalized suppression in behavior, and that the effects were dose-dependent. Human research with this drug in treatment settings is just beginning.[129,143] Compton[149] reviews preclinical and clinical studies and concludes that efficacy has not yet been established. Clinical studies have indicated that buprenorphine is less reinforcing than other opioids in several species. The opioid antagonists, such as naloxone and naltrexone do not suppress cocaine self-administration in primates or in rodents, but do raise the threshold for electrical self-

* The opioid mixed agonist-antagonist buprenorphine is an oripavine derivative of thebaine with partial mu opioid agonist activity. It is a cogener of a potent opioid agonist, etorphine, and an opioid antagonist, dipreorphine. It is less reinforcing than other opioids in rhesus monkeys and baboons.

stimulation.[109] Theoretical rationale derives from some neuroendocrinological and behavioral studies that suggest that dopaminergic systems modulate the endogenous opioid system and the converse.[109] This finding in animals further illustrates that interrelationship. Because buprenorphine also suppresses heroin use by heroin addicts[109] it could be particularly useful in opioid addicts who continue to abuse cocaine, a common problem in methadone maintenance programs in the U.S. Compton discusses a finding of increased cocaine use among methadone-maintained subjects over that in drug-free subjects perhaps because cocaine may attenuate opioid withdrawal symptoms and be "especially rewarding to methadone patients."[149] Financial savings from heroin substitution may also play a role.[149] In one pilot study, buprenorphine was administered in sublingual doses of 2 - 8 mg per day for one month and reduced cocaine-positive urine specimens in methadone-maintained heroin addicts,[109] and in another, 4 or 8 mg per day over 20 days did the same among methadone detoxified patients who were drug free for six days.[129]

Finally, a preliminary study by Gawin, et. al.[110] reports that flupenthixol decanoate appeared to decrease cocaine craving and use, rapidly and markedly and increased average time retained in treatment among 10 subjects who were smokers of "crack" (freebase) cocaine. The drug is a depot xanthine derivative, having both rapid antidepressant activity at low doses and neuroleptic activity at higher doses, and at low doses, it produces minimal sedation or anhedonic side effects. It appears to block dopamine binding at a number of receptor subtypes with substantial activity at D-1 and D-2 at high dose, and inhibitory D-2 autoreceptors, perhaps even at low doses. The duration of action of the depot form is 2 - 4 weeks. Low dose flupenthixol treatment has now been established as being as effective as heterocyclic antidepressants in more than 15 double-blind control trials.[110]

Ten heavy "crack" cocaine abusers in outpatient treatment were given an initial dose of 10 or 20 mg of intramuscular flupenthixol decanoate and prophylactic benztropine (4 mg) for possible extrapryamidal reactions (no subject needed more than the initial benztropine dose). Nine subjects reported rapid reduction of cocaine craving within 3 days of drug administration, and craving remained decreased throughout the first week of treatment. Eighty percent ceased cocaine use during the first week, and the remainder ceased during the second week of treatment. Subjects uniformly described a reduction in dysphoric, anhedonic and anergic symptoms, and more than 70% reported reduction in the magnitude of craving induced by environmental cues. Compared to previous treatment stays, subjects evidenced a 260% increase of weeks in treatment (8.7 to 23 weeks). When treated at higher doses (30 to 40 mg), subjects reported diminished intensity or duration of cocaine's euphoric effects, but not complete blockade when relapses or slips occurred. Unfortunately, the flupenthixol at these higher doses produced a substantial subjective distress, including anhedonia and increased drug craving, which prompted refusal of further administration and discontinuation of treatment.[110] This, again, was an open trial. The rapid onset of antidepressant effect and diminished drug craving appeared to be the most clinically useful effects for stimulant abusers in the withdrawal period. Most

abusers would not tolerate the effects of the higher doses, even though they could achieve partial blockade of cocaine effects.

The opioid blocker naltrexone (a mu-receptor antagonist), which has recently been found useful to block the reinforcement (and decrease the craving), associated with alcohol use in chronic alcoholics in treatment, has not yet been studied in stimulant abusers.[151] But cocaine and amphetamines work directly at the nucleus accumbans and pre-frontal pathways, which are themselves the reward circuitry, and opioid receptor blocking will probably not reduce cravings or reward in the case of stimulants.

Pharmacotherapeutic blockers to the chemical reward such as naltrexone with opioid dependence[88] and more recently the use of naltrexone with alcoholics in treatment,[88a,88b] may well be a helpful adjunct in extinguishing of the alcohol or opioid habit during the early phases when patients are most prone to slip, as long as the medications themselves are relatively free of side-effects so that patient compliance is high.

So far, there is no similar blocking drug for the stimulants, cocaine or amphetamine. Dopamine blocking neuroleptic drugs (such as chlorpromazine) have been proposed, but are unstudied, and use of neuroleptics may increase the craving for stimulants, exacerbate anhedonic withdrawal symptoms, lower the seizure threshold, and are not well-tolerated by patients long-term. The work with flupenthixol decanoate,[110] initially promising, was disappointing in clinical trials, however. Naltrexone has been ineffective in reducing cocaine administration in pre-clinical studies but was more effective than methadone in reducing cocaine use among opioid-dependent patients.[109,151] The problem with the clinical usefulness of naltrexone in opioid-dependent patients has been poor compliance.

Clinical Consideration in Pharmacotherapy

Aside from the difficulties of side-effects of pharmacotherapy and possible minimal effectiveness (particularly long-term), a major hurdle is getting patients to accept the notion that they should replace one drug, in this case a physician-administered one, for their own drugs of choice (which may have successfully ameliorated their subjective life distress and even blocked full comprehension of the illicit drug's negative effects on their lives). Patients enter treatment wanting to be drug-free, and there needs to be much discussion around rationales for using these medications, particularly since they are rarely devoid of side-effects. The most used pharmacotherapeutic agents, antidepressants and anticonvulsants, often have serious side-effects on sexual drive and performance, and addicts are particularly loath to give up sexual behavior, especially when they no longer have the chemical reward of abused drugs.

On the other hand, administering drugs as part of early recovery can have a positive effect on retention in treatment, perhaps not entirely because of their in efficacy in reducing withdrawal symptoms, including craving.[134,142] Introducing the use of desipramine (150 mg per day) into a San Francisco outpatient cocaine treatment program increased

retention from 20% to 60%.[126,134] Patients are being given *something*, and generally are being seen by a physician, and this in itself, in an outpatient treatment setting can improve compliance and retention. Campbell and coworkers found no effect on patient retention, however.[135]

Pharmacotherapy may be tried with everyone entering treatment, or it may be used for selected individuals who have shown a propensity to relapse. One regimen is upon admission, to administer a rapidly-acting dopamine agonist immediately effective on the cocaine withdrawal cravings, and bromocriptine is particularly effective. Since dopamine receptor sites are supersensitive ("up-regulated") in withdrawal, bromocriptine should be used initially at reduced dosage, beginning at 0.625 or 1.25 mg twice or three times a day, and daily increasing gradually up to sometimes 5 mg per day. Desipramine (or probably any antidepressant) or carbamazepine can be begun concurrently with the bromocriptine to achieve a "down-regulation" of dopamine circuits. Bromocriptine appears to work for about 2 weeks, and by that time the antidepressant or anticonvulsant should have begun to reduce cocaine craving, anergia and anhedonia. It is important to administer the antidepressants at standard (high) antidepressant dosages (desipramine, 150 - 250 mg per day). Other antidepressants probably work as well; bromocriptine is said to work well for the initial sleep disturbance from cocaine withdrawal and for the initial intense craving, which prompts thoughts of leaving treatment early. Carbamazepine can be begun with an average daily dose of 400 - 600 mg per day, although, because of sedation, patients often spontaneously reduce their dose to 200 - 400 mg per day after discharge, but continue to benefit. Although typically white blood counts decrease to 2500 or 3000, this generally is not a problem, but must be followed. Halikas,[118,119,141] in his work, has attempted to achieve a blood level of between 4 and 5 micrograms per ml.

If used in conjunction with methadone, carbamazepine will decrease patients' methadone levels, probably because of enzyme induction.[141] Patients will complain of the methadone effect wearing off, or that it is "not holding them," and methadone can be increased gradually in 5 mg increments, usually necessitating no more than a 5 to 15 mg increase (10-15% of the maintenance dose). If using desipramine with methadone, methadone may increase the 2-hydroxy-DMI metabolite, thus decreasing the antidepressant level of total metabolites over what it would be without methadone, and therefore reducing the antidepressant effect. Thus, tricyclic antidepressants may need to be used in higher doses, and blood levels, if available, should be obtained.

Other investigators have tried imipramine, trazadone, buproprion, lithium, alpha-methylparatyrosine, fenfluramine, fluoxetine, mazindol, pergolide, levodopa and carbidopa to either ameliorate craving and other abstinence symptoms or to attempt to block stimulant effect.[150,151] Although animal studies and some initial reports of small samples of subjects in open trials have reported decreased craving or better short-term outcomes, no subsequent studies have verified that the euphoric effects or the reward has been blocked.[150]

To summarize, effects of antidepressants such as desipramine or anticonvulsants are modest and most apparent in the initial phases of treatment.[120,150,151] Long-term, secure abstinence requires intensive outpatient treatment (as described below), attendance at self-help groups (in the U.S., Twelve-step support groups), relapse prevention programming, and high motivation whether or not supportive pharmacotherapy is utilized.

Detoxification and Initiation of Secure Abstinence

Detoxification from stimulants is a relatively simple matter: few, if any, medications are needed, and individuals' withdrawal symptoms (except for drug craving) are seldom as severe or as uncomfortable as those seen with opioid or sedative-hypnotic withdrawal. Depressive symptoms and suicidal feelings are common presenting complaints (or can emerge after the drug is stopped) but normally clear within 72 hours after hospitalization or initiation of secure abstinence after and a realistic plan for appropriate chemical dependency treatment is instituted. The stimulant psychosis from cocaine generally clears without neuroleptic use after the drug disappears from the system, but with longer-acting amphetamines, neuroleptic use may be required for 24 hours initially to manage the patient on an inpatient basis. If the patient is psychotic (usually, paranoid) as a result of the stimulant psychosis, small doses of neuroleptics can be instituted but because of the dopamine blocking effect, they can exacerbate and increase subsequent craving, as explained earlier. Diagnosis of delirium should be a sign of concurrent sedative-hypnotic withdrawal or of extremely high-dose stimulant ingestion and requires emergency treatment and confinement.

If patients are "geared up" or "still speeding," that is, still intoxicated from stimulant use, benzodiazepines, like diazepam or flurazepam, can calm a patient and help him sleep. The usual tenet applies that prescribing benzodiazepines to an outpatient drug abuser (as part of detoxification or to treat ongoing psychiatric disorders) is contra-indicated since the addict, will generally (eventually) abuse them. At the very least, the disinhibition from the benzodiazepine reduces the addict's resistance against relapse; therefore, trazodone (50 - 150 mg) or a low-dose of a sedative antidepressant (25 - 100 mg of amitriptyline or doxepin) is the best outpatient medication for sleep disturbance. If benzodiazepines must be used for persistent generalized anxiety disorder or panic disorder unresponsive to antidepressant treatment, choose a long-acting benzodiazepine with no "street reputation" and prescribe it in low-doses for no more than one week at a time keeping close track of the prescriptions and refills.

As stated before, detoxification from concurrent drugs, especially opioids or sedative-hypnotics on which the addict is dependent, must be done carefully and usually within an inpatient setting.

The physical craving for stimulants, which is part of the physical withdrawal, is the most difficult withdrawal symptom for the addict to tolerate during the early abstinence period.

Cravings are usually experienced in the subtle form of thoughts or vivid memories triggered by conditioned cues, and those thoughts, when acted upon, lead to plans about eventual use. The addict may not initially experience these thoughts about using the drug again as a "craving" as defined by treatment personnel. Such urges are interpreted more as "a desire to use." Patients and clinicians alike often underestimate the power of the physical, neurochemical, neuroadaptational component to drive relapse. They seldom realize how emotionally (limbic system-) driven these early withdrawal cravings are and how difficult it is to exert cognitive control over them. Users detoxing from a high-dose cyclical pattern of binge use may experience more powerful cravings than those with low-dose patterns of use. These powerful cravings are experienced as having great drive components behind them, forcing patients to disguise their desire to use and to attempt to leave the hospital setting using all sorts of rationales. Leaving treatment prematurely practically always means that the patient is about to resume drug use.

When a patient threatens to leave the treatment setting, one should expect that this behavior is driven by cravings and a desire to use drugs. Undermedicated withdrawal is another reason that patients attempt to leave. The clinician must correctly diagnosis what type of drug withdrawal is causing the most serious symptoms since it often reflects a combination of drugs. Explaining this to the addict and medicating the symptoms effectively results in retention in treatment. Untreated (and undertreated) psychiatric symptoms and syndromes also may contribute to a patient's desire to leave treatment.

It is appropriate to medicate stimulant withdrawal cravings with a low-dose of a dopamine agonist such as bromocriptine 0.625 mg q.i.d. for the first day (at a reduced dose because the receptor sites are super-sensitive) and gradually over several days, increase to 1.25 mg q.i.d.. Amantadine has also been reported to be effective but in my experience, less so than bromocriptine. Bromocriptine usually ameliorates the cravings within a period of a few hours, and other chemotherapy (antidepressants, anticonvulsants) to combat withdrawal cravings can then be started while the patient remains in treatment.

The antidepressants and anticonvulsants have been reported by several investigators to ameliorate the cravings of early stimulant abstinence, but they are only partially effective: they do not completely eliminate the withdrawal cravings nor the conditioned habit or the resultant thoughts about resumption of use. Furthermore, they take at least ten days to start reducing drug cravings. They may increase retention in outpatient treatment programs. Desipramine and carbamazepine have been the drugs most well-documented in the treatment of cocaine abstinence, but probably any antidepressant in psychiatric doses or any anticonvulsant such as carbamazepine or valproic acid could be used. It is possible to continue bromocriptine for two weeks while maintaining adequate dosing of antidepressants or anticonvulsants. Down-regulation of dopamine circuitry is thought to occur generally 10 - 20 days after an adequate blood level of antidepressant or anticonvulsant is reached. Dopamine agonists such as bromocriptine can be discontinued. It's important to understand that the use of chemotherapeutic agents to treat the cravings during the withdrawal phase is only an adjunct to formal chemical

dependency treatment described later, and chemotherapy is of only very short term benefit in the maintenance of long term abstinence.

Chemical Dependency Treatment Programming

One must remember that *detoxification alone rarely works* unless accompanied by chemical dependency treatment programming. *Outpatient treatment almost never works* in family practice or traditional psychiatric settings, because these settings do not incorporate elements which appear to be necessary in order to ensure the success of long term abstinence. *Outpatient detoxification often works*, however, when part of an intensive, structured chemical dependency treatment program.

The treatment of chemical dependency disorders requires a program that consists of many elements which are not present in ordinary psychotherapy or medical treatment environments.[136,153,154,156] Such a program can be a combination of inpatient non-hospital-based residential and outpatient treatment, and:

- needs to be long term;
- requires direct monitoring, preferably with urine and alcohol (breathalyzer, saliva tests) testing, or at least visual monitoring and questions about use and observations about changes in behavior indicating possible use;
- provides structure;
- provides therapy focused on the "here and now" of each patient's recovery;
- involves the addict's family in group sessions at least once weekly;
- requires the ongoing assessment of mental status since other Axis I disorders are so prevalent and can appear weeks to months after detoxification and lead to leaving treatment prematurely;
- stresses and facilitates lifestyle change;
- usually includes group therapy[139,153] and self-help groups.

Addicts need structure of at least four evenings per week if employed and day and early evening programming if they are unemployed. Weekend programming would be helpful but may not be attended. Out patient treatment programs generally are held four to five nights per week for approximately the first two months, and then relapse prevention programs following the early abstinence phase are generally twice weekly for another two months. We stress the concept of treatment for a year, but some recent studies have indicated that sobriety stabilizes only after two years of abstinence. A program needs to provide each addict with a realistic, individualized plan for recovery that engenders hope and provides consistent access to formerly addicted individuals who are at various stages of successfully recovering. Besides providing abstinence support, this contact helps addicts regain their dignity and self-esteem. Vaillant[144] believes that alcoholics recover "not because we treat them but because they heal themselves," and programs should do all they can to empower abusers to remain abstinent and change their lifestyles.

It may be necessary to employ strategies which utilize external controls such as contingency contracts, urine analysis, and family or employer coercion, although coercion may backfire as a patient's anger mounts and becomes a precipitant for continued use.* Most stimulant abusers need to relinquish control of their income to another responsible party, such as a spouse, in order to successfully help them through the initial phase of abstinence.

Hospitalization and Confinement

Because of the compelling nature and urgency of stimulant craving, confinement or hospitalization of some patients (particularly those in high-dose cyclical patterns) is necessary to prevent continued access to stimulants, to enforce abstinence and to protect patients against self-destructive acts. Washton, et. al.[92,92a] recommend hospitalization of abusers with severe depression, stimulant psychosis or repeated outpatient failures. Other indications for inpatient treatment include concurrent dependence on alcohol or other drugs requiring withdrawal, severe psychiatric or medical problems, severe psychosocial impairment, lack of motivation to discontinue use, lack of family and social supports, and contact with dealers with ready access to large amounts of drugs. Many advocate hospitalizing freebase cocaine users and intravenous stimulant users for several reasons: the craving from high-dose use is initially too intense to act against, toxic reactions are severe, and the possibility of overdose (especially with freebase cocaine abusers and intravenous users) is great; however, Gawin and Kleber have treated highly motivated cocaine users successfully for six weeks on an outpatient basis with desipramine and weekly psychotherapy combining pharmacotherapy with the methods of relapse prevention and interpersonal psychotherapy.[38,93,94]

Inpatient or residential treatment attempts to ensure that the patient is not exposed to the drug and should incorporate monitored urine specimens for toxicology obtained upon admission, and after each therapeutic pass e.g., to visit family. Random specimens should also be collected to ensure that there is no drug use on the inpatient unit from smuggled supplies.[67,32,94a] Inpatient treatment often provides confrontation of denial, individual psychotherapy, group psychotherapy, family assessment, education seminars, and an introduction to 12-step program involvement. Ongoing mental status assessment and treatment of concurrent psychiatric disorders should occur during initial hospitalization, and 12-step self-help MISA meetings (Mentally Ill Substance Abusers), focusing on psychiatrically-disordered substance abusers, may be helpful for these "dual diagnosis" patients. Since information obtained upon admission from substance abusers about co-occurring drug abuse can be incomplete or unreliable, getting collateral information from friends, partners or family and a complete physical examination and laboratory workup upon admission is recommended.[32,94a]

* Alcoholics Anonymous refers to such coercion as "enabling behavior" and cautions against it.

Family Involvement

Family involvement in treatment is always indicated,[67] and if the patient has no family, involving significant others such as friends or sexual partners in treatment is important. Family evaluation and family therapy is helpful in dealing with the "enabling" and "co-dependence" of spouses and other family members. Once the patient is safe and in treatment, the spouse's anger and rage usually emerges and must be addressed. Patients should be encouraged to discuss their drug dependence with children, spouses, and other family members, and all should be encouraged to attend AlAnon or AlAteen (self-help programs for family members). The spouse's help should be enlisted to reduce enabling the user to continue his abuse. Spouses who are also abusers of stimulants or other drugs must be encouraged to enter treatment, and, should they decide not to do so, the patient should be encouraged to separate from them, at least temporarily. Families can learn to set firm, consistent limits, to say no without making empty threats, and to stop giving money to replace money that the patient has spent on drugs. In treatment, family members can learn to identify and change their own destructive and counter-productive behaviors such as accepting rationalizations for drug use and behavior and rescuing the patient before he experiences the consequences of his use of drugs thereby siding with the patient's continued use of stimulants and avoidance of treatment.[95]

Stimulant abusers, like other drug dependent individuals, must often "hit bottom" and experience the consequences of their behavior (sometimes loss of family, friends and employment) before they accept that they need treatment and must relinquish their drug use. Families must be helped to deal with their helplessness during this important phase and to seek the help of support groups where they meet other families who have had similar experiences. Families must learn that they are not responsible for the patient's slips or relapses and that the patient alone is responsible for his use of drugs and his abstinence.[95]

Psychotherapy and Behavioral Approaches to Relapse Prevention

Individual psychotherapy approaches have employed cognitive/behavioral models,[94,156] relapse prevention,[91,96] cognitive relabelling,[67] supportive/expressive treatments, and combinations[136] to cope with the ambivalence around ceasing use, preventing premature dropouts from treatment, providing education, helping the user cope with craving, managing relapse, exploring core conflicts, and treating underlying psychiatric difficulties, including severe character disorders often present in multiple drug abusers. Research into these approaches with stimulant addicts is relatively new and results are tentative. Group therapy[139,153] and couples counseling, as well as using multi-family groups have also been useful. Developing pleasurable rewarding alternatives[97] to drug use is a crucial but overlooked part of lifestyle change crucial to insulating against relapse, and there is some animal data with cocaine to support its efficacy.[97a]

Psychodynamic treatment approaches, reviewed by Brehm and Khantzian,[99] are sometimes useful for selected individuals as an adjunct to other strategies such as relapse prevention or 12-Step support and concentrate on the role stimulants have played in a person's life, particularly as a modulator of affect and a regulator of self-esteem, exploring the supposed root causes of a person's loneliness, low self-esteem, trouble in handling aggression, etc. Countertransference aspects of psychotherapy with substance abusers, especially with provocative and manipulative patients, is discussed by Kaufman.[133] He outlines three phases of recovery and reviews the psychotherapeutic approaches appropriate to each phase. Psychodynamic psychotherapy alone has little value with stimulant abusers (especially if they are continuing to use) but may be useful as an element in a total program of recovery.[67,99,100,133]

As with any chemical dependency, treatment of the stimulant dependence is the "first order of business," and without concurrent drug abuse treatment, treatment of "underlying" difficulties, whether they be psychological or pharmacological in nature, will not prevent relapse for the longer term unless motivation is high and users are introduced to support groups.

The best known behavioral approach is contingency contracting.[101,102] Subjects agree to participate in a urine monitoring program with some aversive contingency attached to producing a urine sample positive for cocaine or failing to produce a scheduled urine sample. In Anker and Crowley's study, the average contingency contract duration was 3 months and of the people who agree to participate, 81% remained in treatment and abstinent for 3 or more months. Just over 50% relapsed after the contract was terminated, but of those who refused to sign a contract, 90% dropped out or resumed the cocaine use within 2 - 4 weeks of applying to the clinic.[101] Effectiveness of contingency contracting is improved by involving patients' significant others in the treatment.[116]

Supportive behavioral approaches adapting Marlatt's relapse prevention schema[90] have been somewhat effective, especially when combined with self-help groups. Users are helped to develop a concrete strategy for dealing with high risk situations, conditioning factors ("triggers"), and early warning signals and are taught to oppose the process of addiction, reduce stress and change their lifestyles in order to engage in healthy activities.[97,108,153] Internal and external precipitants (conditioning cues, triggers) leading to slips are identified, and abusers are helped to identify alternative behaviors for dealing with such precipitants in the future.[90,153] The hierarchy of four treatment stages in the extinction of conditioned craving is discussed by Gawin and Ellinwood.[96]

A recent study found no difference at six months between using an outpatient cognitive/behavioral relapse prevention model[90,108] or a conventional Twelve-Step recovery support group[107] to treat randomly assigned cocaine abusers who also used either alcohol or marijuana, although there was a high dropout rate from once weekly sessions with both treatment conditions, underscoring that outpatient treatment should be intensive: 4 - 6 days per week for at least one month.

In some experimental programs,[103,104,106,125] active (accelerated) extinction is used, where in the safety of a treatment setting, recovering abusers are exposed to increasingly vivid reminders of their drug use, while at the same time, they are taught relaxation exercises and cognitive/behavioral techniques to oppose the process of relapse, similar to systematic desensitization for anxiety and phobic disorders.[105] The principles of this strategy are outlined by King and Ellinwood.[16] Unfortunately, the craving decreased by these methods in the laboratory setting may not persist when addicts enter the real world.[132]

Drug Monitoring

There should be a program of drug use monitoring with sanctions consistently applied which are non-punitive yet lead in the direction of increased structure for lapses. Thus, patients who lapse (slip) or relapse need more treatment, not less and should progress quickly to the next higher level of care whether that be residential or inpatient. Both lapses and relapses should be studied and processed in group and individual treatment contacts and recommendations individualized and memorized by the addict to prevent future similar slips.

Urine analysis (randomly or twice or three times a week) for stimulants or metabolites[130] helps some patients abstain and insures that they will be honest about slips and relapses. The advantages of urine analysis should be discussed with each patient and his feelings about it elicited and respected in order to further the therapeutic alliance. Although some patients request it and believe it will be helpful in ensuring their continued abstinence from stimulants, others are insulted and believe that it implies distrust by the therapist, or secretly believe that they will use again and want to avoid discovery--another form of denial. Thus, most outpatient programs require urinalysis--patients are adept at hiding their use. Employers and the legal system insist on urine monitoring.

The therapist should decide on an individual basis whether lapses or slips (resumption of use for a short time) will be tolerated as an expected part of attempts at continued early abstinence, or whether a slip is serious enough to warrant recommendations that a patient proceed to the next level of treatment--day or evening partial hospital, inpatient treatment, or long-term residential care. When abusers slip, they need more focus and more treatment, not less, and need progressively increased structure until secure abstinence is achieved. Thus, punitive dismissal or suspension from the program is contraindicated. They may require a half-way house or residential care. During inpatient or residential treatment, the patient who uses on the inpatient unit or who uses drugs during a pass should be placed on an "intensive treatment program," where a diagnostic evaluation for a co-occurring psychiatric disorder is undertaken, the precipitants for the slip are discussed in terms of relapse prevention, a more intensive individual psychotherapy is instituted, and all passes are discontinued. Should a patient slip a second time while hospitalized, a transfer to another treatment facility may be recommended, and possibly, long-term residential placement is indicated. If drugs have been brought into the treatment facility,

the offenders should probably be transferred to another (more secure) unit or to another program, because the occurrence makes the treatment milieu feel very unsafe to other patients, there is much resentment, and it can undermine therapeutic leverage with other patients. The general rule is that for patients who slip during treatment, more, rather than less, treatment is indicated, and staff should be taught never to simply discharge the patient, but to recommend a more intensive program, in the same facility or another.

Relapse Prevention Programming

The first month or two of outpatient treatment usually involves processing problems within the family, personal, and work life brought on by the drug dependency and dealing with the addict's denial about what each will need to do in order to stay abstinent. It is in the second phase of outpatient treatment during the second or third month in early recovery that relapse prevention is best instituted after denial is more conscious, although identifying triggers and strategies to avoid them should be discussed throughout treatment. Early recovery relapse prevention programs[153,154,158] emphasize:

- recognizing early warning signs of relapse;
- combating euphoric recall;
- overcoming the desire to re-attempt controlled use;
- reinforcing negative aspects of use;
- avoiding conditioned stimuli;
- insulating lapses from progression to relapses;
- recognizing and coping with disphoria;
- developing pleasurable and rewarding alternatives.

Washton[153] discusses cognitive distortions and "mind traps" which preceed and lead to relapse such as self-sabotage and setups, feeling cured, testing personal control, idealizing the cocaine high, overreacting to urges and cravings and to slips and relapses, and negative mood states.

Self-Help Groups

Self-help groups for recovering individuals (generally based on the Twelve Steps of Alcoholics Anonymous) provide free and accessible support for an individual's abstinence. But they are "programs of attraction," and although attendance could be coerced (by family, employers or the legal system), real participation cannot be forced. They offer something in return for relinquishing one's drugs of choice, although less immediately gratifying.[144,155] They engender hope, demonstrate caring for oneself and others, foster humility and gratitude for small blessings, and provide a way to look at one's faults, strive for change and help people "make amends" to those whom the abuser may have hurt along the way. They reduce addicts' denial of their need for their drugs and their denial of their need for other people ("I can do it by myself...") in the support of

their recovery.[155,144] These groups often function as an extension of the self which provides soothing, empathy, and an auxiliary ego/superego. Alcoholics Anonymous is recognized as one of the most effective treatments for alcoholism, and participation in such programs is likely to be more important to an individual's continued abstinence than professional treatment.[153] Unfortunately, self-help participation and active involvement is often a late step in the course of the disorder. Vaillant[144] offers some "suggestions for helpers" in referring patients to such a program.

Twelve-step, Alcoholics Anonymous-type programs are the mode and have blossomed into Cocaine Anonymous, Narcotics Anonymous, Pills Anonymous, Co-dependency Anonymous, and the like, but other self-help programs not based on the Twelve Steps have sprung up such as Women For Sobriety and Rational Recovery.

Self-help programs of recovery so far have not developed and flourished in Asia. It is said that this may be due to the Asian's reluctance to share feelings and details about personal and family difficulties in group settings outside the family, among groups of relative strangers or members of other families in the community. However, shame and "face" is common among patients and families of chemical dependents worldwide so there must be more to the explanation. Understanding cultural differences are crucial to the development of effective treatment components, and programs cannot simply be imported thoughtlessly, however well-intentioned. Some thought must be given to how self-help recovery programs could be modified with cultural values in mind, since they have proven so helpful to so many peoples' recoveries.[144]

Extinction of the Habit

The most crucial aspect of treatment is to *maintain drug abstinence*. Detoxification alone is a relatively simple matter. It's easy to get a person off drugs; it's much more difficult to keep him off. Habits, especially drug habits, are formed by operant conditioning, by the (powerful) reinforcing effect (biochemical reward) of the drug "high." It appears to be the positively reinforcing euphoric aspects of the stimulant "high" that are reflected in stimulant craving rather than the negatively reinforcing relief of withdrawal symptoms which typify craving and use in opioid and sedative addiction.[132] *Extinguishing the habit* of drug use is crucially important in the long-term maintenance of abstinence with every kind of drug abuser. If conditioned cues (memories about use and "triggers" to use) repeatedly and consistently fail to be followed by the reward that established them (the drug high), their potency diminishes (but is never forgotten). This can only occur after the patient has left the security of residential or inpatient hospital care. It is only in outpatient treatment, where drugs are available and conditioned cues or triggers abound, that the habit can begin to be extinguished or de-conditioned.

How is it that habits are extinguished? Drug habits are extinguished by pairing the availability of the drug or an environmental cue or "trigger"--something that has come to be associated with the reinforcement of the drug high--with the *absence* of reinforcement,

by not ingesting or injecting the drug. After numerous times of stimulus and no reward, the habit begins to extinguish itself, and the craving or thoughts about use become less frequent and intense and are accompanied by progressively less emotional drive or intensity of feeling. Very simply, abstinent drug users in recovery who are presented with the opportunity to use the drug do not use, and thus do not experience the reinforcement, and instead (and this is crucial) they experience the pride of having avoided a slip or relapse. (Punishment-like unpleasant side effects of the drug abused--in animals or humans--is not an effective deterrent with stimulant abuse.) After numerous instances of rejecting the drug, the user begins to feel physically better as the withdrawal subsides, his pride about no longer using accumulates, and he begins to develop some confidence in his ability to continue abstinence, and ultimately changes his lifestyle, insulating him from further availability.

Numerous non-pharmacologic problems can contribute to relapse at this phase, including hopelessness--about the ability to ever maintain sobriety, about difficulties of his lifestyle or home life with family or job, temptation of the availability of the drug from friends or dealers, and psychiatric disorders such as depression or bipolar illness, to name a few.

Extinguishing the conditioned habit is crucial, probably more important in maintaining sobriety, than either the quality or the intensity of the withdrawal or the effective use of pharmacotherapeutic agents during acute or protracted withdrawal.

What determines successful abstinence? The individual's motivation to discontinue use and achieve long term abstinence is the most important factor for success, but without more formal treatment, even the most motivated stimulant abusers can seldom maintain long periods of abstinence. Acceptance and identification of areas of denial and what to do about them is a crucial step and an equally important factor. Character, in the psychodynamic sense, must play a role. To facilitate abstinence, family supports, self-help groups, and abstinent friendship groups which are readily accessible to the patient are equal in importance to achieving high levels of structure in the addict's day. Initially a structured treatment program provides the needed structure, but steady employment is usually the only solution for the longer term: few unemployed people can maintain sobriety long.

When the drug use is part of the job culture as with some truck drivers, farmers, and communities of fishermen in some parts of Southeast Asia, change of employment is imperative, and yet it is a eventuality that is difficult to get the patient to accept (and readily available alternative employment realistically is difficult to find). Almost no drug dependent person can maintain abstinence in a home or work environment where drugs are being used and readily available.

Sometimes the judicious use of so-called anti-craving drugs, the dopamine agonists, antidepressants, and anticonvulsants, can be temporarily helpful and enhance motivation, but they are never a substitute for formal treatment programming. In such a work environment filled with other users where availability is high and triggers abound, it is the

rare stimulant addict, indeed, who can maintain abstinence for longer than a few weeks with anti-craving drugs alone. Usually a change in work environment is needed.

The addict's ability to construct over time--through lifestyle change--greater and greater degrees of insulation from drug availability and stabilization of a supportive, abstinent environment is an important longer term factor in the maintenance of abstinence. For example, increasing time spent with abstinent friends, (particularly those who are aware of the addict's past drug involvement and supportive of his current abstinence), moving away from channels of availability or social groups where drug use is frequent, changing neighborhoods of residence, changing jobs and often spouses--what 12-step programs refer to as "changing people, places, and playthings"--are all factors that have been frequently documented as part of successful recovery in long term studies of alcoholics.[144]

Even among the "best" patients and programs, "success" rates over the first three and twelve months are low: rates of lapse and relapse are high and total abstinence without slips or failures is the exception. Most stimulant addicts experience at least one or two slips (and often up to five or even ten) before they can achieve year-long abstinence, and the process of deciding to seriously attempt to achieve abstinence may extend over years. Aversive contingencies such as threatened loss of either employment or a relationship, health difficulties, or legal involvement are all potent factors motivating abstinence, as they are with alcoholics.[144]

I know of no program for stimulant abusers which can boast of 50% of its patients achieving relatively complete abstinence over twelve months. Generally the percentage of those who achieve a year of abstinence post-treatment is in the range of 15-25%, perhaps greater among those programs that self-select the most motivated, higher functioning, and employable individuals. Yet professional status, easy employability, a spouse and family, or great financial resources are neither necessary nor sufficient predictors of successful abstinence. In fact, high socio-economic status and wealth are often associated with poor outcomes initially since personal and financial resources allow individuals to surround themselves with enablers and "hit bottom" more slowly than the economically less fortunate.

Thus, clinicians can easily become discouraged, and staff can experience "burnout" (Symptoms: helplessness, apathy, lack of empathy, anger and irritability, immobilization and pressure, and work-related anxiety and guilt). Case conferences and staff support groups which provide a confidential forum for a frank discussion of job concerns help to prevent staff burnout. Such groups should provide continuing education related to job tasks; help to redefine the job as manageable; help staff to become more comfortable with limited capacities and resources and the limits of patients' motivation; help establish boundaries of the job and set limits with patients; and support realistic goal-setting and goal clarification.[167]

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