Is Craving Mood-Driven or Self-Propelled? Sensitization and "Street" Stimulant Addiction

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INTRODUCTION: SENSITIZATION AND PSYCHOSES

Pharmacological sensitization is defined as an increasing effect of a given drug dose after repeated administrations. Detected over 65 years ago during observations of animal behavior, sensitization provided an anti-thesis to the concept of pharmacological tolerance. In modern neuro-science, the sensitization concept has evolved to reflect neuroadaptive, or perhaps neurotoxic, processes and pharmacodynamics, rather than pharmacokinetic changes in plasma or brain concentrations of a drug.

Sensitization was first observed as gradual increases in motor activation following daily readministration of stimulant drugs (e.g., cocaine, amphet-amines). Sensitization has subsequently been demonstrated, assessed, and extended in multiple research domains, including hundreds if not thou-sands of preclinical neurophysiological and neurochemical studies in monoaminergic systems. Sensitization is evoked by some but not all dosages and administration patterns. Sensitization has also been demon-strated in both nonstimulant drugs of abuse and in medications without abuse potential. Hence, neither stimulant properties nor addictive proper-ties are required to produce sensitization.

Both the pursuit of basic pharmacological knowledge and clinical psychiatric and neurophysiological observations drove the extensive work in sensitization research. Clinical observations yielded theoretical impli-cations for sensitization in mental illness, indicating that the neurophysi-ology of sensitization might be part of, or similar to, the pathophysiology of paranoid psychoses. These observations included multiple cases of stimulant-induced paranoid psychoses in stimulant users that appeared soon after clinical use of cocaine and amphetamine became established (Lasagna et al. 1955; Lewin 1924; Maier 1926). The psychotic episodes occurred during or immediately after amphetamine self-administration of substantial doses throughout sustained binges, but in only some abusers. The episodes followed a near-uniform sequence, emerging and

intensifying over time and mimicking a sensitization-like dose-response paradigm, usually occurring only after chronic abuse and repeated binge administrations (Ellinwood 1967; Kramer et al. 1967; Smith 1969). The similarities between sensitization evoked in animals and stimulant-induced psychoses led to an enduring animal model for research on human psychosis and schizophrenia (Borrison et al. 1979; Post et al. 1976).

SENSITIZATION AND ADDICTION

Sensitization has had dramatically less prominence in addiction theory and research, despite the fact that the prototype stimulants used in early sensitization studies had addictive properties. Recently, researchers in basic rather than clinical sciences, particularly behavioral pharmacology, have advanced an entirely new clinical domain for pharmacological sensitization—drug seeking in addiction—speculating that the crucial clinical phenomenon of drug craving is mediated by pharmacological sensitization.

Earlier clinical speculation, although limited, also held that sensitization may play a role in cocaine abuse and craving. A series of clinical pharma-cotherapy studies ensued that evaluated carbamazepine, an agent that limits the acquisition of sensitization, for treatment of cocaine dependence (Hallikas et al. 1991, 1992). However, several controlled trials failed to demonstrate any therapeutic efficacy for carbamazepine in cocaine abstinence initiation (Kranzler et al. 1993). Before the recent extensions in the sensitization concept occurred, it should be noted that 50 years of clinical observation and research during several amphetamine and cocaine abuse epidemics had not resulted in serious suggestions that sensitization-like clinical phenomena were integral to drug seeking and addiction.

Dissimilarities Between Sensitization and Craving

The authors have previously held (Gawin 1991) that the dosing and temporal patterns associated with sensitization do not match the clinical dose patterns displayed in stimulant addiction, and that there is no con-vincing evidence that sensitization is involved in the essential neuro-physiological, neuroadaptive, or neurotoxic processes that subserve maintenance of drug seeking in active addiction. Although the authors' position is based on many considerations, three are preeminent.

1. Clinical reports on the progression of stimulant addiction are quite consistent. They reveal that drug seeking in cocaine or amphetamine addiction does not demonstrate uniform increases in gradual increments as stimulant re-administrations accrue, as occurs in animal sensitization experiments. Development of the craving and bingeing associated with intensive stimulant dependence is instead describedby addicts as occurring almost immediately after switching to smoking or intravenous (IV) administration or after dramatic increases in intranasal dosage (Gawin and Ellinwood 1988). When this stage (named the "high intensity transition") occurs, craving increases abruptly immediately following the experience of dramatically more intensive dose effects and euphoria. In recent years, this transition has produced the near instant and devastating addiction often noted when an individual's first exposure to cocaine is to "crack."

2. Clinical reports indicate that, in the subpopulation of stimulant abusers who experience stimulant-induced paranoia, the paranoia follows a sensitization-like pattern of gradually increasing intensity or evocation by decreasing dose, similar to sensitization patterns found in animal experiments. But, as just noted, this accumulation is different from the pattern of abrupt change in craving. Stimulant-induced paranoia is an extremely unpleasant experience that is by no means desired or craved, but is instead endured because of the competing desire for a euphoric high. For example, addicts often destroy cocaine supplies in response to delusional fears of imminent arrest. Discarding the object of addiction is not consistent with sensitization of the neurobiological substrates of addiction or drug seeking. Sensitization may thus underlie stimulant paranoia, but paranoia does not co-vary with the patterns or qualities of craving or drug seeking. Paranoia is entirely absent in stimulant users despite extreme use (Satel et al. 1991). Thus paranoia and craving are dissimilar.

3. The dosage and administration patterns in addictive street stimulant use(i.e., high dose; very rapid absorption administration routes; and extended binges characterized by multiple, frequent new superimpo-sitions of drug boluses) differ profoundly from the experimental administration paradigms that foster sensitization in animal research (low, single doses by slow absorption routes). Because the immediate psychological effects and limbic neurophysiological effects of cocaine vary as a function of the acceleration of plasma cocaine concentration and not as a function of simple plasma level (Van Dyke et al. 1982), the intracellular central nervous system (CNS) effects of cocaine exposure may be 1,000 times

greater in multidose street cocaine smoking (crack) or injection than in intraperitoneal (IP) dosing in animals (50-fold difference in plasma acceleration rate x 10 to 20 versus 1 dose/day). Thus, extrapolation from slow-absorption, single, low-dose administration in animal research to human street drug use is profoundly uncertain. Only effects that are minimally dose related and uniformly result from virtually any route of repeated cocaine exposure should begeneralized from animal models of sensitization to addicts. It is crucial to be aware that conservative estimates indicate that 5,000,000 to 10,000,000 individuals (almost exclusively low-dose intranasal users) have repeatedly used cocaine without seeking treat-ment; most are free of severe addiction or uncontrollable craving. Thus extensive human exposure has occurred that at least parallels the slow-onset animal sensitization dosing paradigm without any evidence of clinically significant consequences.

Persistence of Sensitization and of Craving

The above points notwithstanding, the persistence of craving as well as itsresistance to therapy are crucial issues in stimulant abuse treatment. Sensitization persists months after its appearance in animals—a characteristic shared by both the vulnerability to stimulant paranoia in human addicts and by vulnerability to stimulant craving in addiction. Thus, despite important dissimilarities implying that sensitization is not the neurophysiological equivalent of subjective craving, it is critical that sensitization be carefully considered in relationship to addiction and craving, not prematurely dismissed. It is plausible that sensitization may somehow contribute to aspects of the neuroadaptive or neurotoxic matrix underlying chronic drug craving and addiction.

IS CRAVING MOOD-DRIVEN OR SELF-PROPELLED?

Robinson and Berridge (1993) have most extensively developed the hypothesis that addiction is linked to sensitization. They suggest that craving for abused drugs results from drug-induced pharmacological sensitization in hypothesized neurophysiological substrates of incentive salience (or, from Robinson and Berridge, the biological substrate for the psychological perception of wanting) to produce frequent, intense per-ceptions that abused drugs are necessary. Put simply, Robinson and Berridge posit that craving is not mood-driven, or equated with a desire to escape dysphoria and/or to experience pleasure by using a drug, but is instead self-propelled, or equated with a toxically upregulated psychological measurement system (sensitized

by drug use) that mis-measures the importance (salience) of further drug use, resulting in more drug use and further propagation of toxicity and craving. Most important, the subjective mood or expected mood of the addict is not a factor; this separates Robinson and Berridge's hypothesis from previous major theories of addiction. The incentive salience hypothesis thus accepts a determinism, but one based on judgment, via a sensitization process, to escape the classic mood-based determinism that is inherent in previous reward theory.

The incentive salience hypothesis encompasses complexly arrayed but largely traditional epistemological, historical, and philosophical arguments, as well as psychological arguments in the traditions of operant and classical conditioning and reward theory. It is less traditional in that it interposes arrays of neuroreceptor, neurophysiological, pharmacological, and clinical medical-psychiatric generalizations and arguments that extend the scope of the hypothesis and its potential influence well beyond academic meaning and discourse. Since desire and craving are crucial components of addiction theory, research, and treatment practices, any importance attributed to sensitization could either advance or misguide addiction treatment and research.

Assessing the full scientific validity of an incentive salience sensitization hypothesis for craving would require extensive experiments on contro-versial preclinical issues in reward and behavioral neuropharmacology, neurophysiology, and psychology, as well as their clinical research correlates. Completing these experiments would require formidable effort and resources. Is such effort warranted in preclinical or clinical addiction treatment research efforts in warring against drugs (rather than basic research)? The authors believe that this can be justified only if it meaning-fully improves clinical understanding and ultimately, treatment. Note that only selected clinical anecdotal citations and generalizations of unclear origin and validity have been used as support in attempts to establish that sensitization-like patterns exist in addictive behavior and that sensitization actually sustains clinical addiction. The authors therefore focus the remainder of this chapter on the most fundamental question: "What is the clinical accuracy of claims made regarding sensitization and the actual clinical foundation for a sensitization-craving-addiction hypothesis?" While exhaustive evaluation of the complex, multidomain incentive salience hypothesis is implausible here, as it exceeds the scope of a single chapter, its foundations can be assessed by examining the fidelity of the theory to current clinical research findings.

Systematically derived, empirical data from clinical and human laboratory research on many characteristics of cocaine dependence are now emerging from recent, often large studies of the characteristics, phenomenology, and natural history of cocaine addiction. These data may aid in assessment of anecdotal observations that were previously reported. Concordance with a sensitization model is not a priority in clinical research; the reports cited were focused on descriptions of cocaine dependence written for a clinical and treatment research audience, and not on the reports' fit with sensiti-zation theory. Nonetheless, these reports provide far superior data on sensitization and stimulant addiction than prior anecdotes; unfortunately, previously published reviews on addiction and sensitization have not attended to this literature.

CLINICAL PHENOMENA AND STIMULANT SENSITIZATION

Clinical Research on Cocaine Paranoia

Satel and colleagues (1991) recently reported the first systematic evaluation of stimulant paranoia. They assessed 50 unselected cocaine- dependent subjects consecutively admitted to inpatient treatment. A structured, 57-item paranoia assessment interview was used as well as standard cocaine history assessments. Two-thirds (68 percent) of the sample described experiencing paranoid psychosis during the cocaine high and postcocaine crash, a greater-than-expected prevalence that has heightened concern over sensitization and possible neurotoxicity in cocaine dependence.

The reported characteristics of cocaine-induced paranoia were uniform and consistent with a sensitization process. One hundred percent of the subsample who experienced paranoia had been paranoia-free early in cocaine dependence, averaging years of binge use before paranoid symptoms gradually became troubling. All described multiple stimulant binges with intensifying anxiety during binges before experiencing frank paranoid delusions; once paranoia appeared, every subsequent cocaine binge induced its reexperience. All subjects described intensification of the paranoia with continued cocaine use. No subject reported any amelio-ration or tolerance of their anxiety or paranoia, and half used anxiolytic street drugs to reduce their intensity. The onset of paranoid delusions after starting a binge accelerated over time, first ranging from 10 to 90minutes after the binge start and decreasing to between 5 and 15minutes by the time

of admission. Half of the subsample engaged in bizarre activities, such as hiding or protracted compulsive rechecking, driven by the paranoia. Thirty-eight percent secured weapons, and six percent had fired weapons to protect themselves from imagined pursuers. The total duration of paranoia averaged about 12 hours, with near total resolution (97 percent) of paranoid symptoms before awakening after the postcocaine crash (sleep). These systematically derived clinical data are consistent with a century of uniform case descriptions. Recently Angirst (1994) and, in part, Brady and colleagues (1991) have reported nearly identical data that replicate and also extend these findings.

The characteristics of irrational fear and paranoid ideation induced by cocaine in chronic street abuse match characteristics of sensitization in animal models: First a dose threshold exists, in a minimal amount and/or duration of use before sensitization, as anxiety and later frank paranoia appear. Second, sensitization inevitably persists and reappears on cocaine readministration, as does paranoia when binges reoccur. Third, symptoms intensify over repeated binges, as do the behavioral effects of sensitization. Fourth, noted acceleration of onset occurs over repeated binges, which should be equivalent to gaining an effect earlier, at lower dose, as in sensiti-zation. Combined, the anecdotal accounts and systematic investigations are unequivocal regarding the characteristics of stimulant-induced paranoia and provide convincing evidence that sensitization, manifested as paranoia, does occur in street cocaine abusers.

The subsamples that did not experience paranoia may have substantial research significance for psychosis in mental illness (one-third of the Satel and colleagues (1991) sample; similar proportions were reported byBrady and colleagues (1991) and Angirst (1994)). Such individuals appeared to have greater immunity to sensitization and stimulant-induced paranoia rather than insufficient cocaine exposure. Lifetime cocaine exposure in the nonparanoid subsample (Satel et al. 1991) was almost twice that preceding onset of frank delusions in the paranoid subsample (1,400 versus 820 grams). The paranoid and nonparanoid subgroups didnot differ on sociodemographics, administration route, settings for cocaine use, and amount or prevalence of other drug use. They were also equivalent in the intensity of cocaine-seeking behavior or craving for cocaine (operationalized as length of use or dependence), intensity of abuse (grams/hr), the rapidity of the transition from use to dependence, and subjective self-reports and ratings.

In preclinical research, the homogenous animal strains used in experimental samples demonstrate much less intersubject variation in sensitization than is evident in stimulant abusers. However, substantial between-strain differences in animal acquisition of sensitization have recently been demonstrated, suggesting that animals can be bred to be sensitization vulnerable or sensitization resistant. Neurobiological contrasts of such animals would provide a powerful model for understanding the genetics and neurobiology of paranoid psychosis and, if resistance to sensitization could be induced, for the potential prevention or treatment of schizophrenia.

Clinical Research on Cocaine Seeking and Addiction: Euphoria, Withdrawal, Craving, and Relapse

Drug seeking in addiction has long been largely attributed to avoidance of unpleasant sensations of drug or alcohol withdrawal combined with the expectation that euphoric sensations would follow drug use. As noted, the hypothesis that sensitized, incentive neurophysiology mediates drug seeking, however, requires neither euphoria nor unpleasant withdrawal symptoms. Clinical data on cocaine seeking and craving in relation to possible sensitization exist in at least four clinical research areas: treatment effects on craving; laboratory experiments on euphoria and craving; inves-tigations of stimulant withdrawal; and large-sample natural history studies of cocaine addiction, its longitudinal course, and abstinence patterns.

Clinical Research on Euphoria

Addicts sometimes complain that they achieve little or none of the high that accompanied earlier drug use and question why, with less compelling reward, they endure the pain and hardship of career drug addiction. Such individuals nonetheless most often continue to pursue drugs, and this paradox constitutes a major stanchion in the clinical foundation for sensi-tization theory on drug seeking. The sensitization view argues that since no reward is experienced, a process other than reward compels drug seeking and abuse in addiction. Alleviation of withdrawal dysphoria is considered a failed explanation largely because drug seeking in addiction frequently occurs before or after classic withdrawal symptoms occur. The logical void is then deemed filled by the concept of sensitization via incentive motivational neurophysiology.

But is drug euphoria truly absent in addiction? This belief is based purely on anecdotal assertion of unclear origin and validity.

Moreover, the assertion is not critically assessed and its meaning for the addict is not considered. No laboratory studies documenting the absence (or presence) of euphoria in addicted drug abusers are cited, nor have clinical survey data been interpreted or presented.

Language, Euphoria, and Drug Abuse Research

The assertion that euphoria does not occur in addicts represents, at best, great clinical naivete. It presupposes the validity of interchanging precise scientific terms with anecdotal street slogans. In clinical research, such terms as “high” are unusable unless they are precisely defined and assessed within structured research parameters, and they are suspect until validated. Statements by addicts about drug euphoria reflect word choices defined within specific addict subcultures, the addict’s level of expectations or wishes regarding drug experiences, and the immediate state of intoxication or withdrawal. In the language of street stimulant addicts, "high" can refer to many disparate constructs, such as experiences of other’s intoxication (e.g., "contact high"); drug-induced agitation or altered perception (e.g., a "trash high"); or transient, peak-intensity drug experiences after rapid administration of potent drugs (e.g., "I got off but it wasn't good enough to get me a real high").

The difficulty of ascribing specific meaning to terms denoting euphoria or other acute drug effects in addicts is best illustrated by the variations in terminology used to distinguish peak versus sustained stimulant euphoria. Transient, overwhelming euphoria occurs seconds after stimulant injection or smoking, as plasma drug concentration elevation accelerates. The onset of this extreme euphoria is termed the "high" by many addicts (but also the "slam," "rush," "wire," "ride," "rip," and others). Nonescalating, sustained euphoria occurs with lower dosages or slowed absorption as plasma drug concentration increases decelerate after intranasal or oral stimulant use,or after the peak injection or smoking effects begin to dissipate. Such euphoria is also termed the "high" by many addicts (also the "ride," "cruise," "wire," "stoke," "rip," and others). Upon recurrent acute use late within a binge, acute tolerance or tachyphylaxis results in greatly diminished peak and sustained effects that pale in comparison with initial doses, but initial doses remain euphorigenic. With chronic use and tolerance, maximal initial peak effects may diminish unless the dosage is increased, but sustained euphoria is still experienced. Thus, for example, addicts alleging that a high was missing acknowledge a positively perceived subjective intoxication and are readily able to ascribe a dollar street value to that experience, but complain of the

lack in abrupt euphoric intensity compared with peak effects of early stimulant intoxications. Similarly, addicts in adjoining urban drug microcultures with inverted but parallel terminology have described the same experience after stimulant use—the relative absence of peak effects but presence of sustained effects—in exactly opposite terms; not getting a high (peak effects) but still enjoying a ride (sustained effects), or as not getting a ride (peak effects) but still enjoying the high (sustained effects).

Hence, complaints about the absence of a high almost invariably reflect acute and/or chronic tolerance with diminished peak effects that suffer in subjective comparison to the euphoric glory of initial doses and preneuro-adaptation peak effects. In light of the long accrual of mounting adverse consequences of addiction, the value of continued drug use becomes increasingly problematic (e.g., "I don't know why I get high").

Laboratory Experiments: Euphoria in Chronic Dependence

The preceding assertions that drug euphoria does occur in addiction are substantiated by the entirety of two decades of human subject research on stimulant and opiate administration. Human subject investigations of illegal addictive drugs have been conducted almost exclusively in chron-ically dependent subjects since the late 1970s. These studies exclude normal or nondependent subjects because of restrictions instituted due to ethical concerns over exposing drug-naive or nonaddicted individuals to powerful, addicting euphoriants. Euphoria, high, dollar value, and similar ratings are the principle subjective measures in such research and have been used to define psychological dose-response relationships of stimulants (Van Dyke et al. 1982).

Numerous human subject studies using balanced, placebo-controlled, double-blind drug administration have been reported. These studies have uniformly confirmed that chronically dependent subjects experience euphoria. The sensitization hypothesis of euphoria or reward in addiction would predict that either human subject research would require preselec-tion of less addicted subjects who still had the capacity to experience a high, or that absence of euphoria would occur repeatedly and plague such research. Yet there are no reports in the experimental human subject literature that support these predictions.

Clinical evidence that diminished drug effects and tolerance occur in addiction has been accumulating for over a century. That euphoric effects can dissipate with tolerance is rudimentary clinical knowledge. For example, both heroin addicts and ex-addicts working as methadone counselors recognize that methadone, via cross-tolerance, blocks the heroin high and that purer heroin or higher doses restore the high. With tolerance, euphoria is harder to achieve; but neither euphoria nor the associated reward motivation disappears. Furthermore naltrexone, an opiate antagonist used in treatment of opiate addiction, does block euphoria. If euphoria is absent, as the sensitization perspective contends, why is naltrexone needed or useful? If sensitization mediates craving without any effect of reward, then craving should be unaffected by naltrexone blockade of reward. However, the clinical research findings are the opposite of the incentive salience prediction regarding reward. Craving comes closer to elimination during naltrexone treatment than during any other pharmacotherapy for addiction and, contrary to incen-tive sensitization theory, returns immediately upon discontinuation of naltrexone with the perception that the drug high is available (Meyer and Mirin 1979).

Euphoria with Craving?

The sensitization view makes one additional anecdotal point in attempting to refute the classic view that drug reward or mood effects are involved in craving or addiction. Reports that cocaine craving in addicts is frequently induced by acute cocaine administration (Jaffe et al. 1989) are cited as evidence of an internal contradiction (presumably fatal) in current addiction theory based on mood effects. The contradiction is that the acute experience of cocaine-induced euphoria and the simultaneous craving for that euphoria are logically incongruous. Sensitization theory proponents then hold that euphoria and craving have been misunderstood. They first refer to the assertion presented above that euphoric mood effects are absent in addiction. Alternatively, they also contend that even if drug effects that increase positive mood do exist in severe addiction, the contradiction means such mood effects are relatively unimportant in drug seeking. Mood is reasoned to be unimportant because if craving is not eliminated by euphoria, then craving must therefore reflect another neurophysiological process independent of mood. This "other process" notion introduces a conceptual void that is then filled by the hypothesized neurophysiological sensitization of incentive motivation to produce craving.

Once again, evidence from nonanecdotal clinical and human subject research literature that has not been previously cited in sensitization and craving discussions better informs consideration of whether and how cocaine-induced mood elevation and craving might coexist. Prior citation of anecdote is clinically correct in that cocaine induces craving with great consistency. This factor is essential to produce day- or days-long binges. Such binges are sustained by an agent, cocaine, that has a half-life for euphoria measured in minutes. Decade-old clinical accounts of patterns of cocaine use during binges describe frequent, regularly spaced episodes of craving as cocaine's very brief euphoria dissipates, resulting in mul-tiple, serial readministrations (Gawin and Kleber 1985). However, it is erroneous to assume that cocaine-induced craving for cocaine occurs at the same time as mood elevation, and that euphoria does not reduce craving. (Rarely, cocaine-induced craving for cocaine is a consequence of low purity and/or doses that are inadequate to produce euphoria, but that instead induce mild sympathetic activation that focuses the absence of expected euphoria, thereby increasing craving. This parallels a priming dose in animal self-administration research). Nearly invariably, induction of craving by cocaine administration escalates as euphoria rapidly dissipates. Such induced craving, however, never appears in the clinical literature as an acute stimulant effect directly covarying with either euphoric, sympathomimetic, or psychomotor activation, or with other effects of ascending plasma cocaine concentrations. Classic clinical descriptions depict cocaine readministration and craving as occurring 20to 60 minutes after IV or smoking administration, not at 5 to 10minutes when euphoria peaks. The timecourses of these parameters, originally observed before the turn of the century, have been supported by sys-tematic assessments of clinical samples (Gawin and Kleber 1984, 1986). These timecourses have recently been experimentally substantiated by several human subject investigations of cocaine that assessed the time-course of craving, cocaine readministration, and euphoria (Fischman et al. 1990; Kosten et al. 1992; Sherer et al. 1988). These experiments clearly documented an inverted temporal relationship between high or rush and craving or drug readministration.

Research on Withdrawal

Based on the following clinical generalizations, the sensitization view of addiction considers withdrawal unimportant in regard to craving and sustaining addiction. First, even though relief from withdrawal symptoms clearly motivates drug seeking during opiate and alcohol withdrawal, effective pharmacological treatments exist that reverse

opiate and alcohol withdrawal. Such treatments, while helpful, do not eliminate all drug craving and drug seeking during withdrawal. Second, addicts very fre-quently crave an abused agent in the absence of appreciable withdrawal symptoms, either before the onset of classic withdrawal when intoxication is minimal but withdrawal has not yet started, or after withdrawal has run its course and relapse occurs. Third, the sensitization viewpoint contends that extreme drug seeking and craving occurs without commensurate withdrawal in several addictive disorders, such as cocaine and nicotine addiction, which they contend have minimal or no withdrawal syndromes.

The first two generalizations are acceptable portrayals of extant clinical phenomena. The last, however, does not reflect current clinical consen-sus or research. It conflicts with current understanding that psycho-logically expressed withdrawal syndromes that produce little objectively observable classic withdrawal symptomatology may nonetheless often be primary determinants of clinical outcomes.

Cocaine withdrawal, in symptom structure if not timecourse, closely parallels nicotine withdrawal; both parallel the subtle psychological distress of the protracted withdrawal syndrome that has been described as persisting beyond resolution of classic physical symptoms of opiate or alcohol withdrawal. These psychological withdrawal syndromes are consistently comprised of anhedonia within a dysphoric cluster of varying psychological symptoms including anergia, anxiety, and nonmelancholic depression. These syndromes have been used to partially explain early relapse, but after classic withdrawal symptoms have waned.

It is essential to note that, contrary to the sensitization viewpoint, such symptoms are deemed subtle only from the standpoint of ease of overt observation. Current clinical consensus holds that these nonphysical with-drawal syndromes explain much of the drug seeking, craving, and relapse that occurs in cocaine dependence in the absence of dramatic physical withdrawal symptoms, particularly in treatment-resistant subpopulations (Gawin 1991; Gawin and Ellinwoood 1988). Psychologically expressed withdrawal thus counters the arguments of incentive sensitization by sug-gesting that dysphoric symptoms drive relapse. Similarly, classic physical opiate and alcohol withdrawal symptoms are treatable with established pharmacotherapies but cocaine, nicotine, and protracted opiate and alcohol withdrawal are not eliminated by the same agents. Thus these withdrawal conditions must be considered along with euphoria

seeking or sensitization of incentive salience in assessing explanations for drug seeking in addiction. It should also be noted, as discussed more fully below, that attempts to combat such symptoms have opened new avenues for promising pharma-cological strategies in treatment of alcohol, cocaine, and nicotine depen-dence (Covey et al. 1993; Gawin et al. 1989; Mason and Kocsis 1991). The efficacy of these treatments is difficult to attribute to any mechanism other than amelioration of dysphoric psychological symptoms.

Dopaminergic Neurophysiology: Withdrawal or Craving? Reward and Anhedonia or Incentive Perception and Sensitization?

The current theoretical foundation of cocaine withdrawal is that neuro-physiological reward systems exposed to chronic exogenous activation by euphorigenic drugs respond through subsequent compensatory down-regulation of these systems, resulting in subsensitive reward responses. This subsensitivity is clinically expressed as anhedonia (Gawin and Kleber 1986), and a substantial body of preclinical research literature reports decreased electrophysiological and neurochemical sensitivity of brain dopaminergic reward systems (Leith and Barrett 1976; Markou and Koob 1991; Robertson et al. 1991).

The sensitization view, which holds that prevailing hypotheses of addiction misinterpret both the significance of reward and of withdrawal anhedonia, dismisses the pivotal association between clinical anhedonia and preclinical electrophysiology. Instead, the sensitization view considers mesocorticolimbic dopaminergic systems, previously imputed to mediate reward and anhedonia, to mediate incentive attributions or salience. The sensitization hypothesis emphasizes that underappreciated components of this system are sensitized and that it is these sensitized components, rather than electrophysiological decrements diminishing well being, that are important in drug seeking. In this view, acute drug administration diminishes incentive motivation and thereby reduces craving, rather than reducing craving by producing euphoria; nonadministration (abstinence) increases incentive motivation and thereby amplifies craving, rather than unveiling anhedonia.

This distinction initially appears academic and perhaps arcane; crack smokers struggling to initiate abstinence will readily declare they care little about the difference between whether very few things feel good or whether, instead, very few things seem important. Most addicts would hold that what feels good is what's important, and effectively

refute this emotional/ cognitive distinction with demonstrative behavior in ensuing relapses.

In populations less philosophically sophisticated than addicts, however, the sensitization perspective on withdrawal and craving has received substantial attention and has the potential to both influence policy and guide future clinical treatment and research. The sensitization view replaces the fundamental significance of perceived suffering with impaired judgments of salience or the broken brain machinery of judging impor-tance. If withdrawal is incorrectly deemed absent or unimportant, further development of effective psychotherapeutic or pharmacotherapeutic tools to assist recovery would suffer.

On the level of public attitude and perception, it has not yet been recognized that the incentive sensitization view unintentionally opens an avenue for moralistic mistreatment of addicts. The false medical belief of the late 1970s that cocaine produced no withdrawal resulted in the percep-tion of cocaine abuse as a moral problem throughout the first 6 years of escalating epidemic use. This perception resulted in disregard of the pain caused by cocaine abuse, rather than a constructive recognition of a societal problem of uncontrolled craving warranting addiction treatment.

Craving in Clinical Cocaine Withdrawal

The sensitization perspective largely considers the current clinical term "withdrawal" to be a euphemism for craving that suffers, from the stand-point of clinical pertinence, from overuse in describing myriad, poorly substantiated symptoms that form a withdrawal syndrome which is only vaguely related to drug seeking. Unfortunately, anecdotal clinical general-izations that equate only easily observable, largely physical, classic symp-toms and that equate withdrawal intensity and importance are cited as a clinical foundation for the sensitization hypothesis of addiction. Recent systematic clinical research has escaped note or appeared too recently to inform prior discussions of these issues.

Classic perspectives on withdrawal consider craving a part of withdrawal. Such perspectives also consider that craving is more than withdrawal, and can be based in memory and anticipated drug reward without the presence of dysphoric withdrawal. In earlier prevailing views of addiction the possi-bility of euphoric experience, amplified by drug availability and by condi-tioned associations that evoke

memories of that drug euphoria (conditioned craving), were believed to drive one component of craving through antici-pation of positive mood changes. This concept subsumes so-called con-ditioned craving. (Conditioned craving is almost wholly absorbed as the craving acknowledged by the sensitization viewpoint, but is altered in sensitization theory by the proposition that such craving is not driven by memories of drug-induced positive mood changes, but rather is prompted by conditioned misattribution of incentive importance.) Dysphoric withdrawal symptoms that are time limited, usually lasting weeks to months, drive another (second) component of craving by anticipated elimination of negative mood.

When withdrawal symptoms are prominent, both sources of craving are considered to exist and interact; as withdrawal symptoms dissipate, euphoria seeking and conditioned craving predominate. The interactions of these components of craving and other variables are complex and include substantial interindividual differences that vary in intensity depending upon perceived drug availability, and follow a variable and fluctuating timecourse. In alcohol or (to some extent) opiate withdrawal, superimposition of dangerous physical symptoms for up to 2 weeks can be a further complication.

The chasm between the sensitization and withdrawal views focuses attention on three crucial questions that require evaluation before the validity of the sensitization view of stimulant withdrawal can be fully assessed. These questions include whether withdrawal exists as a syndrome, whether its symptoms contribute to cocaine seeking, and whether detectable symptoms beyond craving exist that independently create a withdrawal syndrome.

Investigations of cocaine withdrawal have included semistructured clinical assessments disclosing symptom constellations (Ellinwood and Petrie 1977; Gawin and Kleber 1986; Smith 1969) and inpatient assess-ments. These assessments consistently identified subtle withdrawal syndromes. However, these studies had eliminated cocaine availability (but gave low doses of cocaine at study onset, thus inadvertently tapering cocaine exposure and perhaps blunting craving), and used instruments that had not been validated and perhaps were not sensitive enough to measure stimulant withdrawal. Subsequent studies of cocaine withdrawal have used factor analysis and multisymptom inventories in assessing 200to 300 outpatients (Gawin et al. 1992; Margolin et al. 1994).

The later studies confirm that a syndrome exists which is linked to, but different from, cocaine seeking and craving. Several symptom factors exist in cocaine withdrawal. Five 3- to 6-symptom factors have been identified: dysphoria/depression, anergia, anxiety/irritability, pain/nausea, and anhedonia as well as a distinct, separable craving factor. These factors, and the syndrome they constitute, are differentially and significantly linked to cocaine seeking and use. Hence, clinical research data contradict the predicted findings of an incentive sensitization viewpoint for each of the three critical assessment questions noted above. Further, unexpected findings are readily explained by classic withdrawal views but not incentive salience. In pure cocaine addicts carefully selected for an absence of alcohol dependence, the craving for cocaine (but not for alcohol) was correlated first with anhedonia and second with dysphoria, while craving for alcohol (but not for cocaine) was most highly correlated with anxiety/ irritability (Gawin et al. 1992).

These findings illustrate a remarkable specificity of craving, withdrawal symptoms, and drug choice. They further contradict the incentive sensitization viewpoint, since it predicts absence of pertinence to any withdrawal symptoms and could not account for symptom-specific craving linked to a specific drug, while linkage of a withdrawal factor (e.g., anxiety/irritability) to craving for a specific anxiolytic drug that is not the drug of choice (e.g., alcohol) can be simply explained by prior theory as an attempt to alleviate the individual's specific dysphoric component of psychological withdrawal.

Clinical Research on Craving

Systematic research in cocaine, nicotine, opiate, and alcohol abuse treatment has explored multiple assessment instruments as they relate to drug craving. Such research not only evaluates treatment outcome, but also discloses fundamental relationships in addiction through naturalistic assessments in conditions that are uninfluenced by experimental treat-ments. Hence, untreated single timepoint evaluations of craving are available from intake assessments, and repeated assessments of control (placebo) groups can provide data on the stability of symptom or factor relationships to craving over several months. Such data are available from multiple studies of psychotherapies and pharmacotherapies for all agents of abuse. These data are too extensive to fully review here. To summarize, they indicate that craving is complexly related to drug use in stimulant, opiate, alcohol, and nicotine abuse. Preeminent among drug-use factors beyond craving are drug availability (i.e., near absence of craving if drug euphoria is unavailable due to hospitalization or pharma-cological blockade in the absence of acute physical opiate or alcohol withdrawal), the euphorigenic potency of the drug,

psychological with-drawal symptom type and intensity, the prevalence and potency of environmental conditioned cues and alternative nondrug reinforcers, and the prevalence and potency of negative reinforcers (work required for drug use or the punishment potential and type).

To illustrate, data from a cocaine abuse pharmacotherapy trial have been published that elucidate relationships between euphoria, withdrawal, and craving (Brown et al. 1993). At intake, the relationships among standard psychiatric assessment instruments, cocaine craving, and cocaine use were evaluated in 63 cocaine-dependent individuals without dependence on other agents. The study evaluated overall symptomatic distress using a standard symptom checklist, a global severity scale, and the Beck Depression Inventory (a focused index of symptoms associated with severe clinical depression). Standard craving assessments were also used. Cocaine usage, a prima facie index of drug seeking, is shown in relation-ship to these instruments in the correlation matrix of figure 1. Note that craving, overall symptomatic distress, and depression are substantially correlated with reasonable explanation of variance (~30percent explained by each direct relationship). Each of these, however, has substantially less linear relationship to actual cocaine usage (individually explaining an average variance of 7 percent). Patient attributions of craving, but not their actual drug use, are thus strongly related to indices of withdrawal as reflected in both overall symptomatic distress and severity of depression. This example thus directly contradicts the incentive sensitization view that withdrawal dysphoria does not drive craving. These data further reinforce the need for preclinically derived theories of addiction to be assessed against clinical research data rather than relying upon anecdotal evidence.

The absence of a substantial relationship between craving and actual cocaine use refutes a fundamental unstated assumption of the incentive sensitization theory on addiction: craving is presumed to be the equiva-lent of addiction or drug seeking and use. In most outpatient substance abuse treatment trials that demonstrate a pharmacological effect of tricyclic antidepressants, a significant change in craving appears after a delay, occurring 1 to 3 weeks after, not before, a decrease in drug use (Covey et al. 1993; Gawin et al. 1989; Mason and Kocsis 1991). This delayed reduction craving has sometimes been explained as a secondary self-attribution that follows observation of decreased drug taking. It is also possible that decreases in drug use usually, without pharmaco-therapy, increase craving and withdrawal symptom frequency and severity, and that the absence of an immediate rise in craving when cocaine use decreases is direct evidence of the pharmacotherapeutic effect. Further, these studies found that diminished craving generally follows decreases in drug use so substantial that abstinence or near abstinence precludes further reduction in drug intake; the diminished craving thus can no longer be reversed by decreased drug intake, and

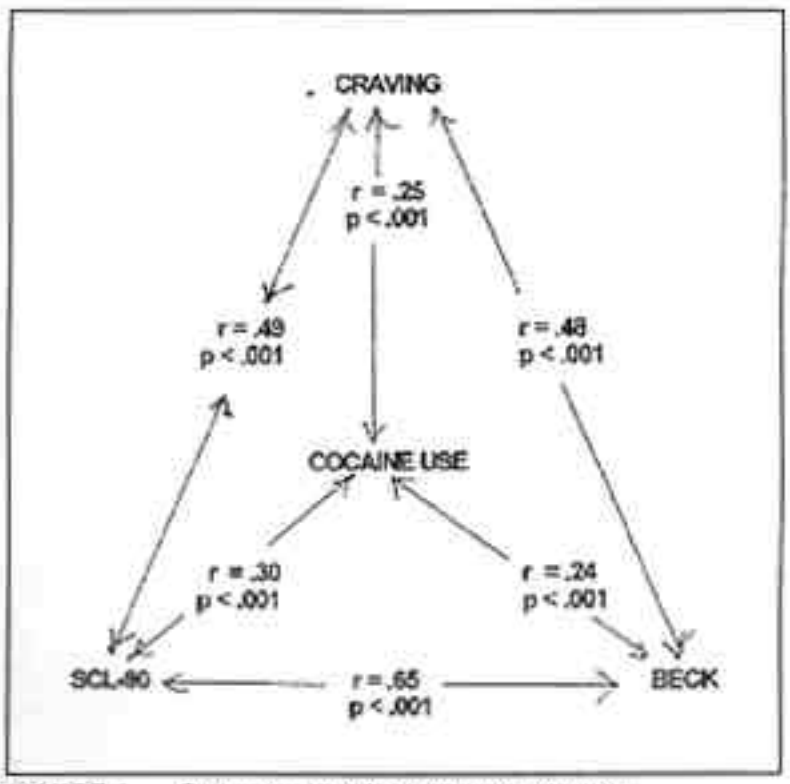

FIGURE 1. *Cocaine use and symptom assessments.*

reduced craving scores follow. As noted previously, the therapeusis associated with reduced drug seeking and craving also decreases depres-sion. This effect supports a withdrawal perspective; because there is no evidence that antidepressants decrease incentive motivation—direct evidence to the contrary exists—the incentive sensitization theory regarding craving and addiction is contradicted.

Human subject research into craving's complexity in relation to addiction has recently begun. A study by Fischman and colleagues (1990) on the effect of the tricyclic antidepressant desipramine on cocaine self-adminis-tration found that human subjects in an experimental laboratory, when denied alternative reinforcers, chose the highest available IV dose of cocaine significantly less frequently when also treated with chronic desi-pramine than with placebo, although they did not cease self-administra-tion. The efficacy of desipramine in decreasing craving for the highest dose can be explained as a result of reduced withdrawal depression that requires a high dose to overcome dysphoria and produce euphoria. Other interpretations are also plausible, such as the medication increasing the

effect of the lower dose to produce greater peak euphoric effects or also blunting peak effects of the higher dose; further investigation is thus under way. It should be noted that these explanations are all based on a reward/anhedonia model of addiction. An incentive sensitization view cannot readily interpret these findings. In a similar single-dose human laboratory study by Kosten and colleagues (1992), desipramine substan-tially accelerated the disappearance of cocaine-induced (or primed) craving for cocaine. This finding can be readily interpreted as evidence that desipramine and not placebo decreases dysphoric craving, resulting in experience of only that craving component related to the desire to re-experience the recent intensity of the high. Again, these data are not consistent with an incentive sensitization hypothesis.

The incentive sensitization perspective places substantial currency in the observation that sensitization and conditioned craving can both be linked to classical conditioning. Sensitization occurs in the environment where prior drug administrations occurred, and can be minimized in animals by shifts from the room and cage where sensitization was instituted. Incentive sensi-tization holds that craving in addiction reflects conditioned associations that evoke memories of the importance of using drugs. If the word "importance" in the preceding sentence were replaced by the word "euphoria," this view would be consistent with current clinical consensus regarding conditioned craving. Further, the commonality of classical conditioning indicates only that associative memory is part of either sensitization and conditioned craving and not that the two are linked. This also does not present a particularly discriminating distinction, since reward and punishment are integral factors that directly affect the strength of both instrumental and associative learning and memory. Further, other basic dissimilarities between conditioned craving and sensitization are discussed below.

Clinical Research on Relapse

Beginning over a century ago, clinicians reported that relapse after long- sustained abstinence in those chronically addicted to stimulants often leads to near-immediate resumption of high-intensity stimulant abuse rather than following the pattern of intermittent and slow abuse escalation that charac-terizes initial oral or intranasal stimulant use prior to the high-intensity transition to binge addiction. If relapse always occurs this way, such clini-cal data would display a pattern similar to sensitization, in that relapse to drug use results in reinstatement of the previously incrementally developed patterns of

severe cocaine use. Of course, such a pattern would not clearly substantiate that sensitization was associated with the effect; many crack abusers do not experience a sensitization-like timecourse but instead immediately display high-intensity abuse patterns.

In the first large-sample natural history evaluation of cocaine dependence patterns, recently completed by Khalsa and colleagues (1994), extensive structured interviews assessed temporal development of cocaine depen-dence, longitudinal abuse patterns, and postabstinence relapse to cocaine use. Subjects were males requesting treatment at an urban Veterans' Administration hospital. These data provide objective, systematic measure-ment of major variables in cocaine addiction that previously have been investigated in small clinical samples and anecdote. The data clearly demonstrate that many (76percent) but not all former addicts who relapse immediately resume the level of drug abuse that existed just prior to initiating abstinence, rather than returning to earlier use patterns. The data thus are consistent with prior anecdote; however, in the 24 percent who gradually resume use, no putative sensitization-like phenonon appear, and addiction remains.

CONCLUSIONS

Evaluation of systematic research findings rather than selected anecdotal evidence substantially alters conclusions regarding the pertinence of sensi-tization to addiction and craving. The research reviewed here objectively substantiates that stimulant-induced paranoia is extremely consistent with classic sensitization. Incentive sensitization is not, however, consistent with research findings on euphoria, withdrawal, drug seeking, or craving as a general concept. The authors conclude that while sensitization provides a superbly fitting model for paranoia, it fails completely as a model to fully explain addiction.

Incentive Sensitization and Pharmacological Sensitization - Logical Discordance

Within stimulant addiction there are parallels to sensitization in conditioned craving and the intensity of abuse resumed after relapse. These data demonstrate the persistence and reinstatement of effects that develop after repeated stimulant administrations.

However, the authors believe that incentive sensitization theory contains severe logical flaws that render these commonalities meaningless. The incentive sensitization view of addiction lacks fidelity to the classically defined preclinical sensitization concept. Pharmacological sensitization differs profoundly from incentive sensitization in one underappreciated respect: it requires that the sensitized effect be an increased acute action of the drug inducing the sensitization. In this regard, all of the clinical effects cited as reflecting sensitization by incentive sensitization theory fail; none of the purported sensitization effects is an acute action produced by a dose of stimulant, but all are instead accompaniments to chronic addiction. Similarly, while severe abuse intensity is unveiled by the resumption of stimulant use, this effect does not occur uniformly upon stimulant readmin-istration, nor is it an acute effect of a single dose. Rather, severe abuse occurs in a logically different category, after acute effects of a first dose have dissipated, when binges are extended, and as the drug is sequentially administered in defining an abuse pattern. This behavior is not an increased acute effect of one drug dose itself.

The absence of fidelity to the sensitization concept as defined in classic pharmacology alters the basic heuristic and logical concordances of incentive sensitization theory, and thus renders the preceding review unnecessary. Nonetheless, the authors believe that the review is instruc-tive and worthwhile because of the attention given this view among nonclinicians, as well as because it illustrates the problems of selective use of clinical anecdote, rather than rigorously examining empirical clinical research data to subserve theory.

Because the fundamental reference of incentive sensitization theory is not an acute drug effect but rather an increasing accompaniment of addiction, the theory can be observed to be based in semantics and epistemology rather than pharmacology or clinical neurophysiology, as follows: Incentive sensitization theory has its focus only on repeated drug admin-istration, increasing something over time in common with classic pharmacological sensitization, and thus has negligible linkage to its claimed foundation in preclinical sensitization research (which, again, uniformly involves the experimental evaluation of acute effects on re-dosing). The label "incentive sensitization" is thus a partial misnomer from the standpoint of classical pharmacology. Incentive sensitization can be distilled as positing that some drugs produce changes in neuro-physiology over repeated administration (previously termed neuroadap-tation). Losing any

linkage to acute redosing with the drug, the statement that “sensitization of the neurophysiology subserving "incentive" processes occurs after chronic drug reapplication" is logically equivalent to the statement that "adaptation of the neurophysiology subserving psychological processes occurs after chronic drug reapplication." The statements differ only in that incentive sensitization specifies a particular sort of adaptation, increases (sensitization rather than desensitization), and a particular type of psychological process, that termed "incentive."

Incentive sensitization is thus simply a logical special case within the psychological component of a broader and much more completely researched concept in pharmacological and toxicological neuroscience: neuroadaptation. Thus incentive sensitization theory is half (the half that goes up and not down) of a theoretical part of neuroadaptation, the part which is limited to the neurophysiology of a putative discriminable neuroanatomical system regulating incentive intent and judgment. Furthermore, the system appears to occupy the identical neurophysio-logical and neuroanatomical locus as that previously identified as the central locus of the reward dimension of mood. Hence the "part" of neuroadaptation defined by incentive sensitization was fully recognized previously. The essential issue reduces to whether attention should be directed at the feeling itself, or at its motivation. At heart, the issue is semantic and epistemological: Should this system be called a "reward" or "incentive" system?

The authors wish to make clear, however, that the most important consequence of this realization is not in the realm of academic discourse, but instead is its effects on policy. There exists substantial risk that theories such as incentive sensitization are not recognized as oversigni-fying terminology. Such theories have the potential to deflect the effort and resources that are likely to advance therapeusis and alleviate clinical distress. The authors are thus in absolute agreement with the basic premise of their patients: How one feels is what’s important, not the terms employed in description.

Is it rational to consider that sensitization is not clinically relevant to craving and drug seeking, but to fear that it might be misinterpreted as such? As noted, carbamazepine has been employed in pharmacotherapy research on cocaine addiction because of a theorized association between craving and sensitization; the rationale for using a drug that had been previously demonstrated to have no effect on expression of cocaine-induced sensitization was not questioned. Although carbamazepine does limit the acquisition and

development of sensitization to cocaine, it is only effective when used to pretreat cocaine-naive animals prior to serial cocaine administrations. Carbamazepine was nonetheless chosen for clinical trials based on the hypothetical hope, never demonstrated in research, that it would affect expression of sensitization, along with hope that craving was manifest sensitization. Chronic crack addicts, who were far from drug naive, were chosen as the sample. (This work has not been directly linked to the more carefully constructed craving/sensitization hypotheses of Robinson and Berridge 1993.) Although poorly piloted and highly ques-tionable from the standpoint of theoretical integrity and preclinical know-ledge, clinical carbamazepine research was rapidly extensively supported and evaluated in controlled, randomized trials with several hundred cocaine-using patients. Resulting double-blind efficacy findings were wholly negative, after not inconsiderable patient risk, research effort, and expense.

The pressures of "wars" declared on drug abuse and epidemic expansion of cocaine smoking partially fueled the fact that decisions regarding carbam-azepine were made without prior systematic data assessment or evidence of a link between sensitization and sustained clinical addiction. The atmosphere demanded new approaches and exaggerated the significance of sensitiza-tion at the probable expense of other preclinical or treatment research with greater likelihood of producing eventual societal gain. This clinical prece-dent illustrates the need to critically assess claims of pertinence in sensiti-zation research, and it stands as a clear warning.

Objective evaluation and careful assessment of the true significance of sensitization itself in addiction is equally, if not more, important in preclinical research. Such significance must be established before its relevance to addiction, based on an extrapolated theory that does not actually reflect sensitization, is used to justify further pharmacological studies of sensitization that use low doses and administration patterns which never occur in humans. Such studies would again result in a misallocation of limited research resources at the expense of other research areas having greater potential for ultimate clinical benefit in addiction treatment.

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