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Testing Drugs for Physical Dependence Potential and Abuse Liability

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol. Drug Abuse, and Mental Health Administration

Testing Drugs for Physical Dependence Potential and Abuse Liability

The Committee on Problems of
Drug Dependence, Inc.

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FOREWORD

The National Institute on Drug Abuse is pleased to publish as a NIDA Research Monograph this updated state-of-the-art review of the procedures utilized for testing drugs for their physical dependence potential and abuse liability. NIDA has a long history of working with the Committee on Problems of Drug Dependence (CPDD) to attain our mutual objective in broadening the knowledge base in this area.

It has been 11 years since the previous review by the Committee on Problems of Drug Dependence, and 9 years since the publication by WHO of Evaluation of Dependence Liability and Dependence Potential of Drugs. During this period, the field has advanced significantly, particularly as new classes of compounds have been included within the range of those known to result in human dependence. In addition, this review represents a major conceptual clarification in distinguishing between testing of physical dependence potential and abuse liability. The rationale this distinction is well described in Chapter II.

The ultimate objective is to develop and refine methods that will allow for the prediction of the human dependence or addiction potential of a compound. Too often, the problems of human drug dependence have been attributed to the physical dependence potential of a drug. The use of the word dependence in two very different senses has contributed its share of confusion. effort to maintain clarity, the authors of the manuscript have consistently referred to measurement of physical dependence liability so as not to confuse that concept with the clinical syndrome of drug dependence. This is particularly important since increasingly the evidence supports the view that the problems of human drug dependence are more closely related to the abuse liability of a drug than to its physical dependence potential.

In the Prefatory note that follows, the importance of these procedures in making national and international regulatory decisions has been emphasized. Not to be over looked is the fact that the laboratory work necessary for the development of these testing procedures has also contributed to the identification and characterization of novel compounds and the elucidation of fundamental biobehaviorial mechanisms of drug action. The recent Text

growth of knowledge of the neural mechanisms involved in drug abuse has been explosive. Along with this has come a rapidly developing ability to synthesize new drugs with markedly greater, specificity, increasing the requirement for refined methods of assessing abuse liability. Future development in the area may be expected to focus on the role of drug interactions, the role of environmental and social factors and, perhaps most importantly, the role of individual genetic differences in the liability to abuse of drugs. The CPDD can be expected to continue to play an important leadership role in providing a forum for the integration of the many scientific, social and legal issues involved in coping with the problems of human drug dependence.

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PREFACE

For many years, the Department of Health and Human Services (DHHS) has had a special interest in developing methodologies for assessing abuse liability of drugs, irrespective of their known or potential therapeutic usefulness. More recently, additional interest in this area has grown as a result of the authorities granted to the Secretary of DHHS in the Comprehensive Drug Abuse Prevention and Control Act (P.L. 91-513) and the Psychotropic Substances Act of 1978 (P.L. 95-633). These statutes provide the Secretary with the authority to determine the abuse liability of drugs and make scheduling recommendations with regard to the need for domestic and international controls in an effort to prevent or reduce the abuse. Thus, efforts to expand our knowledge to make informed scheduling decisions has received support as part of the overall drug abuse prevention effort.

Within the DHHS, the National Institute on Drug Abuse (NIDA) is authorized by the Secretary to conduct the necessary studies for the proper evaluation of the abuse liability of drugs and other substances and to evaluate the nature and extent of associated health risks. Pursuant to these responsibilities, NIDA supports various intramural and extramural research efforts both to determine the abuse liability of new drugs and to develop methods for making more specific determinations about new classes of compounds. These efforts have been significantly enhanced by close collaboration with the Committee on Problems of Drug Dependence and the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases.

It is hoped that this scholarly and comprehensive review of the existing methodologies will be of benefit to both the public and private sector domestically, as well as internationally. In addition to being a unique reference, it can serve as a guide for future drug abuse liability screening initiatives and a foundation on which newer and more specific methodologies can be developed. The monograph may be of assistance to other countries interested in incorporating some abuse liability testing as a requisite for drug registration and assist the World Health Organization (WHO) in its efforts to identify the range of existing parameters available for assessing the abuse liability of drugs required of them by international treaties.

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I. Introduction

The Committee on Problems of Drug Dependence. (CPDD) has been in existence since 1929 and is the longest standing group in the United States concerned with drug dependence and abuse. Its history from 1929 until the early 1970s was summarized by the late Nathan B. Eddy (1973). From 1929 until 1976, the CPDD was associated with the National Academy of Sciences - National Research Council. Since 1976, it has existed as an independent body presently affiliated with ten national societies representing various disciplines concerned with problems of drug dependence and abuse.

A major thrust of the CPDD has been to facilitate the development of safer and more effective therapeutic agents while reducing the risks of dependence and/or abuse. Most of the drugs evaluated by the CPDD are drugs with well-defined current or potential clinical use. Knowledge of the dependence potential and/or abuse liability of a drug proposed for marketing is of obvious importance with respect to its scheduling both within the United States and internationally. By appropriate screening prior to marketing, it should be possible to avoid cases of iatrogenic dependence and/or self-generated abuse that would have occurred and formed the basis for later scheduling of the drug after post-marketing experience.

In some cases, discovery of dependence potential and/or abuse liability might be grounds for a decision not to manufacture a drug. Dependence and abuse are among the costs, along with other adverse side effects, that must be weighed against a drug's potential therapeutic efficacy. Ordinarily, a drug will not be tested for dependence potential and/or abuse liability until other aspects of efficacy and safety have been demonstrated in a scientifically sound and systematic manner employing appropriate standards of measurement and controls to avoid bias. At this point, a serious level of dependence potential and/or abuse liability can counterbalance the prospect for a modest therapeutic advance. Thus screening for dependence potential and/or abuse liability may prevent the marketing of an undesirable new product.

The drug assessment activities of the CPDD. then, have come to serve three general purposes. In the first instance, they have provided

information to the pharmaceutical industry and the public to assist in evaluating the dependence potential and/or abuse liability of new drugs. Secondly, they have advanced the basic scientific purpose of identifying and characterizing truly novel compounds, and stimulating their synthesis. In this regard, the CPDD has collaborated closely with the National Institutes of Health. And thirdly, the CPDD has implemented and supported the assessment of dependence potential and abuse liability in both animal laboratory and human clinical settings. In 1947, the CPDD initiated and supported an animal testing facility at the University of Michigan. In the early 1970s. a similar unit was formed at the Medical College of Virginia. The focus of activity at both facilities has been upon testing opioids, although in recent years other types of drugs have been studied more often. In 1980, the CPDD awarded, on a competitive basis, starter grants to laboratories for the development of clinical procedures for evaluating drug dependence potential and abuse liability in man. And, in 1982, initiatives were undertaken to broaden the scope of CPDD's testing activities to encompass CNS stimulants and depressants.

The CPDD has twice before, in 1966 and 1973, published position papers on the testing of drugs for "dependence liability" in animals and humans (CPDD 1966; 1973). The present paper represents a continuation of these state-of-the-art reviews. A revision is timely now because there have been several new and important developments over the past decade. First, a growing number of opioids of the mixed agonist-antagonist type are in various stages of development as anesthetics and analgesics. Reports indicate that the analgesic effects of these new compounds are not accompanied by the subjective mood changes associated with abuse liability, but the evidence in this regard is inconclusive. Second, considerable public concern has been generated by reports of physical dependence involving commonly used sedatives and anxiolytics even at therapeutic doses. Third, a number of cannabinoids and their homologs are under evaluation as potential therapeutic agents. Fourth, expanded development of anorectic agents and antidepressants has emphasized the importance of abuse liability assessment of the centrally active stimulants. And fifth, the verification of the street-use of dissociative anesthetics (e.g., phencyclidine and its congeners) has added another group of substances with high abuse liability. These substances produce a constellation of effects including sedation, stimulation, and hallucinosis.

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II. Concepts and Definitions

Traditional concepts and definitions of drug dependence and drug abuse are in need of re-evaluation and revision. Advances in knowledge about drug actions, and particularly in research technology, have made possible an operational approach to pharmacological assessment of the risks of dependence on, and abuse of, psychoactive drugs of various categories, yet non-operational terminology still persists. The distinction between "physical" and "psychic" or "psychological" dependence, for example, has long since outlived its theoretical basis. Even the dichotomy between "physical" and "behavioral" factors has not provided a particularly useful framework for analyzing the essential dimensions of drug-related problems. And while the terms "dependence" and "abuse" are generally considered preferable to the word "addiction" as a basis for the development of an operational language in this field, persistent terminological ambiguities must be acknowledged.

One such problem derives from the continued use of the word "dependence" in at least two quite different ways. In the first instance, "physical dependence" is used with reference to the biochemical, physiological, and behavioral consequences of repeated exposure to a drug resulting in tolerance, and an abstinence syndrome when the drug is withdrawn. A second, less technical, use of the term "dependence" (or, more commonly, the phrase "drug dependence") refers to a complex of behavioral phenomena often described by such terms as "loss of voluntary control over drug taking," "compulsive drug use," 'and "reduced range of behavioral options." In this second case, the obvious overlap with the term "abuse" (or more commonly, the phrase "drug abuse") further complicates both technical and non-technical language usage.

In response to these problems, a recently published World Health Organization Memorandum on Nomenclature and Classification (Bull. WHO 1981) recommended substitution of the word "neuroadaptation" for physical dependence, and deletion of the term "abuse" from the drug lexicon on the grounds that it is essentially a value-judgmental term rather than an operational one. In addition, the WHO Memorandum further proposes use of the term "drug dependence syndrome" to encompass virtually all the phenomena currently

described by the two terms "dependence" (i.e., "neuroadaptation" plus "drug dependence") and "abuse." The main advantages of the terminology suggested in the WHO Memorandum lay in its clear differentiation between the primary process (drug self-administration) and secondary consequences (neuroadaptation), and its emphasis on experimentally or clinically operational terms devoid of value judgments.

From a scientific and technical perspective, the phrase "drug dependence syndrome," as defined in the WHO Memorandum, is conceptually indistinguishable from the older term "addiction" when the latter is used to designate the complex of persistent behavioral and physiological changes associated with chronic self-administration of drugs. However, the WHO Memorandum was not designed as an operational guide to the testing of those properties of drugs that might be related to the risk of dependence and/or abuse. In contrast, the present document is intended specifically for that purpose. Since the testing procedures to be described are largely based on concepts and terminology that had evolved before the publication of the WHO document, and that still enjoy wide acceptance, we will not at this time attempt to revise the operational terms that are in general use.

The final resolution of these differences in terminology has not been achieved. Many workers in the field as well as the lay public are still unaware of the new terminology proposed by WHO. Accordingly, for purposes of this discussion we shall continue to use the terms "physical dependence" and "abuse" as conventionally defined. These familiar terms are encoded in the laws and regulations which control the scheduling of drugs and the determination of manufacturing quotas. Should the proposed WHO terminology come into general use, future revisions of the present document will provide for the necessary changes.

"Physical dependence," as used in the following sections of this review. refers to physiological and behavioral alterations that become- increasingly manifest when drug administration is stopped after repeated exposure to a pharmacologic agent. Changes associated with (but not limited to) the development of tolerance and the physiological effects of drug withdrawal are expressed as an abstinence syndrome (Cochin 1970; Kalant et al. 1971; Eddy 1973; Clouet and Iwatsubo 1975). "Abuse" is used with reference to events that precede or accompany strong drug-seeking, drug discrimination, and drug-taking behaviors in association with self-administration of a pharmacological agent, often in a social context (Brady and Griffiths 1977; Griffiths et al. 1980; Brady 1981; Woods et al. 1982). The abuse concept clearly encompasses toxicity' as well, i.e., adverse physiological and/or behavioral consequences (Schuster and Fischman 1975).

The relevance and importance of this distinction between "physical dependence" and "abuse," for drug evaluation purposes, resides in the fact that while both these processes are of obvious public health concern, their defining properties are not coextensive and they do not invariably occur together. The assessment of "physical

dependence potential" in terms of tolerance and withdrawal, while obviously an important aspect of drug evaluation, does not by itself predict the drug-seeking and drug self-administration which are essential features of abuse, and which one attempts to predict by assessment of "abuse liability." Drug-seeking and drug-taking behaviors can be maintained in strength by doses of cocaine or morphine, for example, which produce no significant degree of tolerance or withdrawal (Schuster and Woods 1967; Johanson et al. 1976; Jones and Prada 1977). Conversely, some compounds such as propranolol have clear dependence potential (i.e., development of tolerance after repeated dosing, and an abstinence syndrome after drug withdrawal) at doses which have little or no attendant abuse liability, i.e., do not give rise to drug-seeking or drug-taking (Myers and Austin 1929; Crandall et al. 1931; Ambrus et al. 1951; Rector et al. 1955; Jaffe 1980).

In summary, from the perspective of drug testing, to which this review is addressed, pharmacologic assessment can most conveniently be related to the changes or events antecedent to repeated drug-taking, on the one hand, or consequent to it, on the other. It is primarily the reactive biochemical, physiological, and behavioral consequences, of drug administration, both acute and chronic (in terms of tolerance and withdrawal), which define a pharmacologic agent's physical dependence potential. The proactive drug-seeking, and drug discrimination which occur as antecedents to habitual drug use, on the other hand, together with the adverse effects of such use (i.e., a combination of the drug's reinforcing properties and its toxicity), define a drug's abuse liability.

Physical dependence and abuse, as defined, do of course frequently occur together. Changes in drug-seeking and drug-taking often occur as sequelae to both the acute effects of a drug and to tolerance and withdrawal after chronic drug exposure (Musto 1973). Conversely, the biochemical, physiological, and/or behavioral changes which define physical dependence can be sequelae of abuse-related drug self-administration (Jaffe 1980). But the relative contributions of these distinguishable processes to drug-related problems can vary widely with different pharmacologic agents as a function of such factors as dose level, environmental interactions, and previous drug history (Mendelson and Mello 1982). Moreover, the methods used to assess physical dependence potential and abuse liability, both in humans and in laboratory animals, are quite distinct. Therefore these terms are retained throughout the following description of the methods by which they are assessed.

Beyond the problem of terminology, of course, fundamental issues concerning the validity of biochemical, physiological, and behavioral methods for assessing dependence potential and abuse liability continue to be debated (Martin 1966; Jasinski 1977). The ultimate test animal, and the most precious, is of course, the human. Situations have arisen in which drugs were passed through the animal screens only to show abuse liability in humans. And street users have been able to discover abusable drugs or their combinations which were never tested in animals and were never suspected of abuse liability even after extensive clinical use.

Other drugs, such as the benzodiazepines, may be abused more often by humans than might have been expected on the basis of animal screening studies.

Such considerations notwithstanding, the focus developed in this document on formal changes and their temporal ordering in relationship to the drug intake event does provide an operational basis for characterizing the full range of a drug's functional properties and for evaluating all available measures of its structure (i.e., physico-chemical) and activity (i.e., physiological-behavioral) in comparison to known standards. In the final analysis, such "pharmacological equivalence" remains our most reliable approach to the assessment of physical dependence potential and abuse liability.

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III. General Methodological Considerations

The profile of a specific drug's physical dependence potential and abuse liability is defined by a number of its pharmacologic effects observed over a wide range of doses. Assessment of these effects involves a range of procedures that quantify the responses after acute administration (e.g., analgesia, behavioral performances, EEG patterns) and after chronic administration (e.g., tolerance spontaneous and/or precipitated withdrawal). Furthermore behavioral paradigms for assessing drug-seeking and drug-taking (e-g., drug self-administration procedures), for determining the stimulus properties of drugs (e.g., drug discrimination procedures), and for assessing behavioral toxicity (e.g., sensorimotor psychophysical procedures) have been employed with increasing frequency in systematic drug evaluations. The standardization of such assessment techniques thus makes it possible to provide a comparative analysis of relative dependence potential and/or abuse liability in both animals and humans across a number of drug doses and drug classes with increasing confidence.

Evaluating the acute effects of a drug is a necessary antecedent to the subsequent study of tolerance, and ultimately, physical dependence potential. In this regard, numerous pharmacological assays are employed that serve not only as the comparison response for tolerance studies, but as the basis for screening unknown compounds for physical dependence potential and/or abuse liability, as well. These assessments are made by comparing the effects of the unknown drug to a standard compound (e.g., morphine, pentobarbital, amphetamine, etc.). Once the acute effects of a drug are well characterized, the development of tolerance to these effects can be adequately quantified. While the fact that tolerance develops after chronic administration of a drug does not necessarily mean that the drug possesses significant dependence potential and/or abuse liability, it may serve as a partial explanation for gradual changes in intake over time as observed in drug self-administration studies. Under any circumstances, judicious interpretation of the results of tolerance studies serves an important function in the ultimate assessment of a drug's dependence and/or abuse profile.

Procedures for assessing the relative dependence potential of a drug have historically relied upon either substitution or primary dependence methods. The discovery of specific antagonists has added an important dimension to the study of physical dependence potential by providing a means of precipitating withdrawal signs. Another critical consideration in comparing the physical dependence potential of two or more drugs is the degree to which the effects of the drugs during chronic dosing are equivalent. Procedures for assessing the abuse liability of a drug have focused predominantly upon drug self-administration and drug discrimination paradigms. In the former case, methods have been developed for determining not only whether a drug will be self-injected (e.g., substitution procedures), but for determining the relative reinforcing efficacy of a given drug as compared to standard drugs of abuse (e.g., progressive ratio and choice procedures). Drug discrimination in animals, which approximates measures of subjective reports in humans, has been utilized to measure and compare the discriminative stimulus properties of drugs both within and between .pharmacologic classes.

Most importantly, laboratory animal methodologies have provided an applied technology for quantifying the acute and chronic effects of a drug in relationship to known standards of dependence potential and abuse liability. By and large, these methods complement, and in some cases extend, those employed in human research. Testing in human beings is complicated by the fact that there is great inter-individual variability in reactivity to and tolerance for various substances and that this initial tolerance level can be drastically modified by prior drug experience. Therefore, it is necessary not only to require of volunteers a drug-free period of several weeks to be certain that any drugs taken either therapeutically or recreationally have been eliminated, but control and experimental groups should be matched with respect to drug-taking histories, baseline reactivity, and tolerance. Simple random assignment to drug or control group is usually not sufficient to assure equivalent groups because most drug trials are based on small samples.

In addition to matching experimental and control groups, attention should be paid to obtaining subjects who will represent the population likely to be administered the drug clinically. This means that tests should not be restricted to persons with extensive prior drug experience, and that subjects should come from the age and sex groups likely to be given the drug. And since attrition rates may be high for human drug studies that require weeks or months of administration and follow-up, rewards for participation should be increased in proportion to the length of the study to reduce dropouts. Additionally, attention to methods for endpoint analysis to avoid loss of data for those who do not complete the test period is essential, since those compliant with long and difficult studies are unlikely to be representative of the general population of potential users.

IV. Specific Drugs and Drug Classes

A. General Considerations

Many, though not all, of the substances under consideration are drugs with well-defined clinical uses, and for some, there are currently no good therapeutic alternatives. These facts must be given due consideration in the overall evaluation of drugs with physical dependence potential and/or abuse liability. New compounds in these classes should, however, be expected to have either unique therapeutic properties or fewer adverse side effects than currently available drugs.

B. Opioids

The opioids (opiates) are a heterogeneous set of compounds widely utilized in suppressing the symptoms of pain, in the treatment of cough, dyspnea, and diarrhea, and, in certain circumstances, in the production of anesthesia, either as a primary agent or in combination with non-opiate anesthetics. Certain opioids are also utilized in maintenance programs for the management of opioid dependence and abuse. Morphine remains the major reference compound, though many other agents in this class produce comparable acute and chronic effects. In general, there are three types of opioids: pure agonists, pure antagonists, and those with mixed agonist/antagonist actions. Distinctions between pure agonists and mixed agonist/antagonists can be made on the basis of their effects on any one or all four distinct opioid receptor populations: mu, kappa, sigma, and delta, of which the prototypes are morphine, ethylketazocine, N-allylnormetazocine (SKF 10,047), and enkephalin, respectively. There is now considerable debate over whether the sigma opioid receptors are not, in fact, the same as the phencyclidine receptors or binding sites. This area remains to be clarified. Most of the compounds are structurally related to the naturally occurring 4,5-epoxymorphinans (morphine, codeine, and thebaine). While morphine was formerly difficult to make in the laboratory, many semisynthetic analogues (e.g., diacetylmorphine or heroin, hydromorphone, oxymorphone, hydrocodone, and oxycodone) could be relatively easily synthesized from morphine, codeine, or thebaine. These latter three key compounds can now be synthesized

from readily available simple compounds in good overall yield by a process which can be adapted to large scale synthesis.

Phenylpiperidines and related compounds such as meperidine, alphaprodine, loperamide, diphenoxylate, and fentanyl are purely synthetic drugs. Diphenoxylate and loperamide are particularly useful in treating diarrhea. Meperidine and alphaprodine are useful analgesics with a relatively short duration of action. Fentanyl is used as an anesthetic and in combination with droperidol used to produce neuroleptic analgesia. Propoxyphene, methadone and its congeners, and levo-alpha-acetylmethadol (LAAM) are also efficacious analgesics, but both methadone and LAAM are used primarily in the management of opioid dependence and abuse. Relatively pure antagonists such as naloxone, naltrexone, and nalmefene are essentially free of morphine-like effects, and can block the effects of morphine and other opioids. The efficacy of these antagonists varies with the type of opioid receptor acted upon by the agonist. The opioid agonist/antagonist analgesics represent a unique class of compounds with very different pharmacological profiles. Nalorphine and cyclazocine both possess pronounced dysphoric effects. Pentazocine, butorphanol, and nalbuphine are all effective analgesics, produce physical dependence, and may precipitate withdrawal signs in opioid-dependent subjects. Buprenorphine, a semisynthetic oripavine derivative, is a highly lipophilic compound that is a potent analgesic but can precipitate opioid withdrawal. Because it exhibits a "ceiling" effect to both its analgesic and side effects, it has been classified as a partial agonist of the morphine type.

A recent new use of opiates and opioids has been as the sole agents in anesthesia. Morphine,. as well as fentanyl, and mixed agonist/antagonist analgesics have been used in very large doses. Since respiration is maintained artificially during surgery, the depressant effect on respiration is obviated. The opioid effects are then terminated by administering large doses of naloxone.

With the discovery of endogenous ligands (e.g., enkephalins and endorphins) for the opioid receptor, attempts have been made to synthesize longer acting peptides (e.g., D-ala^2-D-leu^5-enkephalin) with the hope of finding a compound that is selective for subpopulations of opioid receptors.

C. CNS Depressants Sedative/Hypnotics, Anesthetics, Anxiolytics, and Antihistamines

CNS depressants that are employed as sedative/hypnotics or as anxiolytics comprise a wide range of chemically different compounds. While few qualitative differences exist between these compounds, they possess marked quantitative differences with respect to the degree of CNS depression. The older hypnotics include the inorganic bromides, chloral hydrate, and paraldehyde, while the barbiturates (e.g., pentobarbital) are currently more widely used. More recently, the use of nonbarbiturate sedative/hypnotics belonging to various distinct chemical classes has increased steadily. These include the acylureas (e.g., carbromal and bromvaletone), carbamates

(e-g, ethinamate and meprobamate), piperidinediones (e.g., gluthethimide and methyprylon), acetylenic carbinols (e.g., methaqualone), benzodiazepines (e.g., diazepam and nitrazepam), and the aliphatic alcohols (e.g., ethanol).

Another class of compounds that exerts generalized CNS depression is the volatile anesthetics. Abuse of such licit compounds as various halogenated anesthetic gases including halothane, methoxyflurane, and enflurane, is relatively rare. The anesthetic nitrous oxide, however, is currently enjoying a revival of illicit use. Obsolete compounds include the ethers, cyclopropane, fluroxene, and ethylene. Illicit use of compounds typically employed as propellants in commercial spray cans (e.g., fluorocarbons), and various solvents and glues such as aliphatic hydrocarbons (e.g., hexane and naphtha), aromatic hydrocarbons (e.g., toluene, xylene, and benzene), ketones (e.g., acetone and cyclohexanone), esters (e.g., amyl acetate), alcohols (e.g., butyl, ethyl, methyl, and isopropyl alcohols), glycols (e.g., ethylene glycol), and gasoline is more common.

The older antihistaminics (H1 blocking agents) are classified into three chemical. groups: ethylenediamines (e.g., pyrilamine and tripelennamine), aminoalkylethers (e.g., diphenhydramine doxylamine), and alkylamines e. g., chlorpheniramine and pheniramine). Most of the H1 blockers produce some degree of sedation and drowsiness at therapeutic doses. There are some exceptions (phenendamine). Further, at higher doses the H1 blockers have been observed to produce hallucinosis. The primary actions of the H1 blockers are to block the histamine-induced contractions of the bronchiolar .and gastrointestinal smooth muscle with partial effects on the cardiovascular system and no effect on histamine-induced gastric secretions. The latter action is postulated to be another receptor - H2. The prototypic H2 blocking agent, cimetidine, has been reported to have CNS activity especially in the elderly.

D. CNS Stimulants: Anorectics, Local Anesthetics, and Antidepressants

Compounds that stimulate the CNS and/or elevate mood are represented by numerous pharmacological classes. The xanthines (e.g., caffeine, theobromine), phenylethylamines (e.g., amphetamine, pemoline), and diphenylmethanes (e.g., methylphenidate, deanol) all increase; wakefulness, talkativeness, and random motor activity.
often elevated, sometimes with euphoria, and respiration is occasionally stimulated. Anorexia is a common effect as well. In addition to CNS stimulation, compounds like cocaine (which is a benzoic acid ester extracted from the leaves of Erythroxylon coca), as well as its analogues (e.g., procaine, benzocaine) possess marked local anesthetic action. While the tricyclic antidepressants such as imipramine and amitriptyline elevate mood in depressed patients, they are generally without effect in normal individuals. Newer antidepressants of different chemical classes, however, may have such potential.

E. Hallucinogens and Anticholinergics

Many compounds, when taken in sufficient doses, can cause hallucinations that may be secondary to delirium, sedation, or stimulation. The compounds appropriately classified as hallucinogens produce. visual and/or auditory hallucinations not necessarily associated with delirium, sedation, or stimulation. Many compounds are derivatives or analogues of endogenous amino acids. Compounds in this class include the substituted indolealkylamines (e.g., lysergic acid diethylamide or LSD, dimethyltryptamine or DMT, psilocybin. harmine, and ibogaine). and the substituted phenylalkylamines (e.g., mescaline, 2,5-dimethoxy-4-methylamphetamine or DOM). The 3-N-substituted piperidyl benzilates (e.g. ditran) and the classical anticholinergics atropine and scopalamine, when taken in sufficient doses, also produce hallucinosis.

F. Cannabinoids

Residues from Cannabis sativa include a number of chemically distinct compounds with the cannabinoids being the major pharmacologically active group. At least 20 different naturally occurring cannabinoids have been identified and include delta-g-tetrahydrocannabinol (THC), delta-8-THC, cannabinol, and cannabidiol. The most potent compound, delta-9-THC, has been shown to be a potentially useful agent in the management of emesis, glaucoma, and muscle spasm. Many congeners of delta-9-THC have been synthesized, of which synhexyl (a delta-6[a]-lO[a], n-hexyl derivative of THC) and DMHP (a dimethylheptyl side chain congener of synhexyl) were the first to be studied. Significant undesired side effects precluded further studies with these compounds, but other synthetic analogues such as nabilone, SP 106, and CP 44,001 may be potentially useful therapeutic agents in man.

The cannabinoids, unlike other compounds reviewed, present a 'range of problems which have hindered the understanding of their pharmacology. The identification and standardization of the active constituents in these preparations has been difficult. The compounds are relatively unstable, insoluble in aqueous solutions, and have many metabolites, including some that are pharmacologically active. Clearly, the development and refinement of methods for the isolation and purification of the natural alkaloids of the plant Cannabis sativa have been instrumental in the progress that is reviewed here. In addition, a number of synthetic cannabinoids have demonstrated some specificity in their actions, and, as such, may prove to be more useful as potential therapeutic agents. The assessment of the cannabinoids as a class, however, must necessarily involve procedures sensitive to all known actions of these compounds; the standard for comparison is the major active agent, delta-9-tetrahydrocannabinol.

G. Dissociative Anesthetics

The prototypic compound, 1-(1-phenylcyclohexyl) piperidine or PCP produces a wide spectrum of effects, from stimulation and

hallucinations to depression and analgesia. One analogue, ketamine, enjoys a widespread use in veterinary medicine and some special uses as a short-acting anesthetic in man. Other analogues have been synthesized which are essentially based on substitutions of one of three functional groups of the PCP nucleus: phenyl ring, cyclohexyl ring, or the amino group. The latter analogues are not legitimately manufactured or marketed, but widespread illicit synthesis has been documented.

While most studies on the structure-activity relationships of PCP analogues have used compounds with substitutions on the phenyl or cyclohexyl ring, the majority of illicitly synthesized compounds are N-substituted. Small chain alkyl groups (e.g., ethyl, propyl) have been the most common substitutions which N-ethyl-1-phenylcyclohexylamine (PCE) and 1-(n-propyl)-1-phenylcyclohexylamine (NPPCA), respectively. The former compound, PCE, is currently under Schedule I control as is 1-(1-phenylcyclohexyl) pyrrolidine or PCPY. Toxicological manifestations of PCP analogue abuse have also been a major cause for concern with respect particularly to the compound 1-piperidinocyclohexanecarbonitrile or PCC which, upon entering a biological system, releases hydrogen cyanide. While PCC itself is currently under Schedule II control (like PCP), it is a precursor to PCP synthesis and thus tends to be a common contaminant in illicitly synthesized PCP and other analogues. PCP analogue abuse is a complex problem which essentially stems from the fact that the identity of the compound is rarely confirmed and very little information is available about the many easily synthesized analogues.

V. Animal Testing Procedures

A. General Methods

1. Procedures for Characterization of Drug Effects

a. Acute Drug Effects

i) Spontaneous locomotor activity

The jiggle cage method of Harned et al. (1952) determines the effects of test compounds on spontaneous motor activity. Usually, rats are placed in a cage suspended in air by a spring. Movements of the rat are recorded kymographically on chart paper and can be quantified with respect to control animals given vehicle. An additional measure of locomotor activity is obtained using an open-field grid (Brimblecombe 1963). An observer (blind to the treatment) counts the number of squares entered over a set period of time. The photo-cell annular cage is also employed to determine motor activity. Typically, mice or rats are treated with either vehicle or the test compound and the number of times an animal interrupts the light beam over a given interval is recorded. Time-course data are easily obtained with this method using cumulative recorders.

ii) Forced motor activity

A measure of motor impairment (ability of rats or mice to remain on a rotating rod) can be obtained using a variety of procedures, one example being the rotorod assay (Dunham and Miya 1957; Kinnard and Carr 1957). The device consists of a motor-driven, aluminum rod (6-8 cm diameter) which is divided into several segments by circular aluminum plates which serve to limit lateral movements of the animals on the rod. Once the rodent is placed on the rod, it is set in motion and the time until the animal falls off is recorded. Typically, a maximum cut-off of 1-2 minutes is used. Animals can be tested numerous times after a single injection to generate time-course data.

iii) Electroencephalographic (EEG) activity

This procedure employs the brain's electrical activity as a measure of a drug's effect (Klemm 1969). Recently developed computer-assisted analysis (e.g., power spectrum) has permitted not only qualitative but quantitative measures of drug-induced changes in EEG activity. The EEG has been used to quantify acute and chronic drug effects in various species including the mouse (Morley and Bradley 1977), rat (Lukas et al. 1980). cat (Schallek et al. 1967), dog (Wikler and Altschul 1950), and monkey (Gehrmann and Killam 1976). This technique is most often employed in chronic animals which have been implanted with cerebrocortical EEG electrodes, although sub-cortical electrodes have also been employed. The animals are typically allowed to acclimate to the surroundings and control EEG activity is recorded. Once the EEG recording is stable, a drug is administered and' the resultant EEG activity is monitored on a polygraph and stored on magnetic tape for subsequent computerized power spectral analysis. This analysis consists of measuring the amount of energy (or power) as a function of frequency.

Another component of the analysis of the EEG effects of drugs of abuse relates to the quantification of various stages in the sleep-wakefulness continuum. In all mammals, at least three stages are readily distinguished - a waking stage, a slow-wave stage of sleep, and a rapid-eye-movement (REM) stage of sleep. The EEG from mammals can be scored for the onset, duration, and cyclicity of the stages. Transitions between stages are also noted. These form the basis for the evaluation of drug-induced alterations (van Twyver 1969).

In recent years, there has been increasing use of evoked potentials in the EEG to define and quantify the actions of drugs. A constant-intensity stimulus, such as a light flash, a signal tone, or a mild electric shock, is administered repeatedly to the subject, and the EEG activity is recorded during a fixed sweep of the last 500 msec of each stimulus. Summation of these recordings in a computer results in averaging-out of the random background activity, but progressive augmentation of the specific wave pattern of response to the stimuli. Drug effects on the latency and amplitude of each component of the response can then be expressed in precise quantitative terms (Kalant 1978a).

iv) Behavioral performance

Numerous drugs have been reported to modify a wide range of performances including food and water consumption, exploratory and aggressive behaviors, punishment, escape, avoidance, and conditioned suppression responses. With the exception of the conflict procedure (Geller and Seifter 1960), which is relatively selective for anxiolytics, few behavioral paradigms are employed routinely in animal models of abuse liability and/or dependence potential. Consummatory behavior (e.g., food or water intake) has been shown to increase after acute administration of opioid antagonists, but benzodiazepines induce hyperphagia as well. In addition, procedures which employ response rates as a measure of performance appear to be

affected by drugs belonging to a wide range of pharmacological classes. This relationship is also dependent upon the response rate prevailing at the time of drug administration (e.g., law of initial effect); thus, procedures that maintain low response rates are typically increased by many compounds while high response rate performance is typically suppressed. This phenomenon has been elegantly demonstrated using a multiple schedule technique (e.g., mult. FR/FI). Drug-induced changes of response rates in the same animal can be demonstrated to be directly related to the schedule of reinforcement (Dews 1955; Kelleher and Morse 1968).

The contributions of behavioral pharmacology to the assessment of drug abuse liability and physical dependence potential have had their greatest impact in the areas of tolerance and withdrawal. At least three different behavioral factors have been shown to have important effects upon the rate of development of tolerance, and upon the degree of tolerance developed. The first is the presence or absence of a requirement for task performance while the subject is under the influence of a drug. Animals receiving the drug just prior to the start of each training session acquire tolerance more rapidly than animals receiving the same dose of the same drug immediately after each training session (Kalant et al. 1971; LeBlanc et al. 1973). The second factor is the effect of the drug upon the relationship between the performance and its consequences. For example, rats were trained to bar-press for food rewards on a schedule of alternating periods of FI and DRL. Under the influence of the first dose of amphetamine, their response rates increased during both components of the schedule, but this caused loss of rewards only in the DRL component and not during the FI. With repeated amphetamine tests on the same schedule, the rats rapidly developed tolerance to the rate-increasing effect during the DRL portions, while showing no tolerance during the FI portions of the schedule (Schuster et al. 1966). The same phenomenon has been observed subsequently with other drugs (Krasnegor 1978). The third factor is the presence or absence of environmental stimuli linked by Pavlovian conditioning to the administration' of a drug. If an animal receives a dose of a given drug repeatedly in the same environment, it shows more tolerance when tested in the same environment than when tested with the same dose in a new environment (Siegel 1976; Le et al. 1979).

All three sets of observations mentioned in the preceding paragraph have given rise to the concept of behavioral tolerance as distinct from classical or pharmacological tolerance (Krasnegor 1978). However, it has been argued that these are not separate forms of tolerance, and that the behavioral factors simply alter the rate or extent of development of an intrinsic biological adaptation (Kalant et al. 1971; Kalant 1978b). The extent to which behavioral variables contribute to the tolerance will vary according to the specific circumstances. It is important, however, in testing drugs for physical dependence liability, to ensure that the same test paradigm is employed throughout, so that the behavioral influences are kept constant for all the drugs under comparison.

Behavioral procedures for determining the appetitive and/or aversive properties of drugs have as well extended the application of classical conditioning methods to the assessment of drug abuse liability. Conditioned taste aversion paradigms have been employed, for example, in which the consumption of a saccharin solution to which an animal has been previously exposed in association with psychoactive drug injection is subsequently compared with water. Saccharin preference under such conditions indicates appetitive drug effects whereas saccharin rejection suggests aversive properties even though drug self-administration tests may reflect reinforcement effect (Cappell and LeBlanc 1975). A similar "place preference" procedure involves a comparison of the time spent in each of two distinctive environments (i.e., differing in visual, auditory, olfactory, and/or tactile cues) as a function of different drug, drug dose, or vehicle injections under such clearly discriminable conditions. The appetitive effects of cocaine or morphine, for example, are reflected in the increased time spent in the environment associated with such drug injection, while aversive effects produce avoidance of the drug injection site (Mucha et al. 1982).

v) Binding assays

With the discovery of specific receptors to which opioids, stimulants, neuroleptics, and benzodiazepines bind, quantitative study of structure-activity relationships (QSAR) has emerged as a major pharmacological method which has provided extensive information regarding the basic mechanism of action of drugs of abuse. Binding sites in brain tissue have as well been reported for both PCP and its analogues, and the good correlation between binding affinity and potency in clinical use has served not only to enhance understanding of drug/receptor interactions, but to validate the use of this technique as a predictor of drug effects as well. While binding to CNS tissue is normally associated with a drug's physiological/behavioral effects, binding assays involving other tissues (e.g., smooth muscle) have proven equally useful. In fact, guinea pig ileum and mouse vas deferens have been used extensively to characterize the binding characteristics of the opioids and endogenous, opiate-like peptides (Kosterlitz et al. 1973; Woods et al. 1981).

The basic concept in binding studies involves the use of a radiolabelled (e.g, ^{3}H, or less frequently, ^{14}C) ligand (e.g., dihydromorphine, flunitrazepam) which is first incubated with the tissue to which nonlabelled test drug is then added. By measuring the remaining radioactivity on the tissue, the degree of displacement of the labelled ligand can be determined, and thus a measure of relative affinity for the binding site is obtained for the test compound. Additional information regarding the binding characteristics of drugs of abuse is obtained by determining the effects of adding receptor antagonists or electrolytes (e.g., Na+) to the incubation (Pert and Snyder 1974). Differential and incomplete displacement of binding has been interpreted to mean that there are multiple receptor populations for a specific drug class. In many instances, a high correlation between the results of binding

studies and the observed physiological and behavioral effects with certain drugs has been found. This has led to the inclusion of binding characteristics in the pharmacological profile of some drugs.

2. Procedures for Assessing Physical Dependence Potential

a. Tolerance to Drug Effects

The development of tolerance to a drug is reflected by an attenuation of the original response with subsequent exposures to the drug. Thus, the dose must be increased in order to re-establish the original response. By quantifying the acute effects of a drug, it is possible to track the development of tolerance to any one effect. This is particularly important because tolerance does not necessarily develop equally, that is, to the same degree or at the same rate, to all of a drug's effects. Tolerance may be dispositional or functional; the former is primarily due to an increased rate of biotransformation and/or drug elimination from the body, while the latter refers to a diminished sensitivity of the CNS (Kalant et al. 1971). An additional dimension to tolerance which has become evident as a result of refinements in the development of performance procedures is behavioral tolerance. This phenomenon may be apparent only with respect to some specific aspect of the behavioral repertoire which has previously been "learned" under the influence of the drug (see above "Behavioral Performance" section).

The development of tolerance is most apparent when exposure to the drug is continual. Various techniques have been employed to maximize drug exposure, including continual infusions, multiple parenteral injections, addition of a compound to food or drinking water, and implantation of subcutaneous pellets or miniature osmotic pumps.

b. Withdrawal from Chronic Drug Administration

The abstinence syndrome is defined by the physiological and behavioral consequences of terminating chronic administration of a drug (also called abrupt withdrawal). Both the dose and duration of exposure determine the dependence potential of a drug, and the degree of dependence potential differs among drugs from different classes. The basic procedures for assessing these effects, however, are similar in format, and involve two basic techniques: direct or primary (dependence), and single dose substitution (Fraser and Jasinski 1977). In the former, the test compound is administered on a chronic basis to drug-naive animals; the initial dose is usually low, and as tolerance to toxic effects develops, the dose is increased. At the end of the dosing schedule the drug is withheld, and the animals are observed for physical signs and symptoms of withdrawal. Single dose substitution procedures involve rendering animals dependent on a standard drug (e.g., morphine, barbital) for a specified period of time. The drug is then withheld, and the animals are observed for withdrawal signs. Once the withdrawal syndrome appears, a single dose of the test compound is administered

to determine whether the withdrawal signs can be reversed or attenuated.

A recent development in the study of relative dependence potential has been the use of a functionally equivalent dosing regimen for the drugs being compared (Boisse and Okamoto 1978). This procedure takes into account the physicochemical properties of a drug which determine metabolic and elimination rates (and thus, the amount of drug in the body) as a factor influencing dependence potential. The most common procedures for accomplishing functional equivalence are behavior rating scales (for degree of CNS depression) and devices for measuring ataxia (e.g., rotating rod). Doses are adjusted in order to maintain equal degrees of sedation.

Most dependence studies are conducted using spontaneous withdrawal techniques (i.e., the drug is simply discontinued). Techniques for assessing opioid dependence potential, however, have been extended by the development of an opioid receptor antagonist, naloxone. Thus, precipitated withdrawal is possible and the need to wait 12-24 hours for withdrawal signs is obviated. The recent discovery of a benzodiazepine receptor antagonist (Ro 15-1788) has also provided for a similar extension of dependence assessment procedures with this increasingly more prominent class of clinically useful compounds (Lukas and Griffiths 1982).

3. Procedures for Assessing Abuse Liability

a. Drug Self-Administration

Drug self-administration procedures represent the most widely used method for assessing relative abuse liability with drugs belonging to various classes. With the development of a chronic intravenous catheter (Clark et al. 1961; Weitzman et al. 1961) and methods for automated delivery of drugs, studies of drug self-administration were first undertaken in rats over two decades ago (Weeks 1962; Weeks and Davis 1964). Procedures for implanting i.v. catheters in non-human primates have since been refined and detailed (Deneau et al. 1969; Lukas et al. 1982). Chronic intragastric catheters have also been developed for rats (Gotestam 1973; Lukas and Moreton 1979) and primates (Altshuler et al. 1975; Lukas et al. 1982)) and automated drinking systems have been described in reports of oral drug self-administration studies (Meisch and Henningfield 1977; Ator and Griffiths 1982).

Two basic types of drug self-administration procedure are commonly used: 1) continuous or direct, and 2) substitution. In the former, the animal is allowed access to the test compound without prior experience. This procedure is useful in assessing whether an animal will initiate self-injections of the test compound, and if so, whether responding for the compound will change over time. In the substitution procedure, drug self-administration is first established with a standard compound (e.g., cocaine, morphine) known to be reinforcing, that is, animals will work to obtain access to the compound. Once performance and drug intake have stabilized, the test compound is substituted for the standard. The abuse liability

pattern is defined by numerous characteristics including intake, time course, and stability of responding. Once self-administration behavior is established with a compound (e.g., dose-response functions are generated, relative potencies are determined), the next step in characterizing abuse liability is to determine relative degree of reinforcing efficacy. Numerous procedures including progressive ratio, response rate analysis, discrete-trial choice, and concurrent schedule control, have been utilized to address this question.

i) Progressive Ratio Procedures

Progressive ratio procedures involve a two-step operation in which stable operant performance (typically maintained on a fixed-ratio schedule) is first obtained with the reinforcer. Subsequently, the number of responses required for delivery of reinforcement is systematically increased until responding falls below some criterion level. The highest ratio at which performance remained above criterion is referred to as the "breaking point"; Hodos and Kalman (1963) demonstrated that the higher the concentration or volume of liquid reinforcer the greater the breaking point. Because of this relationship the breaking point is taken to represent a measure of relative reinforcer strength.

The extent to which a progressive ratio procedure can provide useful data regarding the reinforcing efficacy of a drug is dependent upon the fulfillment of certain criteria. First, since the actual procedure followed varies substantially between laboratories, it is important to recognize that the measures obtained are not absolute, but rather are relative to some standard. Therefore, it is crucial that all interpretations of reinforcing strength be made on the basis of relation to a standard compound (e.g., morphine, pentobarbital, cocaine, etc.). Second, since the reinforcing properties of drugs are dose related, there is every reason to suspect that the breaking point may also be dose related. Thus, complete dose-effect curves must be evaluated in order to determine not only whether different drugs maintain higher breaking points, but also whether different doses maintain this performance as well.

ii) Response Rate Analysis

Interpretations of relative reinforcing strength can sometimes be measured in terms of the rate of responding prior to the drug injection. The degree to which this applies, however, is dependent upon the schedule of reinforcement employed. Historically, a negative correlation has been shown to exist between drug dose and response rate (Downs and Woods 1974; Goldberg et al. 1972; Pickens and Thompson 1968). The response requirement for these studies was typically a continuous reinforcement or a low fixed ratio, and thus, the direct effect of the self-injected drug was most likely responsible for the decreases' in response rate. Using schedules that employ either a fixed-interval schedule (Balster and Schuster 1973) combined with a time-out (15 minute) period after each self-injection or a fixed ratio schedule with a long time-out period (Griffiths et al. 1981), however, it is possible to observe a

positive relationship between increasing drug dose and higher rates of responding. This relationship does nonetheless have the limitation that, as the direct effects of higher doses of the drug persist for, longer periods of time, response rates will decrease.

iii) Choice Procedures

An obvious extension of procedures that assess the reinforcing strength of a single drug is one which permits an animal to select a preferred drug dose, or to choose between two different drugs. Typically, different colored lights are used to signal the availability of different reinforcers. After initial exposure with various doses of a single drug (Brady and Griffiths 1977) or two different drugs (Johanson and Schuster 1977), the animal is given the opportunity to choose between the doses or drugs by operating a third lever which switches the color of a viewing light indicating which reinforcer is available. Only one reinforcer is available at a time. Completion of the response requirement on the appropriate lever results in delivery of drug previously associated with that color. The percentage of choices of one drug or dose over another and the response rates maintained by the injection are determined to reflect the relative degree of reinforcing strength. Attempts to eliminate possible confounding effects of drug interactions have resulted in procedures which offer choices between drug and food (Griffiths et al. 1975).

iv) Concurrent Schedules

The procedures for assessing concurrent drug availability differ from choice procedures in that concurrent schedules make both drugs (or different doses of the same drug) available simultaneously. Using variable interval schedules, higher rates were generally associated with the response alternative which delivered higher cocaine doses (Iglauer et al. 1975). As with other procedures, this relationship became asymptotic as higher doses were studied.

b. Drug Discrimination Procedures

Assessment of the discriminative stimulus properties of drugs has been recently demonstrated to provide a useful adjunct to self-injection techniques for the evaluation of a pharmacological agent's abuse liability. The value of drug discrimination procedures in this regard relates to the fact that these procedures are designed to utilize the physiological or interoceptive alterations induced by many psychoactive drugs as the "cue" for an appropriate response to obtain food or avoid shock (Overton 1971). Thus, these procedures can provide information analogous to a human testing situation in which subjects categorize drugs with respect to their subjective effects.

The basic procedure involves training animals to respond differentially (depending upon the nature of drug pretreatment) in either a T-maze (e.g., go left if drugged; go right if nondrugged) or a two-lever choice situation (e.g., left lever produces food or avoids shock if drugged; right lever produces food or avoids shock

if nondrugged). Training time can be decreased by introducing differential drug conditions on the first exposure rather than pretraining on both levers or arms of a T-maze (Overton 1979). Once stable responding has been established and the percent of correct responding is high (e.g., ›)85%) then test sessions are initiated in which novel drug conditions are presented in order to assess generalization. Within the context of abuse liability testing, three basic procedures can then be followed. First, generalization of the training dose can be demonstrated for other doses of the training drug (Schuster and Balster 1977). This ensures that the discriminative stimulus of the drug is in fact controlling the responding. Secondly, once an appropriate training drug and dose are chosen, generalization to other compounds within the same pharmacologic class can be assessed to provide evidence for the pharmacological specificity of drug stimulus control. All results must be interpreted in relation to the training drug dose, however, since this can markedly affect the results of such testing (Waters et al. 1972). Thirdly, cross-generalization to drugs belonging to other pharmacologic classes can be assessed in a similar manner. Generally, drugs belonging to the same or similar classes tend to produce training-drug-appropriate responding while drugs from different classes do not (Colpaert and Rosecrans 1978).

c. Behavioral Toxicity

A broad range of performance procedures has been used to assess both the acute and chronic decrements which define the behavioral toxicity of abused drugs. Progress in this area of pharmacology has closely paralleled laboratory developments in the experimental analysis of behavior, and has focused most recently upon psychophysical methods for sensorimotor assessment. The role of behavioral toxicology has become increasingly important in such drug evaluation because substances with only minimal (if any) disruptive behavioral or physiological effects are not generally regarded as having significant abuse liability even though self-administration may be widespread (e.g., caffeine in tea or coffee). In contrast, compounds self-administered even sparingly which produce disruptive physiological/behavioral changes are considered to have high abuse liability (e.g., lysergic acid diethylamide). Drugs may fall anywhere on the continua defined by these parameters and relative abuse liability is most effectively determined by a comprehensive assessment of these interactive behavioral/physiological dimensions.

Most procedures employed are based on standard behavioral paradigms (Weiss and Laties 1975), and,as such, are distinguished from the more traditional assessment of teratology. Performance decrements are usually assessed in terms of motor impairment as an index of behavioral toxicity (e.g., changes in lever pressing to obtain food or avoid shock), although recent developments in the application of classical psychophysical procedures have broadened the scope of sensorimotor evaluation techniques. These refinements in animal psychophysical methodologies have made available valid and reliable experimental procedures for precise measurement of sensory functions in non-human primates, birds, rodents, and carnivores (Masterton et al. 1969; Stebbins 1973; Fay 1974; Dolling 1980). In general, these

advances can be seen to have resulted from a marriage of two technologies--classical human psychophysics on the one hand, and animal learning and conditioning on the other. Further, the training and testing procedures for obtaining valid and reliable measures of sensory function in such animals have been thoroughly documented (Blough 1966; Stebbins 1970). providing convincing demonstrations of their sensitivity and specificity in more general behavioral pharmacology applications.

Most recently, for example, applications of these psychophysical procedures to the evaluation of auditory and visual threshold and reaction time changes in baboons have been reported following pharmacological treatments involving several drugs of abuse (Brady et al. 1979; Hienz and Brady 1980; Hienz et al. 1981). Baboons housed in individual cages and maintained on a 22-hour restricted feeding schedule were trained to press a lever and hold it depressed for varying intervals until presentation of a light flash or tone burst. Correct responding (defined by release of the lever within 1.5 seconds of stimulus presentation) was rewarded with banana-flavored food pellets. A 1-second intertrial interval (ITI) was then imposed during which no stimuli were presented and any lever press reinstated the ITI. Experimental sessions were conducted daily over a Z-hour period with auditory and visual thresholds determined by randomly varying the intensity of the test stimuli from trial to trial and examining the number of correct lever 'releases. Four to five separate measures of thresholds and reaction times were obtained, each based on blocks of 140 trials, thus providing a measure of the time course of drug effects.

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6. Procedures for Assessing Opioids

1. Characterization of Opioid Effects

a. Acute Drug Effects

i) Analgesia

Numerous methods are currently available that provide reliable assessments of the analgesic potency of an opioid. Traditionally, methods have been segregrated into two classes depending on the degree to which a non-opioid (e.g., salicylate) can be distinguished from an opioid analgesic. In the case of the former, Randall and Selitto (1957) have described a technique in which brewer's yeast (0.1 ml of a 20% suspension) is injected into a rat's foot. The ensuing pain and swelling are determined by applying increasing pressure to the foot. Salicylates elevate the pain threshold in the inflamed foot only, while opioids elevate pain thresholds in both hind legs.

Procedures for assessing the analgesic properties of opioids are mainly conducted with rodents and assess the degree of pain from heat (e.g., tail flick, hotplate), pressure (tail compression), or electric shock (e.g., shock titration, stimulation). With the exception of electric shock, the basic procedures are similar and are usually characterized by a group study design, appropriate controls (e.g., for habituation), operationally defined end-point responses (e.g., paw lick, vocalization), and a maximal cut-off time to prevent tissue damage. The tail flick (D'Amour and Smith 1941), hotplate (Eddy and Leimbach 1953), hot water (Janssen et al. 1963), electric stimulation (Knowlton and Cross 1943), flinch jump (Evans 1961)) and tail compression (Dandiya and Menon 1963; Geller et al. 1979) methods all include these features. Typically, animals are first tested for their sensitivity to the system under non-drug conditions. Then, groups of 8-10 rodents receive either the test drug or vehicle and are retested at various intervals (e.g., 10 minutes). The "index of analgesia" can then be obtained by employing the method of Cox et al. (1968) which normalizes the results from different compounds. Analgesia (as measured by an increased latency to respond) is characterized not only by the time to peak effect, but by onset and offset as well. The use of a maximal cut-off time would generally preclude the quantitation of analgesic efficacy. However, calculation of a percent of "maximal analgesia" according to the formula (test)-(control)/(maximum)-(control) X 100 can circumvent the problem. Collins et al. (1964) attempted to obviate the problems associated with the artificial "ceiling" of analgesic effect with opioids by using a rectal electrode method for delivery of electrical stimulation of increasing intensity in the range of 0 to 24 V, at a rate of 1 V/set with rats. Reaction thresholds were measured as a function of the time from the onset of stimulation until vocalization. Drugs were given S.C. or i.p. and animals were tested at 15 and 30 minutes, and then at 30 minute intervals for 3 hours after drug administration. Weak analgesics such as acetylsalicylic acid were inactive, while barbiturates were active only at doses that induced deep CNS

depression. Using the increase in threshold in volts (rather than % of control), the dose-effect curve for morphine increased exponentially with increasing dose while codeine possessed a much shallower, linear curve.

ii) Spontaneous Locomotor activity

These procedures described above in general methods are commonly used to assess the pharmacological activity of opioids. While the measure of locomotor activity does not provide information relevant to the prediction of dependence potential, it does provide a baseline for the study of tolerance and cross-tolerance to other drugs. Opioid-induced changes in locomotor activity are characterized by both depressant and stimulant actions. In general, the biphasic response consists of an initial depressant phase which typically precedes the delayed stimulated phase. Since the overall effect is species-, dose-, and time-dependent, however, it is important to obtain frequent measures of locomotor activity after drug administration rather than single, fixed-time measures (e.g., 30 minutes post injection).

iii) Electroencephalographic (EEG) activity

Visual analysis of the direct EEG has revealed that morphine and its surrogates slow the predominant frequency and increase high-voltage delta activity (Khazan 1975); some analogues such as methadone induce spike-and-dome activity after high doses.. On the basis of EEG and behavioral profiles and naloxone sensitivities, it is possible to distinguish between opioids acting at different receptors (Tortella et al. 1980). While the effect of opioids on the EEG are readily discernible, the need to quantify the changes in both voltage and frequency components has resulted in the emergence of numerous computer-assisted techniques. Currently, power spectral analysis is used to quantify not only the acute effects of opioids, but the development of tolerance, cross-tolerance, and drug-seeking behavior as well (Young et al. 1978).

In the application of EEG procedures for assessing the acute effects of opioids, as described in general methods above, opioid effects may appear in biphasic form. In characterizing the EEG profiles of morphine, methadone, l-alpha-acetylmethadol (LAAM) and its two demethylated metabolites (NLAAM and DNLAAM), for example, an 8-hour post-injection evaluation revealed the appearance of distinct EEG changes 1-2 hours after LAAM which matched those observed immediately after NLAAM (Lukas et al. 1980). Cross-tolerance has also been quantified using power spectral analysis (Lukas et al. 1982) with opioid challenges in LAAM-maintained rats producing attenuation of the EEG voltage and a shift to a higher predominant frequency. The technique also distinguished between high and low maintenance doses of LAAM and, in addition, demonstrated that the development of cross-tolerance to morphine was more complete than that developed to methadone.

Shifts in the predominant EEG frequency during rapid-eye-movement (REM) sleep have as well been used to track drug-seeking behavior in

dependent rats (Young et al. 1978). The REM sleep predominant frequency gradually slows during the 2-hour interinjection interval until the next self-injection of morphine when "reset" to the faster frequency (i.e., about 1 Hz) is observed. Power spectral analysis has also been utilized to characterize the EEG profile of the prototypic mu, kappa, and sigma agonists (Young et al. 1981). The different compounds are defined by a unique fingerprint-like array based on the voltage and frequency components of the power spectrum. Thus, the mu agonist morphine produces a large increase in voltage over the O-10 Hz band while ketocyclazocine (a kappa agonist) produces a definite peak in the 5-8 Hz band with lower activity in the O-4 Hz band. (N-allyl-normetazocine, the putative sigma agonist, produced .a power spectrum characterized by relatively much lower voltage in the O-10 Hz band, and a small, sharp peak at 7.5 Hz.

iv) Behavioral performance

Although behavioral methods have been utilized to assess analgesic activity (e.g., shock titration), conditioning techniques have not generally been used to identify opioids or distinguish them from other drug classes. Behavioral paradigms for the assessment of opioid activity have focused mainly on the measurement of tolerance and, more recently, in the classification of opioids based upon the subclasses of opiate receptor activity. Antagonist-induced (i.e., naloxone, naltrexone) differential shifts in the dose-response curves of opioid effects upon lever-pressing in rats on a fixed interval food reinforcement schedule, for example, have been related to the several presumed subpopulations of opioids (Harris 1980). The agonist morphine was completely antagonized by naloxone or naltrexone while butorphanol, ketocyclazocine, ethylketocyclazocine, and low doses of cyclazocine were only partially antagonized. The rate-decreasing effects of SKF-10,047 and high doses of cyclazocine were not blocked by the opioid antagonists.

v) Seizure threshold

Using the flurothyl-induced seizure assay in rats, opioids have been shown to either decrease, increase, or have no effect upon seizure thresholds. On the basis of these differential effects, opioids have been classified into four distinct subclasses based upon the observed dose-response. relationships, stereospecificity, naloxone sensitivity, and development of tolerance-cross-tolerance (Cowan et al. 1979). The technique for flurothyl administration has been detailed by Truitt et al. (1960) and Adler (1975). Animals are placed in a large volume (e.g., 3-4 1) glass jar. A screen holds a gauze pad inside the jar which is fed by plastic tubing connected to a syringe containing a 10% v/v solution of flurothyl in ethanol. Controlled continuous infusion of flurothyl onto the gauze is maintained by an infusion pump at a rate of 0.103 ml/min. A full-blown generalized seizure usually occurs about 320-350 seconds after the onset of the infusion.

The profile of flurothyl-induced seizures has been described for rats as containing four components. The rat's typical exploratory behavior is interrupted by short periods of "freezing" or

immobility. Between 150 and 200 seconds after infusion onset, jerky, tremor-like movements prevail which are replaced by preclonic or myoclonic jerks occurring 50-100 seconds later. Clonic movements of the forelimbs signal the onset of the full seizure involving both forelimbs and hindlimbs. Test compounds are administered subcutaneously to individual rats 30 minutes before exposure to flurothyl. The time interval between the start of the infusion and the onset of a clonic convulsion is used as the seizure threshold.

vi) Spinal dog preparation

The chronic spinal dog assay (Martin et al. 1976) has been used to assess the pharmacologic effects of many opioids, determine relative potencies, and provide a means of establishing pharmacological equivalence. The technique allows simultaneous measurement of pupillary diameter, pulse rate, pain reflexes, touch reflexes, and body temperature among other physiological processes. The preparation is also capable of differentiating between naive and opioid-tolerant animals and the measures obtained are sufficiently sensitive to allow detection of an opiate abstinence syndrome, even after relatively low doses. Results obtained with this technique contributed to the formulation of opiate receptor subspecies accounting for the effects of any given opiate by its action on one or a combination of three receptors (Gilbert and Martin 1976; Martin et al. 1976).

The preparation involves transection of the spinal cord at either a high (e.g., 5th-6th cervical) or a low (e.g., lOth-11th thoracic) level. Standard measurement of pupillary diameter, pulse rate, respiratory rate, and body temperature follows recovery from surgery (Martin and Eades 1964). Somatic reflexes elicited below the level of spinal cord transection are recorded isotonically (Wikler and Frank 1948) in the following order: patellar reflex, crossed extensor reflex, ipsilateral extension thrust, and the ipsilateral flexor reflex (Martin et al. 1964). The patellar reflex is evoked using a reflex hammer applied at a rate of about once every 3 seconds. Dorgen forceps are applied across the first and fourth toes of a hindlimb for 3 seconds in order to evoke the crossed extensor and ipsilateral flexor reflex. Rapid extension of the toes or pressure applied to the base of the toe pad elicits the ipsilateral extensor thrust.

Control observations of all measures and reflexes are made 30 minutes before acute drug administration, and repeated at 15 and 30 minutes post drug and then hourly for 5-7 hours. Total scores are obtained for each measure by summing the differences between the before and after drug responses. In this manner, the overall pharmacologic profile of a compound is obtained and compared to standard compounds.

vii) Gastrointestinal motility

Acute administration of opioids causes a marked reduction in the propulsive action of the entire gastrointestinal (G.I.) tract. This is associated with an increase in tone, the net effect being to

delay gastric emptying and slow passage of the contents through the intestines. The movement of gastric contents through the G.I. tract can be measured fairly accurately using the charcoal meal method in rodents (Green 1959; Cowan et al. 1977). Groups of rats are food deprived for 18 hours, but water is available up until 1 hour before testing. Twenty minutes after subcutaneous injection or 50 minutes after oral administration of the test compound or vehicle control, the rats are given a charcoal meal (5 ml/kg) via gavage. After a standard time interval (usually 10 minutes) the rats are killed by cervical dislocation and the distance travelled by the charcoal meal along the small intestine from the pyloric sphincter is measured. This distance is then converted to a percentage of the total length.

Opioids significantly slow the passage of the charcoal meal along the intestines. Furthermore, this effect is dose-related for morphine with a maximal effect (i.e., no distance traveled) observed after 3 mg/kg, s.c. (Cowan et al. 1977). Buprenorphine, in doses of 0.01-1.0 mg/kg, s.c., similarly decreases the passage of the charcoal meal, but higher doses (i.e., 10-30 mg/kg) result in a reversal of this effect until the distance traveled is the same as after vehicle control (Cowan et al. 1977). The procedure thus appears to be sufficiently sensitive to detect both agonist and antagonist effects of the opioids.

viii) Body temperature

Opiates produce marked changes in body temperature in many species. The specific effect, however, depends on a number of factors including species, strain, sex, and age of subject, housing conditions, ambient temperature, degree of restraint, the particular drug used, its dose and route of administration. (See reviews by Burks and Rosenfeld 1979; Clark and Clark 1980; Lotti 1973).

Body temperature is commonly measured by means of a rectal thermistor probe at regular time intervals after drug administration (e-g., every 30 minutes for 4-6 hours). Mean changes from pre-drug baseline and areas under the time-response curves are calculated. Opioids thought to act on different receptor types have been studied using variations on this basic technique in several species (e.g., mouse, Rosow et al. 1980, 1982a,b; rat, Geller et al. 1983; cat, Clark and Cumby 1978, Clark and Ponder 1980, Clark et al. 1981).

For continuous measurement, either surgical implantation of a thermistor or restraint of the animal is generally required. The latter condition, however, has been shown to influence the thermoregulatory effects of opiates (Holtzman and Villarreal 1969; Martin et al. 1977). Whole-body calorimetry is a more sophisticated technique that allows continuous measurement of several thermoregulatory-related responses (e.g., oxygen consumption, respiratory water loss) in addition to simple body temperature (Lin et al. 1979).

ix) Pupillary effects

Change in pupil size is a well-known effect of opiate administration. As with body temperature, the direction of change is species-dependent. Man, rabbit, and dog respond to morphine with miosis (constriction); cat, rat, mouse, and monkey exhibit mydriasis (dilation). Until recently, pupil size was commonly measured several times after drug administration by direct observation, with calipers, or by means of still photographs (Nomof et al. 1968; Janssen and Jageneau 1956; Gerald et al. 1976; Jasinski and Martin 1967). More precise, almost continuous measurement can now be achieved through cinematography and infra-red videopupillometry (Tallarida et al. 1977; Murray and Loughnane 1981; Adler et al. 1981). Frequent sampling methods are highly recommended because of the fluctuations in pupil size induced by opioids (Henderson and Graham 1925; Oono 1965; Klemfuss et al. 1979; Tallarida et al. 1977). The entire subject of the pupillary effects of opioids and the methodology for studying such effects have recently been reviewed (Murray et al. 1983).

x) In vitro procedures

These procedures deal mainly with the effects of opioids on smooth muscle tissues such as guinea pig ileum and mouse vas deferens (Kosterlitz and Waterfield 1975). Tissues from naive, untreated animals are used to assess the acute effects of opioids. The animal is sacrificed and the smooth muscle is dissected, washed, suspended in Tyrode's solution, and affixed to an isotonic gravity lever. Contractions are recorded kymographically or via a force transducer. Once stable, the tissue's normal response to electrical stimulation is determined. The procedure is then repeated in the presence of various concentrations of opioid agonists and mixed agonists/antagonists in order to determine relative potencies and efficacies. The opioid-induced attenuation of the electrically produced contraction or twitch is blocked by naloxone and serves as the basis for the determinations of "pA_2" values (Takemori et al. 1969).

xi) Binding assays

The affinity of opioids for binding sites in the CNS can be determined in numerous species including rat, cat, pig, and monkey. Current procedures, based on the original work by Pert and Snyder (19973) Simon et al. (1973) and Terenius (1973) utilize a radiobeled (e.g, ^3H) agonist 'such as etorphine (Simon et al. or antagonist nalaxone (Pert and Snyder 1973) which is incubated with a suspension of whole brain synaptosomes. Alternatively, regional binding can be determined using only selected areas of the brain in the incubation medium, or by photoaffinity labeling (Kuhar and Uhl 1979).

For determination of relative binding affinity, the test compound is incubated in the medium and its affinity for the binding site is reflected by the amount of radiolabeled etorphine that is displaced. The test compound is also studied in the presence and absence of sodium chloride during the incubation. Sodium ions enhance the

binding of agonists while decreasing the binding of antagonists (Pert and Snyder 1973). This technique has been validated by the demonstration that extreme values of a ratio of binding affinity in the presence versus absence of sodium chloride predicts the characteristics of pharmacologic action in the whole animal (Simon et al. 1975; Woods et al. 1979).

2. Opioid Physical Dependence Potential

a. Tolerance to Drug Effects

The opioids exert a wide range of effects on numerous organs and physiological systems. In theory, tolerance to morphine can be assessed for any of its measurable actions; however, tolerance develops to the many different effects of morphine, to different degrees, and at different rates. Furthermore, it is not known whether the mechanisms of tolerance development for each morphine effect have a common basis, although this is often tacitly assumed.

Tolerance to morphine after repeated administration can be evaluated by graded assay methods where a decrease in sensitivity to a given dose of morphine can be measured, or by quanta1 assays that determine the increase in the dose of morphine required to produce an all-or-none effect. In general, chronic administration of opioids leads to tolerance to both the depressant effects (e.g., analgesia, behavioral suppression, EEG effects) and the stimulant effects (e.g., pupillary diameter, gastrointestinal motility). However, the stimulant effects are less sensitive to the development of tolerance. Since it appears that the degree of tolerance developed is directly proportional to the duration of exposure to the compound (both dose- and time-related), methods for maintaining optimal exposure have followed two basic strategies: multiple injections and continuous exposure.

Multiple injections of morphine have been given intraperitoneally, subcutaneously, intravenously, and intracerebrally to produce tolerance, although under certain conditions it is possible to demonstrate tolerance after a single injection. In general, however, a high degree of tolerance is attainable only after frequent repeated injections of high doses of morphine over several weeks. In recent years, the morphine pellet implantation procedure (Way et al. 1969) has been widely used to produce a high degree of tolerance and physical dependence, as well, in the mouse, rat, and guinea pig within three days. One or more specially formulated pellets containing 75 mg morphine base (Gibson and Tingstad 1970) are inserted subcutaneously in the back of the animal after making a small incision.

After implantation of the morphine pellet(s), animals exhibit the characteristic signs of acute morphine effects. In mice this consists of the typical Straub tail and increased motor activity within 30 minutes after implantation of a single pellet. By 24 hours, the acute effects have subsided and the general behavior of the morphine-implanted mice resembles that of placebo -implanted controls. In rats, the typical acute narcotic effects are also

observed shortly after implantation of 1 or 2 pellets. These signs include a cataleptic state, exophthalmos, and shallow respiratory movements (Wei and Way 1975). In the guinea pig, after implantation of 4 morphine pellets, the animals become sedated for 24 hours and have a decreased reaction time to a thermal stimulus when tested by the hot-plate method. Reaction times return to normal 14 hours after implantation. A biphasic change in body temperature and some body weight loss were also observed during the first 2 days after implantations (Goldstein and Schulz 1973). In all three species, tolerance and physical dependence are maximal on the third day after pellet implantation.

In vitro procedures are also available for studying opioid tolerance. Tolerance development in the ilea of guinea pigs can be induced by implanting morphine pellets subcutaneously (Goldstein and Schulz 1973; Huidobro-Toro et al. 1978). A supplementary amount of agonist should be added to the media to prevent abstinence when the preparation is washed. Tolerance in vitro can also be produced in this preparation by incubating segments of excised ileum from naive animals with the agonist at 37OC for 1 to 4 hours (Rezvani et al. 1983); the effect is stereospecific for the active l-isomers and can be prevented by naloxone. Development of tolerance to one opioid is accompanied by cross-tolerance to other opioids of the same subclass.

b. Withdrawal from Chronic Drug Administration

An abstinence syndrome is represented by a 'constellation of behavioral signs that is peculiar to a given species. Not all the signs will appear in one subject and certain of the signs may be exhibited by a nondependent one. In any assessment, therefore, the selection of the signs to be observed and their relative rank ordering of importance are sometimes made arbitrarily. Several dimensions can be considered, including the frequency of occurrence, the intensity of each event, and the probability that such a sign would occur in a given population. For example, withdrawal jumping is a characteristic abstinence sign in the mouse (Collier et al. 1972). The mean number of jumps per mouse, the height of each jump, and the incidence of jumping may all be used to quantify the withdrawal behavior.

In choosing a particular sign of withdrawal for judging dependence intensity, the possibility that experimental manipulation of the dependent state might selectively affect only the withdrawal sign and not the total syndrome must always be kept in mind. This criticism can be met by using several withdrawal signs. However, the rates of development of withdrawal signs are not always parallel and certain intense abstinence signs may suppress the appearance of other signs (Blasig et al. 1973).

The abrupt withdrawal syndrome is difficult to quantify because the protracted course of abstinence requires extended observation for several days. The slow onset and prolonged course of abrupt morphine withdrawal have led to the increasing use of antagonist-precipitated withdrawal for evaluating physical dependence. The

syndrome produced by opiate antagonists, in contrast to abrupt withdrawal, is a rapid, explosive event that condenses in a short time period the abstinence signs of abrupt withdrawal.

Withdrawal signs that appear upon termination of chronic exposure to an opioid fall into three basic classes: autonomic (e.g., blood pressure, pulse, diarrhea, respiratory rate, pupil diameter, body temperature), somatomotor (e.g., nociception, various neuromuscular reflexes, Straub tail, convulsions), and behavioral (e.g., irritability, eating and drinking, sleep, degree of alertness). In general, the autonomic signs appear first and, in the absence of other signs, suggest a mild abstinence syndrome. The appearance of somatomotor effects constitutes a more intense syndrome. Behavioral Changes are observed throughout the course of withdrawal, though they may make their initial appearance after the early autonomic signs.

The dependence potential of opioids has been quantified in numerous species including mice, rats, dogs, and monkeys. The procedures most commonly used to assess withdrawal effects with opioids involve rating autonomic signs, seizure threshold, reflexes, body weight, body temperature, and EEG activity. Body weight in rats falls following either abrupt or precipitated withdrawal and often amounts to as much as 10% of the pre-withdrawal weight. Maximum changes are noted about 1-2 hours after precipitated and 48 hours after abrupt withdrawal (depending on half-life of the opioid). Other species show different time courses of effect depending on pharmacokinetic factors (Akera and Brody 1968; Wei and Way 1975). The antagonist-induced jumping that occurs in opioid-dependent rodents can be utilized to provide a sensitive, precise measure of one sign of physical dependence. Utilizing as an index the dose of naloxone (ED_{50}) to precipitate withdrawal jumping in dependent mice, a decrease in the naloxone ED_{50} over time by 70-fold has been demonstrated as animals become increasingly dependent on morphine after pellet implantation (Way et al. 1969).

Numerous methods have been used to maximize the animal's exposure to opioids, and thus induce dependence. Oral administration remains a favored route because of its ease and minimal maintenance. This is accomplished either by gavage (Stolerman and Kumar 1970), intragastric catheter (Lukas et al1982), or in the drinking water (McMillan et al. 1974). Continuous exposure to opioids has also been accomplished by programmed intravenous injection (Weeks 1962), intraperitoneal injection using a chronic i.p. catheter (Teiger 1974), reservoir implantation (Goode 1971), and pellet implantation (Wei et al. 1973), with the development of miniature osmotic pumps (e.g., Alzet) adding to the sophistication of such implantation procedures (Wei and Loh 1976).

i) Primary physical dependence

Methods for assessing the dependence potential of morphine in rats were developed by Akera and Brody (1968). While the procedure for other species varies, the basic method is as follows:
evenly spaced injections should be used, but dependence can also

easily be produced with two injections per day: 1 in the morning and 1 in the late afternoon or evening. As tolerance to the sedative and depressant effects develops, the maintenance dose is increased. Once the desired dose and duration of exposure are reached, the withdrawal syndrome can be observed either by stopping the injections (abrupt or spontaneous withdrawal) or by injecting a small dose of the opioid receptor antagonist, naloxone (precipitated withdrawal). In general, spontaneous withdrawal is characterized by slow onset (hours), relatively moderate intensity, and long duration (hours-days) while precipitated withdrawal has a rapid onset (minutes), relatively severe intensity, and a relatively short duration (1-2 hours).

ii) Single dose substitution

This method was first described for opiates by Seevers (1936) and has been modified by a number of laboratories (Yanagita 1973). Rhesus monkeys are treated with morphine at a dose of 3.0 mg/kg, subcutaneously four times a day. These animals are maintained on this regimen for long periods of time and thus acquire a relatively stable dependence upon morphine. Minimum exposure duration is 60 days. On a test day, the regularly scheduled morphine injection is withheld until morphine abstinence signs of intermediate intensity are present. This is typically 14 hours after injection. Then a dose of test compound or morphine is 'given S.C. and the abstinence scores are rated on the degree of change from pre-injection. A drug with morphine-like dependence potential will suppress the withdrawal signs while a drug with little or no opioid agonist activity will not affect the progressively more intense abstinence signs. The animals are evaluated l/2, 1, 2, and 3 hours after administration or until they have returned to the pre-injection level. When a lower maintenance dose of morphine (e.g., 0.3 mg/kg, s.c.) is used, specific differences between pure agonists and mixed agonist/ antagonist analgesics can often be detected. Low-dose morphine-induced dependence is maintained by mixed agonist antagonists, while these compounds actually precipitate withdrawal in high-dose morphine-maintained animals. Martin and co-workers (1974) have established a standardized bioassay procedure for assessing the relative potencies for suppressing morphine-abstinence signs.

3. Opioid Abuse Liability

a. Drug self-administration

Procedures for assessing self-administration of opioids have been described using rats (Weeks 1962; Khazan et al. 1967; Moreton et al. 1976). dogs (Jones and Prada 1973), and non-human primates (Thompson and Schuster 1964; Deneau et al. 1969; Woods 1980). Most studies have been conducted using animals that have been prepared with an indwelling intravenous catheter. The animals are given an injection which is contingent upon completing a required number of lever responses (i.e., fixed ratio) or following a single response after a preset time interval (i.e., fixed interval). Two basic procedures are employed: continuous or direct, and substitution. A factor relevant to the conduct of both types of studies is whether opioid

dependence must first be present before morphine or its surrogates will be self-administered.

i) Continuous self-administration

In this procedure (Woods and Schuster 1968) rhesus monkeys are first prepared with an indwelling intravenous catheter and then restrained within a cage using an extension arm and harness system (Yanagita et al. 1965). The availability of morphine for self-injection by lever pressing is indicated by illuminating a small light above the lever. The schedule is then changed to a variable interval 2.5 minutes (the first response after an average interval of 2.5 minutes results in drug delivery). After a period of 15 days, the drug solution is replaced by physiologic saline. Another dose of morphine is then tested in a similar manner. In some instances, to avoid overdose, the maximal number of self-injections allowed is limited to four. Using this procedure, the unit dose of 10 mg/kg/inj was observed to maintain self-injection performance though no signs of abstinence were observed during saline exposure. In contrast, self-injection of higher doses resulted in a distinct abstinence syndrome when saline was substituted for morphine.

An alternative to this procedure permits access to relatively low doses of an opioid to determine whether drug intake increases with duration of exposure in the self-administration paradigm. This procedure is useful in determining whether tolerance develops to the appetitive or aversive properties of the drug.

ii) Substitution

In this procedure, drug self-administration is initially maintained by a standard compound (usually cocaine, morphine, or codeine), and test doses of experimental compounds are substituted upon attainment of stable baseline performance. As a control, the drug's vehicle or saline is also substituted for the same duration of time in order to monitor the extinction of drug-reinforced responding. Comparisons can then be made between the response rates maintained by the standard compound, saline, and the test compound (Woods 1980).

Availability of drug for self-injection is usually indicated by illumination of a light or activation of a tone or buzzer. Upon completion of the response requirement (usually fixed ratios of 30 or 160 responses), the standard drug is delivered via a peristaltic or syringe pump. After stable responding for the standard drug has been maintained, a dose of the test drug is substituted for varying periods from 1 to 15 days. The number of self-injections and the response rates for injection are quantified and serve as the basis for determining abuse liability. Additional doses and test drugs are evaluated in a similar manner.

iii) Reinforcing efficacy analysis

Extensions of the substitution procedure for evaluating the relative abuse liability of opioids have included only a few procedures. Response rate analysis (Woods 1980; Aigner and Balster 1979) and

injection patterns remain the major criteria for rank-ordering compounds with respect to their reinforcing efficacy. Yanagita et al. (1982) using a progressive ratio procedure demonstrated that buprenorphine maintained lower break points than pentazocine. Choice procedures have been used to determine the relative reinforcing efficacy of various doses of heroin (Griffiths et al. 1981). and a recent report (Mello et al. 1981) has described the use of second order schedules to demonstrate the reinforcing properties of buprenorphine.

iv) Tolerance and physical dependence

The relative potency of an opioid is decreased with tolerance development (i.e., higher doses are necessary to maintain self-injection performance), but it is not clear whether the reinforcing properties of the drug have changed, or, alternatively, the animals must titrate their level of dependence. Two types of procedures are available to avoid such problems. First, drugs can be tested in prevously opioid-dependent (but presently non-dependent) animals to minimize any differences which may be due to the animal's drug history (Steinfels et al. 1982). Secondly, cocaine can be used as the standard drug so that the opioid tolerance and/or dependence normally associated with codeine or morphine does not develop. This consideration is important when mixed agonist/antagonist analgesics are the test compounds, since withdrawal may be precipitated upon substitution in an opioid-dependent animal.

b. Drug discrimination

Procedures for assessing the discriminitive stimulus properties of opioids have, for the most part, been developed for the rat and monkey, but the pigeon and gerbil have also been utilized (see reviews Holtzman 1982, 1983). Two basic methods have been employed: shock avoidance (Shannon and Holtzman 1976) and food presentation (Herling and Woods 1981).

In the shock avoidance procedure, animals typically must first press a "starting" lever after which they must press the appropriate lever on the other side of the cage in order to prevent shock delivery. The appropriate lever is determined by whether the animal has received a saline injection (e.g., left lever appropriate) or an injection of the training drug - usually morphine (e.g., right lever appropriate). The similarities in the stimulus properties of other opioids are then tested over a wide dose range, with 90% drug-appropriate responding usually being the accepted criterion for discrimination.

In the food presentation paradigm, monkeys are usually maintained at 80-9096 of their free-feeding weight and then trained to press one of two levers in order to receive a food pellet (Herling and Woods 1981; Woods et al. 1982). The response requirement is usually 20 to 30 lever presses (i.e., FR 20-30) and the appropriate lever is determined by whether the animal has received an injection of an

opioid (e.g., either etorphine or morphine) or saline. Training is continued until 90% or better appropriate responding is maintained.

Using these procedures, a large number of opioids have been characterized with respect to their discriminative stimulus properties (Holtzman 1982; Woods et al. 1982). In order to fully characterize the conglomerate opioid class of drugs (viz a viz, mu, kappa, and sigma agonists and mixed agonists/antagonists), however, it is important that the protocol includes animals that have been trained on drugs other than the pure agonists morphine and etorphine (e-g., cyclazocine, ethylketocyclazocine, N-allylnormetazocine). In addition, different doses of these compounds should be used in order to be able to characterize the full spectrum of a drug's effects (Holtzman 1982). It is also useful to determine to what extent the discriminative stimulus properties of these compounds can be blocked by opioid antagonists such as naloxone or naltrexone. Finally, the animal species utilized must be taken into account, since distinct differences have been observed particularly between the rat, pigeon, and monkey. Drug discrimination procedures have nonetheless been used effectively to differentiate a number of opioids in three classes: opioids that generalize to morphine and are antagonized by naltrexone or naloxone; opioids that generalize to cyclazocine and are not easily antagonized; and opioids that generalize to cyclazocine and phencyclidine and are not antagonized (Holtzman 1982).

c. Behavioral Toxicity

To date, no procedures such as those outlined in the general methodological section have been employed to systematically investigate the adverse sensory or motor effects of various opioids in animals. One study, using size selection discrimination of a visual stimulus, showed that morphine in doses of 1-10 mg/kg decreased reaction times in rhesus monkeys (Brown and Bass 1967). This finding is consistent with other reports that morphine possesses both depressant and stimulant effects which may be dose related.

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C. Procedures for Assessing CNS Depressants: Sedative/Hypnotics, Anesthetics, Aaxiolytics, and Antihistamines

1. Characterization of CNS Depressant Effects

a. Acute Drug Effects

i) Sleep Induction

This procedure determines the hypnotic potency of a compound in addition to characterizing the nature of the sleep state (e.g., light, intermediate, deep). Typically, the fasted mouse is used and the compound is administered orally, although other species and routes may be employed. The procedure described by Gruber et al. (1944) initially begins testing with a dose empirically derived during pilot studies. If sleep is produced, as evidenced by loss of righting reflex, a series of decreasing doses is given (ten different mice per dose) and the ED_{50} is determined. Additional data obtained include the onset and duration of sleep (from the loss to return of the righting reflex) and the duration of symptoms following hypnosis.

An extension of this procedure may be used to identify compounds that prolong or potentiate the sleep time of a test compound. Two groups of fasted mice are used; one group receives 10% of the ED_{50} dose (determined as above) of a compound identified as a sedative and the other group receives vehicle. Thirty minutes later both groups receive pentobarbital sodium at a dose of 6 mg/kg i.p.,and the onset and duration of hypnosis are observed and comparisons are made between the two groups.

ii) Spontaneous Locomotor Activity

The procedures described in the general methods section above are most commonly used to assess the pharmacological activity of these compounds which decrease spontaneous locomotor activity in a dose-related manner. No distinction between compounds within the depressant class can be made using this test, though differences in duration of action can be detected.

iii) Electroencephalographic (EEG) Activity

Using the procedures outlined in the general methods section above, CNS depressants have been shown to induce characteristic shifts in the power of various frequency bands. These shifts have basically consisted of an increase in the overall power, with the greatest increase occurring in the 8-13 and 13-25 Hz bands (Gehrmann and Killam 1976). This contrasts with the narcotics which typically increase power in the O-4 Hz band (Lukas et al. 1980). Using this procedure, various compounds including barbiturates, benzodiazepines, and other depressants have been classified and compared with respect to the particular shifts in power and predominant frequency after their administration (Gehrmann and Killam 1976, 1978; Joy et al. 1971; Schallek and Johnson 1976; Schallek et al. 1967). Benzodiazepines have a characteristic EEG

effect and change the sleep-wakefulness cycles and continuum. Further, one can couple behavioral effects with EEG changes (Gehrmann and Killam 1975).

iv) Behavioral Performance

While numerous operant paradigms have been employed to study the depressant effects of these compounds (e.g., ratio or interval schedule responding for a reinforcer such as food or water), the most widely used method for studying the anxiolytic effects of CNS depressants, particularly the sedative/hypnotics, is the conflict procedure. First introduced by Geller and Seifter (1960), the model was further developed and refined (Cook and Davidson 1973) and subsequently validated by Cook and Sepinwall (1975) as a predictor of anxiolytic effects. This validation was based upon the good correlation between the relative potencies of numerous clinically effective anxiolytic agents (e.g., diazepam, oxazepam, chlordiazepoxide, phenobarbital, amobarbital, and meprobamate) and their attenuation of punishment effects upon operant responding. Basically, the procedure involves imposing a punishment (usually electric foot shock) contingency upon a stable performance baseline (usually a variable interval schedule for food). The schedules can be either alternating or concurrent, with better separation of performance obtained using the latter. The introduction of shock suppresses responding for food, and the administration of a minor tranquilizer attenuates the suppressive effects of the shock. Thus, responding during shock is actually increased after treatment with a benzodiazepine or a barbiturate; this selective effect is typically observed at doses which have little or no effect on non-punished responding (e.g., Cook and Sepinwall 1975). This procedure appears to be relatively specific for sedative/hypnotics, while major tranquilizers (e.g., chlorpromazine), stimulants (e.g., amphetamine), antihistamines (e.g., diphenhydramine). anticonvulsants (e.g., phenytoin), and opioid analgesics (e.g., morphine) lack significant effect. The procedure does not, however, discriminate between the barbiturates, ethanol, and the benzodiazepines.

v) Binding Assays

While the specific mechanism of action of CNS depressants has not been completely elucidated, one common feature is that they appear to interact with gamma-aminobutyric acid (GABA). Currently, no specific neuronal sites have been shown to bind selectively to barbiturates. However, they have been shown to increase GABA activity in a number of in vitro preparations (Eccles et. al. 1971; Nicoll 1978) and more recently, both anesthetic and convulsant barbiturates enhance GABA binding to rat brain synaptosomes (Willow and Johnston 1981).

In contrast, a receptor that specifically binds' benzodiazepines has been identified (Squires and Braestrup 1977; Mohler and Okada 1977) and it has been shown that the binding of GABA to its receptor is enhanced in the presence of benzodiazepines (Haefely 1977). Furthermore, validation of the benzodiazepine binding assay has been

provided by a number of studies (Braestrup and Squires 1978; Mohler et. al. 1978) in which the affinities of benzodiazepines for the binding site correlate well with their pharmacological activities and clinical potencies.

Essentially, the procedure for assessing the affinity of test substances for the benzodiazepine receptor is conducted using tritiated diazepam or flurazepam. Appropriate neuronal tissues are incubated with the radiolabeled ligand, and various concentrations of the test compound are added. The relative binding affinity of the test compound is directly related to the amount of labeled diazepam (or flurazepam) that is displaced. Displacement of the labeled compound is indicated by a decrease in the disintegrations per unit time emitted from the tissue after washing.

The discovery of these specific binding sites has led to the search for an endogenous anxiolytic ligand. Historically, numerous compounds (e.g., the beta carbolines) have been suggested as likely candidates, but no convincing evidence exists to date as to the existence or identity of this substance. A more recent finding that the benzodiazepine derivative, ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5a][l,4]benzodiazepine-3-carboxylate (Ro 15-1788) can bind to the receptor and block numerous pharmacological effects of benzodiazepines (Hunkeler et al. 1981; Darragh et al. 1981; Mohler et al. 1981; Polc et al. 1981), however, 'provides a unique and potentially powerful tool for investigating the acute effects of benzodiazepines and, ultimately, for characterizing the withdrawal syndrome (Lukas and Griffiths 1982).

2. CNS Depressant Physical Dependence Potential

a. Tolerance to Drug Effects

Sedation is the, primary pharmacological effect of this class of compounds. Upon repeated exposure to a standard dose, tolerance develops as seen by an attenuation of the degree and duration of CNS depression. According to Kalant et al. (1971), tolerance may be dispositional or functional. The former is primarily due to an increased rate of drug metabolism and elimination from the body while the latter refers to a diminished sensitivity of the CNS. The extent to which each mechanism contributes to the overall observed degree of tolerance is unclear. For some drugs, at least, information on the relative contribution of these factors can be obtained by conducting pharmacokinetic studies in conjunction with the pharmacological assays. Thus, drug disappearance curves could be constructed that would match (or in some cases, not match) the time-effect curves. While dispositional tolerance may be relatively important when assessing pentobarbital (see review, Conney 1967), it cannot account for both the tolerance developed to barbital (which is only slightly metabolized) and the development of tolerance after intraventricular administration (Stolman and Loh 1975; Lyness et al. 1979). By employing a "maximally tolerable dose" technique, Okamoto and co-workers (1975) have been able to separate the two components of barbiturate tolerance. Essentially, they demonstrated that

dispositional tolerance develops very quickly while functional tolerance develops more gradually.

The degree of tolerance that can be attained is directly related to the time intervals between exposures to the drug (Gruber and Keyser 1946). Numerous techniques have been employed to maximize the exposure of the CNS to depressant drug, including: continual parenteral administration of barbiturates (Kato et al. l964), adding barbiturates to the drinking water (Crossland and Leonard 1963) or to food (Belknap et al. 1973). implantation of a barbiturate pellet (Ho et al. 1975), or delivery of a barbiturate via a subcutaneously implanted miniature osmotic pump (Siew and Goldstein 1978). Whichever method is used, it is apparent that tolerance develops to the mild behavioral effects (e.g., loss of fine motor control, mild ataxia) of barbiturates but not to the lethal effects (see Okamoto and Boisse 1981). Thus, as tolerance develops to a CNS depressant, the therapeutic index decreases.

Numerous animal species have been used to study barbiturate tolerance and graded rating scales for CNS depression have been developed and utilized in the rhesus monkey (Yanagita and Takahashi 1970) and the cat (Okamoto et al. 1975). The effects most often studied include: ataxia. decreased locomotion, decreased respiratory rate, impaired righting reflex, and changes in cornea1 and linguomandibular reflexes and nictitating membrane tone. Regardless of the response -studied. it is important that studies of tolerance include: appropriate dosing schedules and route of administration, full dose-response evaluations, and appropriate controls to account for order effects. In addition, measures of cross-tolerance to another drug within the same class as well as in a different class are extremely important in characterizing the overall profile of a drug.

b. Withdrawal from Chronic Drug Administration

Withdrawal from chronic administration of numerous sedative/ hypnotics has been assessed in various animal species including mice (Ho 1976), cats (Okamoto et al. 1975), dogs (Deneau and Weiss 1968). and monkeys (Yanagita and Takahashi 1973). While. species variability generally exists, the sedative/hypnotic abstinence syndrome is basically characterized by gross behavioral manifestations which include anorexia, hyperirritability, tremors, and convulsions. These signs have been grouped into three levels of withdrawal: Mild - hyperirritability, mild tremor, anorexia, piloerection; Intermediate - aggravated tremor, muscle rigidity, impaired motor activities, retching or vomiting, weight loss (10%); Severe - convulsions, hallucinatory behavior, nystagmus, unresponsiveness to environmental stimulation, hyperthermia, morbidity, and mortality.

Another technique that has been utilized to quantify barbiturate dependence potential is seizure susceptibility. During barbiturate withdrawal a decrease in seizure threshold has been observed after the administration of pentylenetetrazol (Jaffe and Sharpless 1965). and bemegride and picrotoxin (Crossland and Turnbull 1972).

Barbiturate withdrawal has also been assessed using audiogenic seizures (Crossland and Turnbull 1972; Gates and Chen 1974) and flurothyl-induced seizures (Greer and Alpern 1976). Kindled seizures can also be used for this purpose. Alcohol withdrawal has been shown to increase the susceptibility to seizures in animals with previously kindled epileptic foci in the amygdala (Pinel et al. 1975, 1978).

i) Primary Physical Dependence

Nethods for assessing the dependence potential of barbital in naive dogs were developed by Seevers and Tatum (1931) and later extended by Fraser and Isbell (1954). The production of primary dependence on sedative-hypnotic drugs is directly related to the dose, dosing interval, duration of treatment, and the route of administration. Typically, 100 mg/kg of barbital sodium in 4 divided doses is given orally for 60-90 days. It is sometimes necessary to initiate treatment with lower doses and gradually increase the dose as tolerance develops. When comparisons between different drugs are to be made, it is important that the dosing schedules are adjusted such that the pharmacological effects of the drugs are equivalent' (e.g., see Okamoto et al. 1975). Quantitative measures of withdrawal signs are equally important when attempting to compare the dependence potential of numerous compounds. In this regard, the method of Jones and co-workers (1976), which describes a bioassay for sedative dependence potential, appears to be the most sophisticated and perhaps the best validated system to date.

In general, comparative studies indicate that the use of monkeys and carnivores provides clearer and more profound withdrawal effects, but that rodents offer the advantage of being cost effective. This is especially true during preliminary screening procedures where a large number of experimental subjects is required. Historically, the assessment of the dependence potential of a compound required that exposure to the drug be terminated. The recent discovery of the specific benzodiazepine receptor antagonist (Ro 15-1788), that can block numeruds pharmacological effects of the benzodiazepines (Hunkeler et al. 1981; Darragh et al. 1981; Mohler et al. 1981; Pole et al. 1981), has provided a unique and potentially powerful tool for studying the benzodiazepine withdrawal syndrome.

Administration of Ro 15-1788 to baboons that had been treated with diazepam (20 mg/kg/day) via an intragastric catheter for only 7 days produced numerous signs of withdrawal including bruxism, nose rubbing, retching and vomiting, abnormal body postures, tremors and convulsions (Lukas and Griffiths 1982). The withdrawal signs were more frequent and of greater intensity when the duration of diazepam exposure was increased to 35 days. Furthermore, when compared with spontaneous withdrawal from diazepam, the Ro 15-1788 precipitated abstinence syndrome was characterized by a relatively rapid onset (i.e., 7-10 minutes), intense signs, and short duration (i.e., 4-8 hours). In contrast, spontaneous withdrawal (obtained by simply stopping the diazepam) was characterized by a slow onset (i.e., 5-7 days), relatively milder signs, and a long duration (i.e., 8-13 days). Ro 15-1788 has also been used to precipitate withdrawal

signs in benzodiazepine-treated mice, rats, cats, and squirrel monkeys (Rosenberg and Chiu 1982; Cumin et al. 1982; McNicholas and Martin 1982).

ii) Single Dose Substitution

This method was first described by Deneau and Weiss (1968) and involved the administration of barbital sodium (100 mg/kg/day) to dogs for periods of up to 2 years. The termination of drug resulted in the appearance of withdrawal signs, the severity of which was assessed using an objective point-scoring system. A test compound was then administered (at a dose previously determined during pilot, acute studies) for 5 consecutive days and its effectiveness in reversing the withdrawal signs was determined. A total of twelve compounds were evaluated in this manner and all except glutethimide were found to completely substitute for barbital. After the 5-day substitution period, the test compound was withheld and the abstinence signs were quantified. Similar methods have been developed for the monkey (Yanagita and Takahashi 1973), cat (Okamoto et al. 1975), and rat (Essig 1966). More recently, Jones et al. (1976) have developed a quantitative bioassay for comparing the dependence potential of various CNS depressants in the dog. In order to effectively compare the dependence potential of various compounds, it is necessary to incorporate procedures which ensure that the drugs are functionally equivalent; two drugs are functionally equivalent only if they produce the same peak, residual, and total degree of CNS depression.

3. CNS Depressant Abuse Liability

a. Drug Self-Administration

Procedures for assessing self-administration of sedative/hypnotics have been described using rats (Walton and Deutsch 1978), and non-human primates (Yanagita and Takahashi 1970, 1973; Griffiths et al. 1981). While the intravenous route has been employed most often, the development of other methods including intragastric (Yanagita and Takahashi 1973) and oral (Ator and Griffiths 1983) self-administration has recently been reported. Drug injections are usually contingent upon completion of a fixed number of responses on a lever (i.e., fixed ratio schedules), but interval and second-order schedules have also been used effectively. Two basic procedures are employed: continuous or direct, and substitution.

i) Continuous self-administration

In this procedure (e.g., Yanagita 1976) the intravenous route is preferred as long as solubility characteristics permit. The subjects (usually monkeys) are first given the opportunity to self-inject the drug vehicle alone, and once low and stable response rates are achieved, a dose of the compound to be tested replaces the vehicle at one-quarter to one-half the minimal effective dose (as determined during the acute studies) for 2 to 4 weeks. If, at the end of this period, the animal still has not increased its rate of responding, then an automatic injection schedule is superimposed on

the self-injection schedule for 2 more weeks. Response rates and daily self-injections are monitored during this period. Then the automatic injections are terminated and the self-injection unit dose is decreased by one-half to one-fourth to determine whether response rates increase. Finally, the subject is again exposed to 'the vehicle alone while response extinction is characterized and the subject is observed for possible withdrawal signs. Using this procedure, pentobarbital and alcohol were reported to be self-administered at moderate rates while diazepam, chlordiazepoxide, and oxazepam were self-injected at lower rates (Deneau et al. 1969; Yanagita and Takahashi 1973; Yanagita 1976).

ii) Substitution

In this procedure, drug self-administration is initially maintained by a compound known to reinforce self-injections (e.g., cocaine, codeine) and test doses of experimental compounds are substituted upon a stable baseline performance. As another control, saline or the drug vehicle is also substituted in order to assess extinction as well as to serve as a measure of the animal's operant level of responding. Comparisons are then made between self-injection rates following saline substitution and substitution of an appropriate range of doses of the test compound.

While the number of responses required for drug- delivery in the continuous procedure is usually only one, larger numbers (e.g., 30, 160) are typically employed in substitution procedures. In addition, the opportunity to self-inject a compound is usually limited either by programming brief sessions (Schuster and Thompson 1969) or by imposing time-out periods between drug injections (Griffiths et al. 1981) as compared to ad libitum availability in the continuous self-administration procedure. This latter procedure tends to reduce the confounding effects of previous drug injections upon operant behavior, and thus provides a more reliable measure of the extent to which the "drug-seeking" performance is maintained by the reinforcing properties of the drug per se.

Using the substitution procedure and cocaine (0.32 mg/kg/injection) as a baseline drug (fixed ratio 160 schedule of reinforcement and a 3-hour time-out after each drug self-injection); Griffiths et al. (1981) showed that the three barbiturates secobarbital. pentobarbital, and amobarbital all maintained rates of responding that were comparable to those maintained by cocaine. In addition, numerous benzodiazepines (e.g., diazepam, clonazepam, chlorazepate, flurazepam, and medazepam) sustained rates of responding that were higher than vehicle control, but lower than those of cocaine.

iii) Intragastric, oral, and inhalation self-administration

Yanagita and Takahashi (1973) reported that rhesus monkeys self-administered pentobarbital and alcohol via an intragastric catheter, though lever pressing rates were not as high as when the compounds were given intravenously. In this same study, intragastrically delivered diazepam maintained more robust self-administration than

either chlordiazepoxide or oxazepam. Using a similar procedure Altshuler et al. (1975) found that rhesus monkeys would self-administer chlordiazepoxide intragastrically, but not diazepam. Gotestam (1973) and Davis et al. (1978) reported that intragastrically administered medazepam and chlordiazepoxide, respectively, were reinforcing to rats while Walton and Deutsch (1978) found no evidence for intragastric or oral self-administration of diazepam.

The difficulty with intragastric self-administration studies appears to reside in factors relating to drug delivery. Typically, absorption from the stomach is relatively slow, and previous studies by Stretch et al. (1976) have shown that response rates for cocaine self-injection decrease when the delivery of the drug is delayed after completing the operant task. Thus, the onset of drug effect may in fact be anywhere from 5-30 minutes (depending on the drug) after the injection. Controlled fasting prior to test sessions (to maximize drug absorption) and appropriate stimuli associated with drug delivery may 'facilitate intragastric self-administration, and the use of second order schedules may prove helpful.

Because of taste and volume factors associated with drug solutions, it has been difficult to conduct oral self-administration studies (Wolf et al. 1978). Forced consumption of chlordiazepoxide in rats has been accomplished by making the drug solution the only source of fluid (Harris et al. 1968; Kamano and Arp 1965). This procedure, however, has not been effective in inducing higher intake of chlordiazepoxide during testing. An alternative procedure employs a schedule in order to induce high fluid intake (Falk et al. 1972; Sanger and Blackman 1978). This paradigm (schedule-induced polydipsia) has been used to enhance chlordiazepoxide consumption in rats (Sanger 1977) and ethanol (Henningfield et al. 1981) and methohexital (Ator and Griffiths 1983) in primates.. During a 3-hour session in which water was available via a drinking spout, the entire daily ration of food biscuits was delivered at the end of the first hour in the study by Ator and Griffiths (1983). This procedure induced a large increase in drinking during the remaining 2 hours. Then, on subsequent days, increasing concentrations of methohexital were substituted in place of the water. At a methohexital concentration of 0.8 mg/ml, the volume consumed in the first hour of the session (before food delivery) typically exceeded 30% of the session total and overt behavioral effects (e.g., ataxia) were observed. Drinking and drug intake remained at high levels after the food-inducing procedure was discontinued and food was made available at the end of the session.

Administration of CNS depressants via inhalation as a means of assessing abuse liability has been studied only in the rhesus monkey (Yanagita et al. 1969). The subjects were fitted with an intranasal catheter which provided a means by which lacquer thinner fumes could be forced into the lungs by compressed air. The animals pressed a lever, received a Z-minute exposure. to chloroform or ether, or 5 minutes of lacquer thinner. Goldstein (1972) has also used the inhalation route to render mice tolerant and dependent upon ethyl

alcohol, but the procedure has not, as yet, been employed routinely as a self-administration paradigm.

iv) Reinforcing efficacy analysis

Extensions of the substitution procedure for evaluating relative sedative/hypnotic abuse liability have involved the application of numerous procedures including progressive ratio performance (Brady et al. 1975; Yanagita 1976). response rate analysis (Griffiths et al. 1981), concurrent or choice schedules (Findley et al. 1972), and second order schedules (Kelleher 1975). Two basic findings have evolved from these studies. First, barbiturates appear to maintain higher levels of performance than benzodiazepines, though not enough comparative data is available to rank-order depressants belonging to other pharmacological classes. Secondly, compounds with short durations of action appear to have a greater reinforcing efficacy than their longer-acting analogues.

v) Tolerance and physical dependence

There is little or no data available on the effects of tolerance and dependence on the reinforcing efficacy of CNS depressants, hypnotics, or anxiolytics, nor on the effects of a prior history of dependence in this regard. Griffiths et al. (1981) have reported, however, that there was no difference in the benzodiazepine-maintained self-administration performance of baboons before and after barbiturate self-administration.

b. Drug Discrimination

Procedures for assessing the discriminative stimulus properties of sedative/hypnotics have been described in pigeons (Herling et al. 1980), gerbils (Jarbe and Holmgren 1977), rats (Overton 1979). and primates (Ator and Griffiths 1982; Winger and Herling 1982). The most frequently used procedures in rodents have involved either a T-maze (e.g., turn left if drugged; turn right if not drugged) or a two-lever choice situation (e.g., left lever produces food or terminates shock if drugged; right lever produces food or terminates shock if not drugged).

The stimulus properties of benzodiazepines have been studied by Overton (1982) with animals trained to discriminate a number of benzodiazepines from saline (e.g., chlordiazepoxide, diazepam, flurazepam, oxazepam). When compared under similar conditions, training progresses more quickly with barbiturates than with benzodiazepines. Compared to several other drug classes (stimulants, hallucinogens, antipsychotics), however, the benzodiazepines appear more discriminable. If, however, other drugs are substituted in chlordiazepoxide-trained animals, generalization (i.e., increased probability of drug-appropriate responses) is observed for all other benzodiazepines, most other sedative/hypnotics, but not for neuroleptics. indicating at least some specificity of effect (Colpaert et al. 1976; Barry and Krinuner 1978).

Although pentobarbital- and ethanol-trained animals generalize to benzodiazepines (but not to stimulants, opioids, or hallucinogens) animals can be trained to discriminate chlordiazepoxide from pentobarbital (Barry and Krimmer 1978). A certain asymmetry in cross-generalization has been noted in that generalization from a benzodiazepine to a barbiturate has not been demonstrated as reliably as generalization from a barbiturate to a benzodiazepine. For example, baboons trained to discriminate pentobarbital from drug vehicle showed generalization to lorazepam, but not all baboons trained to discriminate lorazepam showed generalization to pentobarbital (Ator and Griffiths 1983). These same investigators have reported that a specific benzodiazepine receptor antagonist, Ro 15-1788, completely blocked the discriminative stimulus effects of lorazepam but not of pentobarbital. Similarly, Herling and Shannon (1982) showed that Ro 15-1788 blocked the discriminative stimulus effects of diazepam but not of pentobarbital.

c. Behavioral Toxicity

Procedures for assessing the acute effects of sedative/hypnotic compounds on psychophysical processes (i.e., auditory and visual thresholds and reaction times) have been developed over the past two decades. Data provided to date suggests that only studies using primates are sensitive enough to effectively and completely evaluate the sensory-motor effects of psychotropic drugs. It has been reported, for example, that barbiturates impair the processing and interpretation of sensory input (Pragay and Mirsky 1973; Bartus and Johnson 1977). Rhesus monkeys treated with pentobarbital show a dose-dependent decrease in correct responding to tachistoscopically presented stimuli as a function of systematic reductions in stimulus exposure time. More recently, Hienz et al. (1981) demonstrated that pentobarbital produces changes in absolute visual thresholds which may account for the apparent impairment of information processing. Baboons housed in individual cages and maintained on a 22-hour restricted feeding schedule were trained to press a lever and hold it depressed for varying intervals until presentation of a light flash or tone burst. Correct responding (defined as release of the lever within 1.5 seconds of stimulus presentation) was rewarded with a banana flavored food pellet. A l-second intertrial interval (ITI) was then imposed during which no stimuli were presented and additional lever presses reinstated the ITI. Experimental sessions were conducted daily over a 2-3 hour period.

Auditory and visual thresholds were determined by randomly varying the intensity of the test stimuli from trial to trial and examining the number of correct lever releases. Using this procedure, 4 to 5 separate measures of threshold and reaction times were obtained, each of which was based upon 140 trials. In this manner, the time course of drug effects was also measured. Pentobarbital produced consistent, dose-related increases in visual thresholds with a corresponding increase in both visual and auditory reaction time (Hienz et al. 1981). Over the same dose range, however, no effects were observed for auditory thresholds, suggesting a specificity in pentobarbital's psychophysical profile. In contrast, benzodiazepines such as diazepam produced increases in both auditory

and visual thresholds which, unlike the effects of pentobarbital, persisted for several days after injection. This procedure has also been used to assess the effects of long-term administration of benzodiazepines to determine whether tolerance develops to these effects, and whether terminating extended benzodiazepine treatment affects sensory-motor processes.

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D. Procedures for Assessing CNS Stimulants: Anorectics, Local Anesthetics, and Antidepressants

1. Characterization of CNS Stimulant Effects

a. Acute Drug Effects

i) Spontaneous locomotor activity

The administration of CNS stimulants in relatively low doses generally results in an alerting response accompanied by an increase in locomotor activity and associated behaviors (e.g.. exploration, grooming, and rearing). This effect is dose dependent in the low dose range. After higher doses a different spectrum of effects emerges; stereotypic head-bobbing, gnawing, sniffing, and licking prevail with little or no increase in locomotion.

The procedures described in the general methods section above are most commonly used to assess the pharmacological activity of these compounds. Although the precise mechanisms underlying these actions may differ for various CNS stimulants, all presumably have the common effect of increasing activity of neuronal catecholaminergic systems. Present evidence indicates that the increased locomotor activity is mediated by both noradrenergic and dopaminergic systems, while stereotypy is mediated by dopaminergic systems only (Lewander 1977).

ii) Electroencephalographic (EEG) activity

Using the procedures outlined in the general methods section above, CNS stimulants have been shown to induce characteristic changes in the EEG. These effects have been studied using two basic procedures: acute EEG effects, and sleep-awake profiles. Relatively large doses of amphetamine cause cortical EEG desynchrony in conscious cats (Bradley and Elkes 1957) correlated with an alert and excitable behavioral state. Similar results were reported in the dog (Schallek and Walz 1953). A variant of this acute procedure involves the use of amphetamine to alter (e.g., reverse) the EEG effects of CNS depressant. Using this approach, Schallek et al. (1967) demonstrated that d-amphetamine abolished the pentobarbital-induced peak in the 8-14 Hz band and reduced the amplitude.

The assessment of changes in the EEG sleep-awake cycle requires a much slower recording speed and, usually, a concurrent measure of muscle activity in order to identify the various states of alert, resting, drowsy, slow-wave sleep, and rapid-eye-movement (REM) sleep. Nicotine's transient alerting effects have been documented in the cat (Domino 1979) using this approach.

iii) Behavioral performance

Numerous operant paradigms have been employed to study the effects of CNS stimulants. These include performance maintained appetitively on ratio and interval schedules as well as aversively maintained shock avoidance responses. One of the general

principles which has emerged from this research is that the effect of CNS stimulants on operant performance is dependent upon the ongoing rate of responding. Under a wide variety of experimental conditions, it has been demonstrated that CNS stimulants increase low baseline response rates and decrease high baseline response rates (Sanger and Blackman 1976). The rate dependency analysis of the actions of CNS stimulant drugs has recently been extended to behaviors other than schedule-controlled operants (Dews and Wenger 1977), demonstrating that this principle has wide applicability across a variety of conditioned and unconditioned behaviors in a variety of species.

iv) Anorexia

While numerous procedures have been employed to assess the appetite-suppressive effects of drugs, the method of Randall et al. (1960) serves as the standard. Groups of six rats are fasted for 18 hours but receive water ad libitum. Consumption of a weighed amount of dry food is then measured over any desired time period (e.g., 4 hours) following injection of saline or of various doses of the test compound. The potency of the test compound is expressed as the anorexic dose 50% (AD50) which reduces food consumption by 50%. Alternatively, anorexic effects can be measured by monitoring an animal's free feeding behavior using operant techniques. With nonfasted baboons controlling their food consumption by depressing a lever for delivery of a 1 g pellet, the relative potency of various amphetamine analogues has been compared on the basis of the degree of suppression of the lever-pressing response (Griffiths et al. 1979).

v) Intracranial electrical self-stimulation

Rats are surgically implanted with electrodes in discrete brain regions (e.g., lateral hypothalamus, medial forebrain bundle) and then subsequently allowed to depress a lever which delivers constant current stimulation in 0.5 second trains of a 60 Hz sine wave after each response. Once stable intermediate response rates are achieved by adjusting the electrical stimulation parameters, the effects of various drugs are studied. Drugs are given via an intravenous catheter during the experiment or via i.p., s.c., or i.m. injection just prior to session onset. Typically, CNS stimulants such as amphetamine increase the rate of self-stimulation, presumably by facilitating the effects of stimulation-induced release of norepinephrine (Ritter and Stein 1973), though recent experiments employing discrete brain lesions cast doubt on norepinephrine's role (Phillips et al. 1977) and suggest that dopamine may be more important (Hollister et al. 1974).

2. CNS Stimulant Physical Dependence Potential

a. Tolerance to Drug Effects

Tolerance develops to some of the physiological and behavioral actions of CNS stimulant drugs. For example, tolerance develops to the anorexigenic actions of these drugs and cross-tolerance between

certain members of this class has been demonstrated (Woolverton et al. 1978). Acute tolerance or tachyphylaxis is prevalent with indirect-acting stimulants (e.g., those that cause the release of endogenous catecholamines - such as amphetamine), but direct-acting agents usually are not subject to this phenomenon. The general methods described in previous sections apply to the assessment of tolerance to CNS stimulants as well. Tolerance does not seem to develop to the reinforcing effects of CNS stimulants, however, thus playing little or no role in the assessment of the abuse liability of CNS stimulants.

b. Withdrawal from Chronic Drug Administration

A number of investigators have reported the occurrence of withdrawal effects when repeated administration of amphetamine is abruptly terminated. The withdrawal profile consists primarily of non-specific sedation or reduced motor activity (Lewander 1977). The occurrence of such withdrawal signs has not been used as a defining characteristic of dependence potential with CNS stimulants primarily because of a lack of systematic and valid evaluation procedures. Furthermore, no procedures have been developed to classify drugs on the basis of their ability to substitute for amphetamines and prevent the occurrence of the abstinence syndrome.

3. CNS Stimulant Abuse Liability

a. Drug Self-Administration

Procedures for assessing self-administration of CNS stimulants have been described using rats (Pickens and Thompson 1968; Gotestam and Andersson 1975), cats (Balster et al. 1976), dogs (Risner and Jones 1976). and primates (Deneau et al. 1969; Balster and Schuster 1973; Griffiths et al. 1976; Johanson et al. 1976). Though the intravenous route has been most commonly used, self-administration has been reported to occur via the intragastric (Altshuler and Phillips 1977), oral (Magour et al. 1976), and inhalation (Siegel et al. 1976) routes.

i) Continuous self-administration

Procedures for continuous self-administration have been described in detail elsewhere, in the general methods section above. Because animals generally fail to titrate their intake of CNS stimulants resulting in toxic overdoses (Johanson et al. 1976), continuous self-administration techniques are generally employed within the context of time- or dose-limited paradigms (e.g., Gotestam and Andersson 1975; Risner and Jones 1976).

ii) Substitution

Procedures for the assessment of the abuse liability of CNS stimulants using the substitution/limited access method have been described in the general methods section above. Cocaine has most often served as the baseline drug, although amphetamine has also been used. Using cocaine as the baseline drug and a 3-hour timeout

period after each ingestion, Griffiths et al. (1976) compared the selfiadministration of eight phenylethylamines in the baboon. A cyclic pattern of self-administration emerged over the 15-day substitution period in which 2-4 consecutive days of high intake were followed by 2-3 days of low intake.

iii) Reinforcing efficacy analysis

Extensions of the limited access and substitution procedures for evaluating relative CNS stimulant abuse liability have involved the application of numerous procedures including progressive ratio performance (Griffiths et al 1978; Risner and Silcox 1981), bioassay (Risner and Jones 1975, 1980), rates of response (Balster and Schuster 1973). and discrete-trial choice (Brady and Griffiths 1977; Johanson and Schuster 1975). In general, the results have confirmed the sensitivity of these methods to detect differences between the various CNS stimulants with respect to their reinforcing efficacy, with cocaine—revealed as one of the most potent, efficacious reinforcers—serving as the standard for comparison.

b. Drug Discrimination

Procedures for assessing the discriminative stimulus properties of CNS stimulants have been established in a number of animal species (Schuster and Balster 1977; La1 1977). Rats learned to discriminate between injection of d,l-amphetamine and saline, and in addition, generalization was obtained with methylphenidate but not with atropine (Harris and Balster 1971). In a subsequent study, d-amphetamine-trained rats generalized to l-amphetamine, but not to nicotine, mescaline, fenfluramine, or LSD (Schechter and Rosecrans 1973). Additional evidence for the specificity of these procedures has been provided by Overton and collegues (Overton 1966; Overton and Lebman 1973), who demonstrated that animals trained to respond to sedative/hypnotics responded to amphetamine as if it were saline (i.e., no cross-generalization between drug classes was observed). Similarly, generalization between d-amphetamine and cocaine has been demonstrated in the rhesus monkey (Ando and Yanagita 1978).

c. Behavioral toxicity

Procedures for assessing the behavioral toxicity of CNS stimulants have been refined for use in squirrel and rhesus monkeys, baboons, and pigeons. Methamphetamine impairs pigeon's performance in visual discrimination tasks (Dews 1955), while d-amphetamine decreases the accuracy of visual stimulus duration discriminations in this same species (Stubbs and Thomas 1974). In both rhesus monkeys (Brown and Bass 1967) and baboons (Hienz and Brady 1981) d-amphetamine decreases reaction times to visual and auditory stimuli. This effect is dose-dependent, however, with increases in reaction time predominating after higher doses. The decreased reaction times following d-amphetamine occur in the absence of changes in size discrimination thresholds (Brown and Bass 1967) or brightness discrimination (Thurmond 1965) in the monkey. In the squirrel monkey, however, d-amphetamine and methylphenidate produce modest increases in masked auditory thresholds (Delay et al. 1979).

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E. Procedures for Assessing Cannabinoids

1. Characterization of Cannabinoid Effects

a. Acute Drug Effects

i) Spontaneous locomotor activity

In general, administration of cannabinoids results in decreased motor activity over a wide dosage range. Most studies have been conducted in rats and have used the interruption of photoelectric beams (Kubena and Barry 1970; Brown 1972). the time to leave a platform (Cohn et al. 1972), exploration of a shuttle box (Hendrikson and Jarbe 1971), or merely gross observation (Phillips et al. 1972) as measures of activity. Mice (Holtzman et al. 1969), gerbils (Grunfeld and Edery 1969), chickens (Abel et al. 1972). and dogs (Grunfeld and Edery 1969) have also been the subjects of studies on the motor effects of cannabinoids.

Davis et al. (1972) demonstrated a biphasic effect of delta-9-THC in rats over a ten-day period of dosing. Both excitation (on first two days) and depression (third through the tenth days) were observed using the photoelectric method of monitoring locomotor activity. In a study by Hardman et al. (1971) using dogs and monkeys as subjects, a number of THC analogues were studied and two were found to decrease activity at low doses (e.g., 0.1-0.2 mg/kg, i.m.). But high doses induced a biphasic response characterized by initial CNS stimulation followed by prolonged depression. This finding was confirmed for monkeys by Scheckel et al. (1968).

ii) Analgesic activity

Several laboratories have studied the antinociceptive effects of cannabinoids using a number of different methods and in a variety of species. Many pre-1974 studies used rats or mice in the tail-flick or hot-plate procedures to demonstrate the analgesic activity of delta-9-THC (Buxbaum 1972; Gallager et al. 1972; Bicher and Mechoulam 1968). but Harris (1971) and Domino et al. (1971) obtained inconsistent results. Hill et al. (1974) demonstrated that the doses required for analgesia in these methods cause decrements in motor activity. Thus, a retardation in the animal's physical capacity to respond may partially explain the inconsistent finding in earlier studies. Other studies using electrical tooth pulp stimulation with dogs (Kaymakcalan et al. 1974) and shock titration (Scheckel et al. 1968) have shown that delta-9-THC possesses analgesic activity. Wilson and May (1975) have shown, however, that the analgesic activity of delta-&and delta-9-THC is mainly due to the 11-hydroxy metabolite.

iii) "Hallucinatory" behavior

While no systematic objective procedures have been developed to assess whether animals experience hallucinations following drug injection, numerous aberrant behaviors have been observed in higher

mammals. For example, Joachimoglu (1965) observed dogs that had received hashish to be trying to "grab an apparition in the air" and to direct their eyes toward nonexistent objects in the air. Similar accounts of abnormal behaviors have been reported to occur in monkeys (Scheckel et al. 1968), with emphasis on apparent visual "hallucinations."

iv) Dog ataxia test

Delta-9-THC and other cannabinoids with psychoactive effects in man have particularly unusual effects on the overt behavior of dogs. A rating scale for the effects has been developed to allow quantitation (Dewey et al. 1972; Martin et al. 1975). Test drugs are given i.v. At low doses a slight reduction in activity can be seen, but at modest doses a distinctive "prance-like" walk with exaggerated responses to stimulation is produced. At higher doses, behaviorally active cannabinoids produce a static ataxia. The dogs remain standing in one place but sway from side to side. The test can be used to screen for THC-like activity as well as to estimate potency differences among cannabinoids.

v) Schedule-controlled behavior

A recent review of the THC effects upon schedule-controlled behavior has been provided by McMillan (1977). The use of such operant techniques has been most effective in elucidating numerous characteristics of the THC pharmacologic profile including their effectiveness via various routes of administration, the time course and degree of tolerance development, the long-term or irreversible cumulative effects after cessation of exposure, and the cumulative effects after repeated administration (Ferraro 1976).

vi) Electroencephalographic (EEG) activity

As described in the general methods section, two basic procedures are employed to assess the EEG effects of the cannabinoids: acute changes in the frequency and voltage characteristics, and alterations in the sleep-awake cycle. In the former, the data are quantified using visual inspection, voltage integration, frequency analysis, or power spectral analysis. Animals prepared with chronic cerebrocortical or depth electrodes are given acute injections of either the active constituents of marijuana (e.g., delta-9-THC) or crude marijuana extract. The resulting EEG effects are then characterized with respect to the voltage content or predominant frequency of various bands such as delta (O-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), or beta (13-25 Hz). Measurements are obtained at specific time points after injection (e.g., 30 minutes, 1 hour, 2 hours, etc.). Power spectral analysis has been utilizied to more precisely quantify the voltage and frequency components of the EEG of rats given delta-9-THC (Buonamici et al. 1982). The EEG voltage was reduced by 50% of control 1 hour after i.p. administration of 10 mg/kg of delta-9-THC. Return to control levels occurred over the course of 8 hours. During this period prominent EEG bursts of 6 Hz appeared to override the continuous EEG training. Similar findings

were reported for delta-9-THC administration in the rabbit (Willinsky et al. 1975).

Characterization of the effects of cannabinoids on sleep-awake activity has been studied in the rat (Masur and Khazan 1970; Moreton and Davis 1973). Changes in the distribution of the various phases of sleep (as measured using the method of van Twyver 1969) have suggested that time spent in slow-wave sleep is decreased and wakefulness is increased (Moreton and Davis 1973). In addition, this study compared REM-sleep-deprived with non-REM-sleep-deprived rats and found that they differed in the degree of dissociation of REM sleep phasic and tonic events, and with respect to the profile of REM sleep rebound.

Both of these techniques provide excellent baselines upon which to study tolerance development. Rats (Moreton and Davis 1973; Pirch et al. 1973), pigeons (McMillan et al. 1972), dogs (Dewey et al. 1972), and monkeys (Stadnicki et al. 1974) all show tolerance to delta-9-THC or crude marijuana. Two reports, however, have failed to find EEG tolerance to delta-9-THC in the cat (Lipparini et al. 1969; Barratt and Adams 1973).

2. Cannabinoid Physical Dependence Potential

a. Tolerance to Drug Effects

Tolerance to the analgesic effects of cannabis has been reported to last up to 64 days after a single injection in the rat (Kaymakcalan 1973). Similar persistence of tolerance to the behavioral depressant effects of delta-9-THC has been reported in the dog (Dewey et al. 1972). This prolonged duration of tolerance coupled with the fact that tolerance to the sedative and ataxic effects develop slowly relative to other effects suggests that results obtained with procedures which depend upon locomotor activity to assess cannabinoid effects must be interpreted with extreme caution. Such procedures should incorporate 1) controls for ataxia and/or sedation, 2) standardized dosing and testing schedules, 3) multiple test doses, and 4) appropriately long "wash-out" periods before subsequent dosing. Wikler (1976) has reviewed the literature in this area.

b. Withdrawal from Chronic Drug Administration

Procedures for assessing the abstinence syndrome in chronic cannabinoid-treated subjects have not been as well standardized as those for assessing opioids and CNS depressants. Such studies using rats or mice have reported definite abstinence signs in some cases (Cutler et al. 1975; Karler and Turkanis 1976), while others using convulsive thresholds as an indicator (Chesher and Jackson 1974; Leite and Carlini 1974) failed to demonstrate withdrawal. The most conclusive evidence for a dependence potential of cannabinoids has been provided by numerous studies with monkeys, using intravenous (Kaymakcalan 1972), oral (Stadnicki et al. 1974; Snyder et al. 1975)) and inhalation (Heath 1976) routes of administration to maximize exposure to the delta-9-THC. Behavioral signs of

withdrawal from chronic delta-9-THC administration appear after about 12 hours and continue for about 5 days. They include yawning, anorexia, piloerection, hyperirritability, aggressiveness, scratching, biting and licking fingers, pulling hair, tremors, twitches, penile erection and masturbation, eating feces and staring, and grasping at invisible objects (Kaymakcalan 1973). Similar increased aggressiveness was observed by Stadnicki et al. (1974) with the addition of EEG desynchrony and "hallucinations." Snyder et al. (1975) reported a disruption of operant performance for liquid reinforcement upon termination of delta-9-THC.

Precipitated withdrawal procedures have involved two different strategies. Since the spontaneous withdrawal signs from delta-9-THC resemble opioid withdrawal signs (Kaymakcalan 1973) and delta-9-THC alleviates morphine withdrawal signs (Bhargava 1978), naloxone has been used to precipitate withdrawal in delta-9-THC-maintained rats (Hirschhorn and Rosecrans 1974; Kaymakcalan et al. 1977). Secondly, observations suggesting that serotonergic mechanisms may be involved in the action of delta-9-THC (Sofia et al. 1971) prompted Taylor and Fennessy (1978) to administer the potent serotonin uptake inhibitor, clomipramine, in order to precipitate withdrawal signs in delta-9-THC-treated rats. Withdrawal signs were similar to those reported to occur in spontaneously withdrawn animals, though Taylor and Fennessy (1978) failed to observe spontaneous abstinence signs when delta-9-THC was discontinued.

3. Cannabinoid Abuse Liability

a. Drug Self-Administration

Procedures for assessing self-administration of cannabinoids have been described using rats (van Ree et al. 1978; Takahashi and Singer 1979) and rhesus monkeys (Kaymakcalan 1972; Pickens et al. 1973; Harris et al. 1974). Both intravenous and inhalation (Pickens et al. 1973) routes have been used.

i) Continuous self-administration

Studies using this procedure have failed to show that delta-9-THC reliably maintains self-injection performance in drug-naive animals, though subjects previously administered the compound passively do self-inject (Kaymakcalan 1972; Harris et al. 1974; van Ree et al. 1978). Takahashi and Singer (1979) have also reported that food-deprived rats self-administered more delta-9-THC than non-food-deprived rats. Regardless of the procedure used, however, animals self-administering delta-9-THC show lower response rates than those reported for opioid, CNS depressant, or stimulant self-administration.

ii) Substitution

Using cocaine (Kaymakcalan 1972) or phencyclidine (Pickens et al. 1973) as baseline drugs, substituted THC has been reported to maintain self-injection behavior; however, other substitution studies with delta-9-THC and other behaviorally active cannabinoids

fail to find evidence for reinforcing properties (Harris et al. 1974; Carney et al. 1977; Young et al. 1981). No studies have as yet been conducted to directly compare the relative reinforcing efficacy of delta-9-THC and related cannabinoids.

b. Drug Discrimination

Procedures for assessing the discriminative stimulus properties of cannabinoids have been reported with rats, gerbils, pigeons, and rhesus monkeys. Using "T" maze performance in rats, it has been demonstrated that delta-9-THC, delta-8-THC, and hashish' were all capable of acting as discriminative stimuli resulting in better than 75% correct responses by the 10th trial (Jarbe and Henriksson 1974). Generalization gradients for various doses of delta-9-THC have been shown to correlate very well using a number of procedures including rat two-lever discrimination (Balster and Ford 1978)) T-maze (Jarbe and Henricksson 1974)) conflict (Barry and Kubena 1972). and shock-escape maze (Jarbe et al. 1976).

An extension of these procedures provides information relating to the degree of cross generalization from delta-9-THC to other cannabinoids. Barry and Krimmer (1975) showed that crude marijuana extract generalized to delta-9-THC in a two-lever discrimination task in rats. Further, it has been shown that numerous metabolites of delta-9-THC generalize to the parent compound. The 11-hydroxy delta-8- and delta-9-THC compounds both generalize to delta-9-THC at relatively low doses (Balster and Ford 1978). Cannabinol and cannabidiol did not generalize to delta-9-THC (Barry and Kubena 1972; Jarbe and Henricksson 1974).

Finally, the discriminative stimulus properties of delta-9-THC are fairly specific in that many psychoactive compounds do not generalize to it. Pentobarbital, alcohol, chlordiazepoxide, chlorpromazine, morphine, methamphetamine, cocaine, atropine, LSD, mescaline, and phencylidine are among those' tested that fail to generalize to delta-9-THC (Barry and Kubena 1972; Jarbe and Henricksson 1974; Jarbe et al. 1975; Barry and Krimmer 1975.

c. Behavioral Toxicity

Procedures for assessing the effects of cannabinoids on sensory-motor performance have encompassed a number of specific techniques and animal species. Elsmore (1972) demonstrated that delta-9-THC impairs auditory discrimination in the monkey, while Ferraro and Grilly (1973) reported that delta-9-THC produced dose-related changes in response speed on visual matching-to-sample performance in the chimpanzee. The acute and chronic effects of marijuana on complex operant performance have been quantified in the squirrel monkey (Adams and Barratt 1974); In addition, delta-9-THC appears todisrupt learning differentially, depending on the paradigm used in rodents (Robichaud et al. 1973). This finding has been expanding to include both cannabis extract and delta-9-THC. Stiglick and Kalant (1982, 1983) showed that when these compounds are given chronically by gavage to rats, impairment of learning on radial-arm maze, DRL food-reinforced performance, and habituation in an open field

develops and persists for long periods of time after drug administration has ceased. While a number of studies have characterized the behavioral toxicologic profile of delta-9-THC, no studies to date have attempted to compare these effects with those produced by other cannabinoids.

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F. Procedures for Assessing Hallucinogens and Anticholinergics

1. Characterization of Hallucinogen and Anticholinergic Effects

a. Acute Drug Effects

i) Abnormal behaviors

Numerous animal species including mice, rabbits, and cats exhibit characteristic abnormal postures or behaviors after receiving acute injections of lysergide-like hallucinogens. Head twitching in mice and hyperthermia in rabbits have been noted, but these observations have not evolved into' a standardized testing procedure. The cat limb-flick model of Jacobs et al. (1977) has received attention as a more refined procedure for assessing hallucinogenic activity. Moreover, this abnormal behavior has been shown to be associated with a decreased firing of serotonin-sensitive neurons in the raphe nucleus. The success of methods for recording single unit activity in freely moving animals has been responsible for obtaining these electrophysiological correlates of behaviors. Cats are given an acute injection of the test compound and then observed in an open-field environment. The limb-flick is seen in control, non-treated cats only in response to the presence of a foreign substance on the paw. In LSD-treated cats, the paw is raised from the ground and then rapidly shaken or flicked away from the body. The number of limb-flicks per unit time is then tabulated and used as an index of a test drug's LSD-like activity.

Another approach to studying psychotomimetics has focused on the complex relationships within social colonies of non-human primates. On a test day, only one of 5-10 monkeys is treated and the entire colony is observed for abnormal or "emergent" behaviors. Each animal is treated on separate days, and the direct effects on the treated animal are tabulated,as is the behavior of the untreated monkeys. Behavioral checklists are used by "blind" observers; Heinze et al. (1980) utilized this procedure to study the effects of 5-methoxytryptamine in Stumptail macaques. Schlemmer and Davis (1983) have reviewed the literature comparing various models of psychotomimetic-induced behaviors.

ii) Spinal dog preparation

This technique (which is described in detail in the opioid section) has been used to characterize compounds with respect to their LSD-like activity (Nozaki et al. 1977). In general, LSD and related compounds produce a spectrum of effects including whining, eye tracking movements, increased respiratory rate, hyperthermia, increased latency to skin twitch, and facilitation of the flexor reflex. Thus, it is the entire profile of effects in this procedure that is utilized to determine a test compound's LSD-like activity. An extension of this technique involves the use of specific pharmacologic antagonists (e.g., cyproheptadine, phenoxybenzamine, chlorpromazine) in order to further differentiate these compounds with respect to their LSD- vs. amphetamine-like profiles.

iii) Schedule-controlled behavior

The basic procedures for assessing the effects of hallucinogens on operant performance are similar to those described under general methods above. LSD and congeners differentially affect positive reinforced behavior depending upon the prevailing response rate and schedule (Appel 1968; Dews and Wenger 1977). These techniques have been most useful in providing information on relative potencies of hallucinogens (Appel and Freedman 1965), demonstrating that -LSD is about 10 times more potent than both psilocybin and d-amphetamine and 100 times more potent than mescaline. The available data indicate that the use of aversive control procedures does not provide information that can be interpreted as unique to this class of compounds (Appel et al. 1967).

iv) Electroencephalographic (EEG) activity

Procedures for assessing the EEG effects of LSD and related compounds have been developed for the mouse (Morley and Bradley 1977)) rat (Depoortere and Loew 1971), rabbit (Long 1962; Khazan and McCash 1965), cat (Killam and Killam 1956)) and monkey (Walter et al. 1971). Most of these studies have focused on acute effects described in terms of bursts of spikes, spindling. and desynchronization. Increased wakefulness and delayed onset and decreased duration of REM sleep have also been reported (Depoortere and Loew 1971).

Attempts to quantify the EEG effects of hallucinogens with respect to frequency and voltage components have been successful in both mice and cats. Mescaline, dimethoxy-amphetamine (DMA), and related ring-substituted phenylisopropylamines produce hypersynchronous slow-wave activity associated with abnormal stereotypic behaviors in the cat (Fairchild et al. 1967). These effects contrast with amphetamine which produces desynchrony concomitant with behavioral alerting and hyperactivity. These data provide a framework within which relative potencies of test compounds for hallucinogenic activity can be determined. Winters and Wallach (1970) demonstrated that cats treated with hallucinogens exhibit hypersynchronous EEG peaks in the 2.5-3.0 Hz range. Morley and Bradley (1977) have used power spectral analysis to quantify the EEG effects of N,N-dimethyltryptamine in mice. A dose-dependent hypersynchrony at 2.5-4.5 Hz was observed to persist for up to 60 minutes after injection. In addition, anticholinergics produce slow wave hypersynchrony associated with alteration in behavior consistent with models of hallucinosis.

v) Binding assays

Stereospecific ^{3}H-LSD high affinity binding was demonstrated in the mid 1970s (Bennett and Aghajanian 1974; Bennett and Snyder 1975) and has since provided a basis for associating serotonin and LSD with specific neuronal structures. The physiologic significance of binding potencies has not been identified because of the poor correlation of lC50 values and hallucinogenic activity (Freedman and Boggan 1982). Greater success has been achieved when correlations

are made between changes in binding following in vivo treatment with compounds that produce known functional changes in receptors (e.g., 5,7-dihydroxytryptamine). Increases in LSD binding in specific brain areas have been demonstrated in reserpine or para-chloroamphetamine-treated rats (Bennett and Snyder 1976).

2. Hallucinogen and Anticholinergic Physical Dependence Potential

a. Tolerance to Drug Effects

Tolerance appears to develop fairly rapidly to many of the effects of LSD and related compounds. Most notable have been studies that employ behavioral procedures (Freedman et al. 1958; Appel and Freedman 1968). EEG activity (Wallach et al. 1972). and measures of cardiovascular reflexes in the spinal dog preparation (Martin and Eades 1972). Because the degree of tolerance developed to almost all hallucinogens is so complete and occurs so rapidly, these procedures are not particularly useful in quantifying the dependence potential per se. Because marked cross-tolerance between compounds of similar chemical structure is widespread (Martin and Eades 1972; Vaupel and Nozaki 1975), however, screening for LSD-like activity using this procedure may be useful.

b. Withdrawal from Chronic Drug Effects

To date no studies have demonstrated that the termination of chronic administration of hallucinogens results in an abstinence syndrome (McIsaac et al. 1970).

3. Hallucinogen and Anticholinergic Abuse Liability

a. Drug Self-Administration

i) Continuous self-administration

Deneau et al. (1969) demonstrated that rhesus monkeys would not initiate self-administration of mescaline either spontaneously or after 1 month of programmed administration. LSD may, in fact, possess aversive properties, since Hoffmeister (1975) has demonstrated that rhesus monkeys will respond in order to terminate stimuli associated with the delivery of this compound.

ii) Substitution

Using cocaine as the baseline drug, Griffiths et al. (1979) demonstrated that four hallucinogenic amphetamine-like compounds (DOET, DOM, mescaline, and PMA) do not maintain self-administration in baboons.

b. Drug Discrimination

Procedures for assessing discriminative stimulus properties are perhaps the most well developed of those currently available for assessing compounds for hallucinogenic activity. The discriminative

stimulus properties of LSD, mescaline, and related compounds are apparent after relatively small doses (Cameron and Appel 1973; Hirschhorn and Winter 1971). In addition, the number of trials to criterion is relatively small, suggesting that these compounds generate strong interoceptive stimulation. Appel et al. (1978) have investigated the conditions under which such performances occur and report generalization gradients for doses other than the training dose as well as for other stimuli (e.g., tones, lights, etc.).

There is good generalization or cross-transfer between the discriminative effects of LSD, mescaline, psilocybin, and quipazine (Appel et al. 1978). These procedures thus provide useful information for classifying these and other compounds with respect to pharmacologic class (Kuhn et al. 1977).

c. Behavioral Toxicity

Procedures for assessing the degree of behavioral toxicity of the hallucinogens have been, for the most part, directed at quantifying the sensory-motor performance of animals. Blough (1956, 1957) demonstrated that LSD could improve pigeon's accuracy on a complex visual discrimination task while elevating the absolute visual threshold. Species differences are apparent, since LSD impairs auditory frequency discrimination in the cat (Key 1961) but not the rat (Dykstra and Appel 1974). Auditory generalization gradients were unaffected by LSD in pigeons (Dykstra and Appel 1972). Finally, Brown and Bass (1967) showed that LSD increases the visual reaction time in rhesus monkeys while increased visual thresholds in this species were reported by Ando and Takada (1979).

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G. Procedures for Assessing Dissociative Anesthetics

1. Characterization of Dissociative Anesthetic Effects

a. Acute Drug Effects

i) Spontaneous locomotor activity

Using an actophotometer, Chen (1959) demonstrated that the predominant response of rodents to PCP was that of excitant hyperactivity. This effect, however, was dose and species specific in that higher doses induced stereotypic and depressed behavior, and primates were only sedated after PCP administration.

ii) Forced motor activity

Using the rotorod assay described under general methods above, Kalir et al. (1978) and Vincent et al. (1979) have demonstrated that PCP and some of its analogues disrupt forced motor activity in a dose-related manner. In addition, the relative potency for this effect has been found to be positively correlated with the relative potency for binding to a neuronal receptor.

iii) Electroencephalographic (EEG) activity

The EEG profile of PCP was first characterized in animals by Domino (1964). In a comparative study, Gehrmann and Killam (1976) demonstrated that of all the CNS depressants tested, PCP and ketamine produced the greatest increase in EEG voltage in all frequencies of the primate. More recently, Mattia and Moreton (1981, 1982) have also characterized the EEG profile of PCP and ketamine using power spectral analysis. Lower doses of PCP produced increased voltage in the theta band while larger doses produced two distinct peaks of activity (one at O-5 Hz and the other at 7-8 Hz). Ketamine demonstrated a similar profile, but was about 10 times less potent that PCP.

iv) Behavioral performance

Because of the complex nature of PCP's pharmacology, multiple schedules seem to be the most appropriate paradigms to assess the effects of PCP on operant performance. This is especially true since the finding that the effects of psychoactive agents on operant performance are related to the schedule employed (Dews and De Weese 1977; McKearney and Barrett 1978). In this regard, rodent (Murray 1978; Woolverton and Balster 1979) and primate (Chait and Balster 1978; Brady et al. 1980) data have shown that low doses of PCP increase low rates of responding (e.g., fixed interval) and decrease high rates of responding (e.g., fixed ratio). Three analogues, PCE, TCP, and ketamine, have been shown to produce qualitatively similar effects on operant performance; the only differences observed were in the relative potencies of these compounds.

v) Binding assays

Using techniques similar to those used to demonstrate the existence of opiate receptors, a component in brain membrane has been shown to bind [^{3}H] PCP with a high degree of specificity and with a fairly high affinity (Vincent et al. 1979; Zukin and Zukin 1979). In addition, PCP and 3 of its analogues have been shown to displace [^{3}H]quinuclidinyl benzylate (muscarinic receptor) and [^{3}H]dihydromorphine (opiate receptor) with a respectable degree of specificity (Vincent et al. 1979; Su et al. 1980). The "PCP receptor" appears to be most concentrated in the synaptic, fraction of cerebral cortex and corpus striatum, while significant, but somewhat lower, degrees of binding were found in hippocampus and thalamus.

While there has been some early controversy regarding the specific binding of PCP to glass wool fibers, the more recent studies have demonstrated significant correlations between the relative potency of PCP and its analogues in the rotorod test and binding affinities (Vincent et al. 1979; Zukin and Zukin 1979). The ultimate impact of the presence of PCP receptor may reside not in the advancement of our understanding of PCP's mechanism of action, but in its possible usefulness in rapid screening of drugs for PCP-like activity and in the search for a PCP antagonist which would provide a valuable addition to the current strategy of treating PCP intoxication.

2. Dissociative Anesthetic Physical Dependence Potential

a. Tolerance to Drug Effects

Repeated administration of PCP to monkeys and rats results in a decreased disruption (2-4-fold change) of operant performance (Balster and Chait 1976; Chait and Balster 1978; Woolverton and Balster 1979; Woolverton et al. 1980). Various behavioral paradigms were used including a chain schedule procedure for food reinforcement and a fixed interval schedule procedure for milk. Similar degrees of tolerance were observed regardless of whether PCP was administered before or after the test session. First dose behavioral tolerance of PCP has also been reported to occur in the rat (Ruffing and Domino 1980). This phenomenon was found to be dose related; however, the duration of complete suppression of lever-pressing activity was used as the dependent variable and not response rate as reported in the earlier studies. Regardless of the technique employed, it appears that marked tolerance develops to at least some of the effects of PCP.

b. Withdrawal from Chronic Drug Administration

Using a continuous access self-administration paradigm, rhesus monkeys were observed to readily initiate self-injections of PCP (0.1 mg/kg/inj) and increase their drug intake over the course of 20 days (Balster and Woolverton 1980). Daily intakes of up to 7.4 mg/kg were achieved, and previously depressed food intake had returned to baseline (indicative of tolerance development). The animals maintained a state of continuous intoxication which was

sustained when the dose was increased to 0.5 mg/kg. Substitution of saline after 58 days of exposure resulted in the appearance of numerous abstinence signs and symptoms including increased vocalizations, bruxism, oculomotor hyperactivity, diarrhea, refusal of preferred food, piloerection, and tremors. Less common signs included ear and facial twitches, priapism, abdominal contractions, emesis, and convulsions. The time course of withdrawal was characterized by an initial recovery from , the PCP-induced intoxication at about 4 hours after saline substitution. Onset of hyperresponsive behaviors became evident at 8-12 hours, with the maximum number of symptoms occurring 12-15 hours post-substitution. The syndrome dissipated over 24 hours, however, and all withdrawal signs were immediately reversed by PCP (0.25 g/kg, i.v.). This study also showed that PCP blood levels were in the 105-280 mg/ml range during self-administration, and declined to O-12 mg/ml with saline substitution.

3. Dissociative Anesthetic Abuse Liability

a. Drug Self-Administration

The rhesus monkey has been shown to self-administer PCP intravenously (Pickens et al. 1973; Balster et al. 1973; Balster and Woolverton 1980) and orally (Carroll and Meisch 1980; Carroll 1982). In the primate studies, not only did PCP maintain self-injection performance when substituted for cocaine, but animals with no prior history readily initiated self-injections of PCP (Balster et al. 1973). The self-administration profile of PCP was (like many other drugs of abuse) characterized by an inverted U dose-response curve and while the number of self-injections decreased as the dose was increased, the total intake per day increased. When the fixed ratio for delivery of an injection was increased from 1 to 5, the number of self-injections also decreased.

Finally, self-administration studies with PCP analogues such as ketamine (Moreton et al. 1977) and numerous N-substituted analogues (Risner 1982) have shown that all of these compounds maintain self-injection performance similar to that of PCP. The only differences observed thus far were those of relative potency. Using a bioassay procedure that predicts relative potencies, parallelism of curves, and relative maximal effects, Risner (1982) demonstrated that eight structurally related analogues of PCP were self-administered by the dog. The thienyl-substituted analogue was the most potent, followed by PCP, y-substituted alkyl analogues, monohydroxylated metabolites, and ketamine.

b. Drug Discrimination

Procedures for assessing the discriminative stimulus properties of phencyclidine and related compounds have been developed and refined for both the rat and the squirrel monkey. Overton (1975) initially demonstrated that PCP and ketamine shared similar discriminable effects which were dissociable from the stimulus effects of pentobarbital. Similar stimulus generalization curves were observed for PCP, cyclohexamine, and ketamine, while ditran did not

generalize to the PCP cue (Jarbe et al. 1975). These procedures have been used by two laboratories to evaluate a series of PCP analogues with respect to similar stimulus properties using food reward in the squirrel monkey (Brady and Balster 1981) and shock avoidance in the rat (Shannon 1981). Both studies demonstrated that N-substituted phenylcyclohexylpiperidines generalize to the PCP cue and, in addition, provided a basis for rank ordering the compounds by relative potencies. Shannon (1981) studied 17 analogues of PCP and found that neither the 4-hydroxycyclohexane metabolite nor three carbonitrile analogues generalized to PCP.

c. Behavioral Toxicity

Procedures for comparing the sensory and motor effects of dissociative anesthetics have been limited to a single report (Lukas et al. 1980) showing that both PCP and ketamine disrupt auditory and visual thresholds and reaction times in unrestrained baboons. The data demonstrated a definitive difference in time course with PCP markedly disrupting reaction-time performance throughout the two-to-three hour test session, while recovery from ketamine's effects were evident after one hour.

Three studies, however, have assessed PCP effects on size discrimination in rhesus monkeys (Brown and Bass 1967)) matching-to-sample task in pigeons (McMillan 1980), and acquisition and performance of conditional visual discriminations in Patas monkeys (Thompson and Moerschbaecher 1982). In general, PCP produced dose related increases in reaction times and percent errors.

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VI. Human Testing Procedures

A. General Methods

1. Procedures for Characterization of Drug Effects

a. Acute Drug Effects

i) Analgesia

Procedures for the evaluation of the pain-relieving properties of drugs in humans have developed along essentially two distinct lines of investigation based on the origin of pain. In one, the empiric drug trial, the studies are carried out in patients being treated for clinical pain, usually, though not invariably, in a hospital setting. In the other, the psychophysiological approach, the studies are usually of experimentally induced pain and carried out in normal volunteers or ambulatory chronic pain patients, most often in a laboratory setting. Although the measurement of pain is common to both methodologies, there are fundamental differences in concept, applicability, and results of the two approaches.

In clinical pain, the strength of the stimulus is an unknown, and inferred only from the medical history, physical examination, ancillary clinical laboratory data, and the physician's past experience. In a clinical drug trial meeting the basic requirements for a well-designed study, the patient's report of pain is accepted at face value and the effectiveness of any drug in relieving pain is considered to be meaningful only in relative terms - that is, relative to an appropriate standard drug or control medication. By contrast, in psychophysiological experiments in which pain is experimentally induced, the external stimulus is measurable and controlled by the investigator or subject whose subjective responses can be scaled in terms of the strength of the stimulus. Psychophysiological methods more often measure the effects of drugs on one or more components of the pain complex and express the results in absolute terms - that is, in terms of the criterion itself.

It has been long recognized that pain is a highly complex, multifaceted experience with strong affective and motivational

components (Beecher 1959; Sternbach 1968; Melzack and Torgerson 1971), and great strides have been made in the development of laboratory methods for parceling out and measuring these elusive variables (Clark 1974; Tursky 1975; Gracely 1980; Price et al. 1983). Early psychophysical tests concentrated on the pain threshold and the dol scale of pain intensity (Wolff et al. 1941; Hardy et al. 1947, 1952). A wide variety of measurable external stimuli have been employed, including radiant heat and other forms of thermal stimulation, electrical shocks, a variety of pressure and physical devices, chemical methods, and arterial occlusion (Beecher 1957; Stevens et al. 1958; Smith et al. 1966; Yanaura et al. 1977; Lim et al. 1967; Procacci et al. 1979). But the ability of methods based solely on measurements of pain threshold to predict the efficacy of an analgesic in the clinical setting has been disappointing (Kutscher and Kutscher 1957; Beecher 1959; FDA Guidelines 1979).

The results of experimental procedures to measure pain tolerance have been more concordant with the clinical experience but have raised ethical issues and, like clinical pain, they are unidimensional - measuring only pain intensity. More recent developments of psychophysical measurement procedures have, however, made it feasible to evaluate some of the qualitative as well as the quantitative aspects of the pain experience. Most of these approaches are based on signal detection theory (Green and Swets 1966), magnitude estimation and ratio stimulus scaling (Stevens 1975), or cross-modality matching techniques (Tursky 1975). These methods have provided means of estimating the contributions of discrimination sensitivity and response criterion shifts in evaluating placebo effects and in the diagnostic evaluation of individual and group expressions of pain, particularly in patients with chronic benign pain. Measures based on signal detection theory have also been employed to distinguish analgesics from psychotropic drugs (Chapman 1977; Wolff et al. 1976; Yang et al. 1979). For reliable results, however, psychophysical metholds generally require that the subject submit to large numbers of painful stimuli under conditions which limit use in seriously ill patients with either acute or severe pain due to trauma or disease. Thus, in spite of the more rigorous controls which can be applied in the laboratory, the well-designed controlled clinical drug study is still regarded as the crucial test of a drug's analgesic properties (FDA Guidelines 1979).

Psychophysical measurements of pain also include multidimensional pain descriptor scales and attempts to generate independent magnitude estimates for each of the pain descriptor categories. The McGill Pain Questionnaire (Melzack 1975) has been used chiefly to characterize clinical pain although, more recently, it has also been used to measure the efficacy of analgesics (Heidrich et al. 1983). This questionnaire consists of sets of words designed to quantify three dimensions of the pain experience in terms of the intensity ratings and number of descriptors chosen by the patient with pain. Other recent studies employing magnitude estimation, ratio stimulus scaling, and cross-modality matching procedures have shown that verbal meanings to an individual may be appropriately quantified

either by the individual or a similar group of individuals (Gracely et al. 1978). These techniques have proven effective in distinguishing the sensory from the hedonic effects of narcotics and anxiolytics (Gracely and Dubner 1981). The advantages of these methods lie in their potential for characterizing how drugs act, rather than as a means of evaluating the analgesic efficacy or potency of new drugs.

Scientifically acceptable principles for the conduct of clinical analgesic drug trials were pioneered and elucidated over 25 years ago by Beecher (1957). He emphasized that while reliance must be placed on the verbal report of the patient with "pathological pain," reliability and validity can be achieved by appropriate experimental designs and controls including the double- blind technique, randomization of treatments, appropriate active drug standards and placebo controls, and statistical verification of the significance of the results. On this foundation, a number of different drug testing models have been developed using either single or repeated, fixed or graded, doses of the test drug and reference standard, with or without placebo controls, and administered by one or more of several different routes to patients with acute or chronic pains of diverse etiologies (Keats 1956; Houde et al. 1960; Lasagna 1960; Bellville et al. 1968; Sunshine 1980). In addition, a well-designed study should include an internal control - a means of demonstrating within each study that the sample population and the experimental procedure are capable of discriminating between a.known active drug standard and a placebo, or between graded doses of the standard - in terms of the analgesic data generated (Modell and Houde 1958; Houde et al 1965). There are many factors, however, which enter into the choice of the appropriate experimental design, standards and controls, and methods of collecting and analyzing the data. Among them are the general pharmacological profile based upon laboratory animal and preclinical data, and the expected role the drug will fill in medical practice (FDA Guidelines 1979). Pharmacokinetic characteristics of the test and reference drugs will also influence the choice of single or repeated doses, and crossover or non-crossover experimental designs, the timing of drug administration and data collection, and the manner in which the results are analyzed. Decisions are commonly based on whether a drug 1) is morphine-like, 2) has associated narcotic antagonist properties, 3) is aspirin-like or, 4) does not fit any of these stereotypes (FDA Guidelines 1979).

Because of the great variety of clinical pains for which analgesics with potential for abuse are employed, there is no single experimental design or method of conducting a clinical analgesic drug assay which is appropriate for all situations. The procedure followed most frequently is to employ fulltime trained observers, usually registered nurses, who administer the study medication for complaints of moderate or severe pain. Observations are generally made prior to and at frequent regular intervals for 4 to 6 hours after medication or until pain is reported to have returned to its premedication intensity. For pain which is short-lived, such as postpartum pain (Bloomfield et al. 1970) and that following many types of surgery including the extraction of impacted molars (Cooper

and Beaver 1976), the patient receives only one treatment or test medication, and comparisons of the drugs are made in parallel patient groups. Studies carried out in situations in which the pain is expected to be more long-lasting, such as in patients undergoing more formidable surgical procedures, and patients with pain due to cancer, some form of crossover design may be employed in which each patient receives single doses of each test drug on separate days (Houde et al. 1965). The objectives of most of these studies are not only to test for analgesic efficacy but also to provide an estimate of the potency of the test drug relative to a known or established standard analgesic. The methodology for chronic or repeated dose administration of new drugs has not been as well characterized, but some. procedures incorporating many of the features of the single dose studies have been reported (Wang et al. 1981; Ouellette 1982). These methods allow for comparisons of the effects of the initial doses of drugs with those at proximate steady-state levels. This can be of considerable importance in evaluating drugs which are cleared from the body more slowly or have active metabolites.

Virtually all of the methods of evaluating pain in clinical settings rely on the patient's own report. While a number of objective methods - including the measurement of a variety of autonomic signs (Beecher 1957) and biochemical correlates of pain (Terenius 1978), of recordings of evoked brain potentials (Chapman et al. 1979)) and of observations of behavior (Fordyce 1976) - have been employed in a variety of clinical settings, these methods have had limited applicability and have been of questionable reliability in predicting the efficacy of an analgesic (Houde 1982). Most clinical methods employ some form of categorical or ordinal scale for rating pain severity. Typically, analgesia is measured indirectly in terms of changes in pain intensity levels on a 4-5 point scale at intervals after administration of the test medication in comparison with the levels of pain before administration. Analgesia is also measured directly in terms of pain relief estimates. Comparison of analgesic drugs is generally made in terms of the cusum of observational period scores and commonly expressed as SPID [sum of pain intensity differences] or TOTPAR [total pain relief] (Forrest et al. 1963). Quanta1 measures of pain relief or comfort have also been employed successfully, often together with the graded rating scales, but they tend to be less sensitive (Wallenstein and Houde 1975).

Visual analogue scales (VAS) are also being used to measure pain intensity, pain relief, and mood effects. The VAS is usually presented in the form of a 100 mm horizontal line with no other markings except at their ends which are identified as "no pain" and "worst possible pain," "complete pain relief" and "no pain relief," or "best mood" and "worst mood." The patient places a mark between these extremes to indicate his subjective impressions. The VAS has also been presented in the form of a dial, pain thermometer, and vertical line, but none of these variations provide any advantages (Huskisson 1974; Littlejohns and Vere 1981). Good agreement has been found between the ordinal pain scales and the VAS, but the latter tend to be more sensitive (Ohnhaus and Adler 1975;

Wallenstein et al. 1980). Despite some debatable assumptions of the mathematical properties of the ordinal scales employed (Littlejohns and Vere 1981), the results of clinical relative analgesic potency assays by most investigators have, in general, been consistent whether analyzed by standard parametric tests or by non-parametric tests (Fucella et al. 1977).

In summary, there are basic differences in the approach to measuring pain when the objective is the evaluation of an analgesic and when the objective is the evaluation of the nature of pain. The latter is recognized as a complex process whose multidimensional features can best be delineated in a controlled laboratory setting using a variety of psychophysiological methods. By contrast, the assessment of analgesic potency and efficacy of a drug is judged in terms of a unidimensional scale of pain intensity and compared with an established standard analgesic in a clinical setting. The two approaches to measuring pain complement eash other, but the psychophysical techniques are limited in their ability to detect the effects of simple analgesics and by their often not being applicable to studies of analgesics in patients with acute pain.

ii) Electroencephalographic (EEG) activity and sleep

The EEG recorded from multiple scalp electrodes has been utilized in two basic modes to assess 1) acute effects of a compound on the electrical activity of the brain and 2) effects of a compound on the sleep-awake cycle. While the basic equipment is similar, these two types of studies involve procedural differences that relate to recording session length, methods of analysis, and in some cases, recording montage and method of electrode attachment (Fink 1968).

The acute effects of a compound are usually evaluated during a relatively short (e.g., 3-5 hour) recording session (Itil 1972) employing an abbreviated method of attaching the scalp electrodes. Electrodes are usually placed according to the l0-20 system (Jasper 1958) but not all 21 possible electrodes are utilized. Recording montages are usually selected on the basis of special interest or because the experiment is designed to study the drug-induced changes in certain neuronal structures immediately below the electrodes. Before administering the drug, a sufficiently long period is customarily devoted to obtaining control, awake recordings under various conditions, (e.g., eyes closed and relaxed, eyes open and relaxed, and eyes open and concentrating). These sessions serve as the basis for assessing drug-induced changes (Longo 1977). The EEG effects can also be correlated with subjective ratings of euphoria and other physiological responses (Volavka et al. 1973). Quantitation of the EEG effects is either by visual inspection, integrated voltage, period analysis, or power spectral analysis.

The study of effects of drugs on the sleep-awake cycle necessitates some procedural refinements. Recording sessions typically last 6-8 hours and the EEG train is described by visual inspection in terms of frequency and amplitude components. These procedures have provided standardized characteristics that define the various phases

of sleep (Rechtshaffen and Kales 1968; Niedermeyer 1982). The sleep profile has identifiable onset and duration characteristics involving the various sleep stages I-IV and REM sleep, as well as amplitude and frequency characteristics involving the clinically relevant band widths of delta (O-4Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-25 Hz).

Sleep stages have been characterized by their EEG profiles and rarely by simply observing the subject (Harvey 1980). During stage 0 or awake, beta activity predominates while the eyes are open and alpha activity while the eyes are closed. Stage I or the decending/ dozing stage is characterized by theta, alpha, and beta activity with occasional bursts of eye movement. The onset of sleep during stage II is heralded by the appearance of sleep spindles and K complexes and the disappearance of alpha and beta activity; theta waves, however, remain. Stage III or deep sleep transition is differentiated from Stage II by the appearance of slow delta waves along with the other waveforms. Deep sleep or Stage IV occurs when only delta activity prevails with little or no eye movement. Rapid-eye-movement or REM sleep is a stage that typically follows IV. It is characterized by many different frequencies, but no spindles or K complexes are seen. There is a corresponding increase in the amount of eye movement. Most dreaming occurs during this stage.

Quantification of the EEG activity has been, accomplished by integrating the amplitude (Goldstein et al. 1963) using a pulse generator. Temporal frequency changes have also been identified using period analysis (Burch et al. 1964), by measuring the time interval between two successive baseline crossings of the EEG waveforms. EEG power spectral analysis is based upon the analog-to-digital conversion of the EEG activity which is then mathematically fitted to a sine/cosine signal. The Fast Fourier Transform (Grass and Gibbs 1938; Walter 1963), when applied to such data, results in a fingerprint-like array that characterizes the amplitude and frequency components simultaneously.

2. Procedures for Assessing Physical Dependence Potential

a. Tolerance to Drug Effects

The development of tolerance to a drug effect is reflected by an attenuation of the original response with continued exposure to the drug. The extent of tolerance is determined by the specific drug, the parameter being assessed, and the dose and duration of treatment. Thus, once the acute effects of a compound are characterized, the development of tolerance can be tracked during treatment.

The assessment of tolerance to a drug's effect must take into account numerous factors (Martin and Sloan 1977). First, with chronic administration, the drug's pharmacologic profile may change due to differential tolerance development to some of the effects and not others. This complicates subsequent reassessment of the drug's effects. Secondly, an appropriate baseline of effects must be established. The time interval from the last dose to the initiation

of the procedures for assessing tolerance must be carefully determined, since certain acute effects may be confounded with the appearance of early abstinence signs. Thirdly, appropriate dose-response relationships should be demonstrated before chronic exposure is begun. Thus, a "tolerance index" can be used to compare different drugs (Martin and Fraser 1961).

b. Withdrawal from Chronic Drug Administration

The assessment of the dependence potential of a class of drugs generally focuses upon procedures far identification and quantification of the behavioral and physiological changes following cessation of chronic drug exposure. Characteristically, such effects depend primarily on the drug being studied, the maintenance dose, and the duration of treatment. Two different techniques are employed to assess the consequences of withdrawal from chronic drug exposure. Direct or primary dependence assessment involves using a drug-free (but not necessarily a drug-naive) subject given increasing doses of a test compound for a predetermined length of time (Fraser et al. 1957). Upon withdrawing the drug, the subjects are assessed at regular intervals for changes in physiological processes, vital signs, and subjective or "mood" changes. These signs and symptoms are rank-ordered with respect to their degree of severity and then used as the basis for describing the syndrome as either mild, moderate, or severe (Martin and Gorodetzky 1965; Jasinski et al. (1971b).

The substitution procedure uses subjects currently receiving a compound on a chronic basis. The test compound is then substituted for a predetermined length of time, usually on a double-blind basis (Jasinski 1977). The signs and symptoms are recorded and tabulated, with the presence or absence of signs reflecting the degree of similarity between the test drug and the standard drug.

3. Procedures for Assessing Abuse Liability

a. Drug Self-Administration

Drug self-administration procedures have evolved over the past 18 years and at present have been refined by the introduction of more standardized techniques and an adherence to certain basic guidelines (Bigelow et al. 1976). Assessments of true drug-seeking behavior must satisfy the following criteria: 1) ingestion or injection of the drug must be optional (Mello and Mendelson 1965), 2) the behavior must be observed during a number of experimental manipulations (Nathan et al. 1970). and 3) the drug self-administration patterns must be established over an appropriately long time interval (Cohen et al. 1971).

In general, two basic subject populations have been studied. Normal volunteers reporting to the lab for only a few hours each day have been used for short-term determinations of reinforcing efficacy (Johanson and Uhlenhuth 1978), while residential ward settings have been used with drug-experienced subjects (Bigelow et al. 1975; Mello and Mendelson 1978; Fischman and Schuster 1982). In the short-term

studies, subjects receive a physical examination and are given drug or placebo either orally or by injection. Typically, double-blind conditions are observed. At various time intervals, the subjects are asked to evaluate their feelings while physiological responses are monitored. This procedure provides baseline data against which choice procedures (i.e., between two different drugs) can be evaluated.

In residential ward settings, subjects usually are given control of access to drug. In addition, they are required to work (e.g., ride an exercise bicycle for 15 minutes) in order to obtain drug (Griffiths et al. 1979). This procedure tends to reduce variability and increase sensitivity by restricting the drug availability. The residential ward setting also provides a built-in control for environmental factors such as social interactions (Bigelow et al. 1974). This procedure is also conducive to studying the patterns of drug self-administration over time as a basis for the assessment of tolerance and dependence.

Prior to the initiation of studies with a volunteer participant, an extensive drug history should be obtained. In addition, the subjects should be evaluated for current tolerance and/or dependence to certain drug classes either by giving a test dose or by requiring a controlled observation period to determine whether withdrawal signs appear.

b. Self-Report of Drug Effects

Procedures for assessing changes in subjective feelings have been developed to aid in the identification of drug-induced effects superimposed on the subject's baseline mood state. The most widely utilized test, the Addiction Research Center Inventory or ARC1 (Hill et al. 1963) is a series of 550 questions that are answered "yes" or "no. " The content of the items reflects a broad range of physical, emotional, and generally subjective effects of drugs. Additionally, certain questions are designed to provide some measure of personality and psychiatric stability (Haertzen et al. 1963). In some circumstances, an additional 50 questions are asked which provide information on the sociologic profile of the subject. The most useful information obtained when applying this test is the average scores on the 38 recommended scales (see Haertzen 1974), since these averages can serve as a standard for comparison in the classification of subjects or groups. Essentially, validation of the ARCI has resulted in the identification of six psychiatric groupings and ten drug conditions. The six psychiatric groupings are: normal, mentally ill, alcoholics, criminals, opiate addicts, and simulated mental illness. The ten experimental drug conditions are: no-drug, morphine, cyclazocine and nalorphine, pentobarbital, chlorpromazine, LSD, benzedrine, alcohol, opiate withdrawal, and chronic opiate maintained.

Many pharmacological studies have used short forms or single scales of the ARCI. These forms can be quickly administered and are especially useful in demonstrating whether a drug effect is present, its potency, and its duration of action. Three scales in particular

have been used to identify sedative-(PCAG), euphoric-(MBG), and psychotomimetic-(LSD) effects (Martin 1967; Jasinski et al. 1971a). Morphine and morphine-like drugs elevate MBG scores but not PCAG or LSD, while nalorphine and nalorphine-like drugs elevate LSD and PCAG scores but not MBG scores. Central nervous system depressants elevate PCAG scores and not LSD or MBG scores. The utility and validity of these short forms have been individually substantiated by the good correlations of relative potencies and time-action curves for the resultant assessment of subjective effects and other physiological responses such as pupillary diameter and nystagmus (Martin 1967; Jasinski et al. 1971a).

The method of classification of subjective effects inherent in the ARCI is based on discriminant function procedures described by Rao (1952). The advantage of this procedure is that it provides a mechanism that corrects for individual differences and variability. Full details of the correcting procedures are provided by Haertzen (1974).

Various studies have shown that ARCI scales may have a factor analytic or structural significance that is constant in going from one group to another or in testing from one condition to another. When individuals are tested under different conditions, however, different individuals may be placed in the same category. The successful implementation of the ARCI and resultant predictive power of the scales are also dependent on the specific test-taking instructions given, and as such, should be standardized (Haertzen 1974).

c. Behavioral Toxicity

Procedures for assessing drug-induced changes in human performance have been developed and refined for psychomotor and reaction time procedures. Little consistent data are available on more complex behaviors and functions, however (Johnson and Chernik 1982). The role of such behavioral toxicology assessment has become increasingly important because substances with little or no disruptive behavioral or pharmacological effects are not regarded as having significant abuse liability. In contrast, compounds that are used even sparingly which produce marked disruptive changes are considered to have high abuse liability. Since drugs may fall anywhere on the continuum defined by these parameters, relative abuse liability is most effectively determined by a comprehensive assessment of these interactive dimensions.

A relevant issue that must be addressed when conducting these studies is whether the procedure distinguishes between drug-induced sensory. decrements (or improvements) on the one hand, and motor impairment on the other. While it is quite clear that relatively large doses of CNS depressants will sedate a subject so that he is incapable of performing, these types of studies do not provide a complete profile of the drugs being assessed. Rather, the determination of the threshold dose for performance decrement and the duration of such decrement more appropriately characterize the behavioral toxicity of a compound. Recently, performance decrements

that occur the day after a hypnotic is used ("hangover effect") have been studied more closely (Johnson and Chernik 1982; Hindmarch 1980; Wittenborn 1979). These studies have been generated primarily in response to the Institute of Medicine's report dealing with the issues surrounding the relationship of short- versus long-acting hypnotics and performance decrements (Solomon 1979).

The assessment of performance is also useful in the evaluation of subjects on chronic methadone maintenance (Rothenberg et al. 1977) and the enhancement of performance after caffeine and amphetamine (Weiss and Laties 1962). Basic changes in auditory and visual thresholds following marijuana administration have also been documented (Caldwell et al. 1969).

Acute studies are conducted over the course of a few hours with appropriate collection of pre-drug control performance before administration. Depending on the procedure employed, the evaluation is conducted continuously, or in discrete sessions separated by standard time-out periods until the drug effect has peaked and waned. In studies designed to assess the "hangover effect," the subject first undergoes an assessment of performance during the day, and then receives the drug either later in the day or at bedtime. Performance is again assessed at various times the following day.

Procedures typically employed include visual tracking (Borland and Nicholson 1974), auditory vigilance (Jones et al. 1978), and tests such as continuous arithmetic (Epstein and Lasagna 1968). time estimation (Pfaff 1968), free recall (Murdock 1962), and digit symbol substitution (Wechsler.1944). In addition, some procedures are designed to mimic real life situations such as automobile driving (Biehl 1979; Hindmarch et al. 1977), while one study has actually employed real-life driving in downtown traffic (Klonoff 1974).

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B. Procedures for Assessing Opioids

1. Characterization of Opioid Drug Effects

a. Acute Drug Effects

i) Analgesia

Methods of assessing the analgesic efficacy and potency of opioids are greatly influenced by the singular pharmacological properties of this class of drugs - which includes not only the opiates and their semisynthetic and synthetic derivatives with both morphine-like and morphine antagonist properties, but also a large and growing number of chemically unrelated compounds with similar disparate attributes - linked together in that they are believed to act upon the same family of CNS receptors, though with different affinities and intrinsic activities. Among their most distinctive features are that they include some of the most potent and universally efficacious drugs for the control of clinical pain and that their analgesic properties are greatly influenced by their repeated use and by prior exposure to drugs of the same class. These factors are important determinants not only of the setting and subject/patient population in which opioids are evaluated, but also of how opioids are evaluated for their analgesic efficacy.

The analgesic properties of most opioids are readily demonstrated in double-blind, controlled clinical trials employing categorical or visual analogue scales of pain intensity or pain relief. Moreover, in clinical assays of graded doses of opioids in patients with either postoperative or cancer pain, the analgesic response [measured in terms of pain intensity reduction or pain relief] has been observed to be linearly related to the logarithm of the dose (Houde et al. 1965). Relative analgesic potency assays comparing graded doses of parenteral morphine to those of other opioids have shown remarkably consistent results in terms of the cusum scores of these parameters of pain relief (SPID, TOTPAR) in studies of patients with postoperative and cancer pain (Wallenstein and Houde, 1975).

Unlike many nonopioid analgesics, the opioid's can be administered by several parenteral or enteral routes. However, their potencies are substantially influenced by the route of administration (Beaver et al. 1977). Flexibility in dose and route of administration provides an opportunity to evaluate the opioids in a wide variety of pain models, but, since many have substantial abuse liability, they are generally tested in hospitalized patients with severe or acute pain. Graded parenteral doses are usually the most efficient and often the only feasible method of administering these drugs in this setting. The most frequently employed pain model used for assaying patient opioid analgesics is postoperative pain, although analgesic assays have also been carried out in patients with cancer, biliary or renal colic, myocardial infarctions, severe or extensive burns, and women in labor (Lasagna 1960).

Although the effects of various opioids can be demonstrated in a variety of laboratory models employing experimentally induced pain, these techniques have not consistently and accurately predicted the clinical efficacy of new analgesics (FDA Guidelines, 1979). However, some of the psychophysical scaling techniques which were developed using normal volunteers have been applied to the clinical setting and have been useful in distinguishing the sensory and hedonic actions of morphine from those of diazepam (Gracely et al. 1978). Psychophysical procedures which assess pain in its different dimensions have also provided useful guides to the appropriateness and usefulness of opioids in certain chronic pain syndromes (Sternbach 1978).

The design of a clinical analgesic study of a new opioid will primarily be determined by the role it is expected to fill - or the opioid that it is expected to replace - in the therapeutic armamentarium. Drugs that are expected to substitute for codeine are commonly tested orally against codeine or propoxyphene, either alone or in combination with aspirin, acetaminophen or one of the newer non-steroidal antiinflammatory drugs. These studies are most frequently carried out in patients with postpartum pain, oral surgery pain, headaches, or rheumatic and orthopedic pains (Beaver, 1966). A variety of acceptable experimental designs are employed including single fixed dose comparisons of the test drug with a known analgesic standard and placebo control, parallel line assays of graded doses of the test drug and standard, with or without a placebo control. Factorial studies have also been carried out of fixed doses of the test drug, standard drug, combined test and standard drugs, and a placebo control (Houde et al. 1960). Ordinal and visual analogue scales are most frequently employed, and the results analyzed using standard parametric and nonparametric statistical tests (Fucella et al. 1977; Quiding et al. 1981). Relative oral/parenteral analgesic assays can also be carried out using graded doses of the two forms of the drug and a double placebo technique in which each study medication consists of both a capsule (or tablet) and an injection, one containing the active drug and the other a placebo (Beaver et al. 1967).

Opioids that are being considered as analgesic substitutes for morphine or its surrogates are frequently tested first in parenteral, graded dose, relative to analgesic potency assays with morphine as the reference standard. The relative potency comparison allows for an assessment of acute side effects or adverse effects at equianalgesic doses of the test drug and standard. These assays have been carried out as non-crossover, twin crossover (incomplete block) or complete crossover designed studies in hospitalized patients with moderate to severe pain following major surgery and in patients with advanced cancer (Wallenstein and Houde 1975). Categorical and VAS measures of pain intensity are customarily employed and standard parametric and non-parametric statistical analyses are carried out on the peak and total (SPIC, TOTPAR) scores. Multivariate analyses can be performed on the data using computer programs. Concomitant assessment of the patient's emotional status can also be carried out using the McGill Questionnaire (Heidrich et al. 1983), as well as by adjective check

lists and visual analogue measures of mood (Kaiko et al. 1981a). In addition, differential effects on mood can be demonstrated between morphine and some of the newer nonsteroidal antiinflammatory drugs in doses which are equianalgesic in terms of measures of pain intensity (Wallenstein 1981a,b). In similar analgesic assays, equianalgesic doses of morphine and heroin produced almost identical changes in mood (Kaiko et al. 1981a,b).

Since the empirical clinical analgesic assay is meaningful only in terms of comparison between a test drug and a reference standard, differences between the test and standard drugs in cross-tolerance to a prior opioid will influence the estimate of their relative potency. That effect appears to be minimal in most studies of postoperative and postpartum pain, and even in cancer pain when the test and standard drugs are different from the prior medication, and when prior opioid exposure has not been excessive in dose, frequency, or duration. However, when assaying agonist/antagonist analgesics this can be a problem because sensitivity to the antagonist actions is directly proportional to the degree of physical dependence, and this effect can override both the agonist actions of the test drug and the diminished efficacy of the standard drug as a consequence of cross-tolerance (Houde 1979).

Assessment of analgesic potency based on chronic administration of opioids has been limited and tends to be confounded by a large number of uncontrollable variables which can develop in the course of the analgesic assay. Nevertheless, short-term repeated dose comparisons of fixed doses of opioids have been carried out in a noncrossover design. In these studies, the patients received the test or standard drug for periods of up to two to three days, on request (prn), for moderate or severe pain. Ordinal scale measurements of pain intensity and pain relief were made on the first, second, and third days of the study prior to and at 1/2, 1, 2, 3, 4, 5, 6, 7, 8 hours following study medication, or until pain returned to premeditation level (Wang et al, 1981; Ouellette, 1982). These studies provide comparisons of the analgesic effects of the test and standard drugs on the first day with those of the second and third days. Proximate plateau plasma concentrations of the drugs will be reached at that time if their terminal elimination half lives are sufficiently short, as they would be with morphine, the usual standard in these studies. Graded doses of at least the standard drug are recommended as an internal control - or measure of the sensitivity of the study - since placebo controls without rescue medications would be inappropriate in a double-blind, repeated dose study of this design.

ii) Electroencephalographic (EEG) activity and sleep

As mentioned in the General Methods Section, the EEG is used to measure both the acute effects of drugs and long-term effects on the sleep-awake cycle. Almost all studies to date have used visual inspection techniques to characterize the EEG profile of opioid administration. In general, morphine or heroin acutely administered to nontolerant, nondependent subjects produces a number of changes

in the EEG consisting of: slowed alpha frequency, appearance of delta activity, and an increase in theta activity (for review, see Martin and Kay 1977). Fink et al. (1968), Zaks et al. (1969), and Volavka et al. (1970) demonstrated that heroin-induced changes in the EEG were time dependent and could be divided into an early response (first 4 minutes) and a later response (5-32 minutes). The most prominent effect was that the alpha activity was increased early in the response and subsequently decreased in the late response. Additionally, these studies showed that these EEG effects of heroin could be reversed or blocked by naloxone. Similar techniques have been applied to assess the acute effects of methadone (Isbell et al. 1947) and cyclazocine (Fink et al. 1969).

The use of power spectral analysis to quantify the effects of opioids has been relatively limited. Volavka et al. (1974) demonstrated that the above-mentioned changes in EEG activity were related to other physiologic measures such as respiratory rate and heart rate, and the behavioral measures of subject's mood. Power spectral analysis has also been used to monitor the EEG changes in heroin addicts during induction and maintenance on methadone (Feinstein and Hanley 1975). The EEG effects of heroin were characterized by a prominent, sharply peaked narrow band (9-10 Hz) of activity. When the subjects were started on methadone, this alpha peak was substantially attenuated and the predominant frequency was shifted to 11-12 Hz. In one subject who continued to use heroin (verified by urinalysis), these shifts did not occur.

Studies on the effects of acute opioid administration on sleep-awake patterns have been limited to only a few laboratories where such extensive amounts of data can be gathered. Kay et al. (1979) compared the effects of acute morphine, heroin, and methadone in nondependent opioid abusers using double-blind, cross-over design. Subjects were given single i.m. doses of drug or placebo at weekly intervals. Each experiment consisted of one adaptation night followed by an injection night. All three compounds produced similar changes (as revealed by computer-derived bisector analysis) in the EEG and muscle activity. These included increased time awake, increased muscle activity, increased alpha activity, and decreased theta activity and decreased spindling. Using standard bioassay techniques (Finney 1964), heroin was about twice as potent as morphine, which was found to be equipotent with methadone. Other physiologic measures such as ocular activity and respiration correlated very well with the EEG sleep stages.

iii) Gastrointestinal motility

The opioids are the most effective antidiarrheal drugs currently available. Procedures for assessing the passage of intestinal contents through the G.I. tract have been developed and incorporate one of three basic designs: 1) monitor the appearance of an orally ingested dye in the feces (Rothman and Katz 1964); 2) monitor the progress of a barium-treated meal through the G.I. tract using X-ray technology (Manousos et al. 1967); and 3) intubation (Hunt and Spurrell 1951) for sampling gastric contents. The effects of acute doses of various opioids can then be assessed by the percent of

retarded progress of a meal through the G.I. tract. A continual slow passage of markers through the G.I. tract is indicative of a lack of tolerance to the constipating effects of opioids. Tolerance to the effects of opiates on gastrointestinal motility develops only extremely slowly. In man, tolerance to the constipating effects of methadone may become apparent after as long as three years of continual use (Kreek 1973; 1978).

iv) Cough

Procedures for assessing the antitussive effects of opioids have relied mainly on the use of subjects with pathological cough (e.g., obstructive emphysema or chronic bronchitis) rather than experimentally induced cough (e.g., inhalation of noxious vapors). The significant developments in this regard relate mainly to methods utilized to record the incidence and severity of coughs. Sevelius and Colmore (1966) developed a method that uses a contact throat microphone coupled to a voice-activated tape recorder via a long flexible cord. This provided the subject essentially 'unrestrained movement within the private room. Subjects reside in the room for at least 6 consecutive days; the first 2 days are used to record control cough levels. At a specified time (usually in the morning) subjects receive either codeine, placebo, or a dose of test substance. Cough rates are then calculated on an hourly basis until the next morning. The number of coughs after medication is represented as a percent of the number of coughs after placebo.

One method of experimental induction of cough utilizes citric acid aerosal spray (Bicker-man 1956). Normal subjects are used, and after receiving placebo or an antitussive, are exposed to the spray. The frequency of coughs is recorded and used as an index for the degree of cough suppression.

2. Opioid Physical Dependence Potential

a. Tolerance to Drug Effects

The nature and characteristics of the development of tolerance to the effects of opioids in man have been extensively studied. The basic premise behind the techniques employed to study tolerance relates to obtaining accurate measures of dose-related drug effect in the non-tolerant or opioid-free subject first. Then, once the treatment regimen has been established, controlled reassessments of the effects of single doses of the same opioid or a test compound (cross-tolerance evaluation) can begin. This is most effectively accomplished when multiple doses are studied. Thus, a ratio of the effective doses in the nontolerant and tolerant state can be calculated and becomes the "tolerance index" for that compound (Martin and Fraser 1961).

Numerous problems exist when attempting to quantify the degree of tolerance to opioids. First, because of different durations of action, the time between the last maintenance dose and the administration of the test dose for tolerance assessment can be critical. Predetermined objective criteria must be established in

order to maintain uniformity between test sessions. Another problem is that with repeated administration of opioids, the profile of effects changes. For example, non-tolerant subjects report feeling euphoric and sedate while tolerant individuals report apathy, anhedonia, and withdrawal from social interactions (Haertzen and Hooks 1969; Martin et al. 1973).

b. Withdrawal from Chronic Drug Administration

Procedures for assessing the dependence potential of opioids in man have focused upon three main areas: substitution, single dose suppression, and primary dependence. Typically, individuals with a history of opioid use are employed since the procedures necessitate a chronic steady state preparation.

In the substitution procedure, subjects are maintained on morphine at a dose of 240 mg/day, s.c., given in divided doses. This treatment is continued for 30 days,after which test procedures can be initiated. Under double-blind conditions and beginning with the evening dose (e.g., 10 p.m.), a dose of a test substance, placebo, or the usual morphine dose is administered. This substitution is continued for 24 hours during which the subject is observed at 1-hour intervals. Signs and symptoms such as restlessness, emesis, fever, hyperpnea, blood pressure, and body weight are scored according to the Himmelsbach procedure (Jasinski 1977). The intensity of withdrawal (should these test substances fail to substitute for morphine) is scored on the basis of the signs present and include: Mild - yawning, lacrimation, rhinorrhea, perspiration; Moderate - muscle tremor, dilated pupils, goose flesh, anorexia; Marked hyperpnea, restlessness, insomnia, elevated blood pressure; Severe - emesis, diarrhea, weight loss. The original technique as proposed by Himmelsbach (1937a) was adapted to incorporate a point system based upon the composite signs of abstinence (Himmelsbach 1937b; Kolb and Himnelsbach 1938)) updated by Fraser and Isbell (1960), and was reviewed by Jasinski (1977). By systematically varying the dose of the test substance, the relative degree of its dependence potential can be determined.

The single dose substitution procedure (Himmelsbach and Andrews 1943) was based on the premise that a compound that possesses morphine-like activity should be able to suppress abstinence signs in morphine-dependent subjects. This relatively quick method of assessing a drug's dependence potential is conducted in subjects that are stabilized on morphine as described above. At a specific time, the morphine injections are terminated and the time course of withdrawal is recorded. At 30 hours after the last morpine injection, a dose of the test compound, placebo, or the normal morphine dose is given and the evaluations continued. The relative dependence potential of a compound is thus defined by its capacity to ameliorate the signs and symptoms of withdrawal. Morphine dependence is then reestablished for 1 week, at which time another experiment is performed.

The conduct of primary dependence studies on opioids has not been utilized as extensively as the substitution techniques. This is

mainly due to the paucity of suitable volunteer subjects and the concern over the toxicity of the test compounds during long-term administration. While the chronic administration of a compound is considered to be the definitive test of its dependence potential, this procedure is rarely performed first and usually is only incorporated after the results of substitution or single dose suppression studies are known. The procedure employs the use of doses of the test compound that are equivalent to (i.e., similar analgesia, suppression scores, degree of miosis, etc.) 240 mg of morphine (Jasinski 1977). Care must be exercised to avoid the accidental accumulation of drug or metabolites that result in toxic reactions. Typically, the length of exposure is 18-20 days followed by 10 days of placebo administration. Alternatively, naloxone can be administered in order to precipitate withdrawal (Jasinski and Nutt 1972), althougti this procedure is not widely used. Regardless of the method used, the appearance of signs and symptoms of abstinence is graded and the relative degree of dependence is determined.

3. Opioid Abuse Liability

a. Drug Self-Administration

Because of numerous medical and ethical considerations, unresricted self-administration of opioids such as morphine or heroin is not possible. However, procedures that employ limited access have been developed and provide ample opportunity to study the reinforcing properties of opioids in human volunteers residing in an inpatient ward (Mello et al. 1981, 1982). In these studies, heroin was available every 6 or 8 hours and was self-injected (under supervision by a physician) at a unit dose of 10 mg, i.v. The contingency placed upon the subjects was that they work for points that could then be used to "buy" the heroin dose. This was accomplished using standard operant procedures that employed a fixed ratio 300/fixed interval 1 second schedule of reinforcement. As an added incentive for the subjects to remain on the research ward, points could also be earned for money which would be paid upon completion of the study.

Once stable response patterns are established, various manipulations of the experimental conditions can be employed. To date, no studies have been conducted that substitute unknown compounds for the heroin. Rather, studies have been directed at pharmacological interventions which include observing the changes in heroin self-administration during chronic naltrexone (Mello et al. 1981) or buprenorphine (Mello et al. 1982). Both naltrexone and buprenorphine significantly decreased the number of heroin self-ingections as compared to placebo conditions. Thus, these studies satisfy the three criteria defined previously: optional drug injections, various experimental manipulations were performed, and the availability for heroin self-injection was over a 30-35 day period.

An alternative procedure employs subjects that are receiving methadone as a maintenance therapy for opioid dependence (Stitzer et

al. 1979, 1983; McLeod et al. 1983). In the studies by Stitzer et al. (1979), participating subjects were maintained on an outpatient basis but were required to attend the clinic each day for their dose of methadone. On two days of the week, immediately after consuming their regular dose of methadone, subjects were offered a choice between an additional dose of methadone (0, 1, 5, 10, 25 or 50 mg) and money (either $1 or $5). The selected item was given immediately. In addition, subjects completed a 60-item symptom check-list four times a week in order to assess signs of opioid withdrawal. Urines were also analyzed for illicit drugs. These studies demonstrate that methadone serves as reinforcer in methadone-maintained subjects and that the relative frequency of choosing methadone over money increased. as the dose of methadone was increased. Further, the number of choices for methadone was greater when the alternative was $1 when compared with $5. This procedure provides an excellent model of human abuse liability testing and can be expanded to include the assessment of other opioids, drugs belonging to different classes, and different alternative choices.

McLeod et al. (1983) utilized methadone-maintained subjects that resided on a research ward. Subjects regulated their own methadone dose by completing a fixed number of responses on an operant console during a 6-hour interval. Both constant and progressive ratio procedures were used. Non-contingent pretreatment with methadone reduced methadone self-administration. Subjects who required an increasing number of responses (i.e., progressive ratio) for a 4 mg unit dose of methadone, were more likely to detoxify than those whose response requirements remained constant.

b. Self-Report of Drug Effects

The present instrument used to measure the subjective effects of acutely administered opioids is the single dose opioid questionnaire originally developed by Fraser et al. (1961). It consists of four questions, the first of which simply determines whether the subject feels the drug or not. Question two asks the subject to identify the drug by comparing it with prototypic drugs of various classes. The various physiological sensations are assessed in question three while question four asks the subject to rate his degree of "liking" of the drug. Concomitant with this assessment, observers blind to the experiment rate the subject using similar questions.

The Morphine-Benzedrine Group Scale (or MBG) of the Addiction Research Center Inventory (ARCI) is a multiple scale questionnaire that has been used to identify compounds that produce opioid-like effects (Jasinski et al. 1971). Morphine-like compounds. will elevate the scores on the MBG scale in a dose-related fashion, so that bioassay statistics (Finney 1964) can be used to determine relative potencies between a standard (e.g., morphine) and a test compound. With the development of opioids that possess mixed agonist/antagonist effects, the other two questionnaires, Pentobarbital, Chlorpromazine, Alcohol Group Scale (PCAG), and the Lysergic Acid Diethylamide Scale (LSD) must be used in order to characterize the full profile of behavioral effects of a test compound (Jasinski 1977).

Such studies are usually conducted within a crossover design in which each subject receives two or three doses of the standard drug (e.g., morphine), an appropriate blank or placebo, and two or three doses of the test drug. All drugs are given under double-blind conditions. Double-dummy procedures are employed if the test drug is given orally and is to be compared to parenterally administered morphine. This entails giving the subject both an injection and a liquid (or pill) to consume for each assessment. Thus, on placebo days, the subject will receive a saline injection and drink a glass of the liquid vehicle (usually orange-flavored Tang or equivalent). Drugs are administered in random order with a minimum of 7 days between sessions. Questionnaires are completed a number of times after drug administration. The responses are quantified using a standard scoring system, and dose response curves are constructed using the mean responses for the standard test drug.

c. Behavioral Toxicity

Procedures for assessing the toxic effects of opioids on behavior have been limited in scope. The two main studies in the literature employed subjects currently enrolled in a methadone maintenance program and compared them with matched non-dependent controls (Gordon 1970; Rothenberg et al. 1977). Gordon (1970) assessed single and choice reaction times to a visual stimulus. Subjects were seated in front of a console that contained 6 neon lights in a row on a display screen and 6 corresponding buttons on a panel parallel to the table top. Lights were programmed to remain lit until a response was made. Three basic conditions were studied: simple reaction time, multiple-discrimination-multiple-response, and multiple-discrimination-single-response. Waiting periods (from completion of response to next stimulus presentation) were varied randomly. The single reaction time required that the subjects simply depress the button that corresponded to the illuminated light. The multiple discrimination-multiple-response condition required that the subject depress the buttons in the identical sequence that the lights were illuminated. The multiple-discrimination-single-response condition required that the subject simply select one of the buttons in the sequence of up to 6 stimuli. Methadone-maintained subjects achieved the shortest reaction times; this trend was consistent across the different experimental conditions.

Rothenberg et al. (1977) also used a visual discrimination task except that the environment was much more rigorously controlled than in the previous study. Between 1 l/2 and 2 1/2 hours after their morning dose of methadone, subjects were placed in the apparatus (head restraint and chin support) in order to minimize head movement-induced artifacts. Four different tests were administered including letter recognition (3 different letters), continuous performance (interval between test stimuli was 10 msec), reaction time (the letter X was flashed on the screen and subject's time to depress a microswitch was recorded), and reaction time with money incentive (same conditions as previous test except that subjects were paid for each response that was faster than a predetermined value). Non-opioid-dependent subjects were similarly tested under

non-drug conditions and after receiving various doses of methadone. Methadone-maintained subjects consistently performed faster than controls, and money incentive reduced reaction times equally for both groups. Acute doses of methadone produced dose-related increases in reaction time.

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C. Procedures for Assessing CNS Depressants: Sedative/ Hypnotics, Anesthetics, Anxiolytics and Antihistamines.

1. Characterization of CNS Depressant Effects

a. Acute Drug Effects

i) Anxiolytic and Sedation

Objective measures of anxiety in human subjects are relatively difficult to obtain. Muscle tension (which can be effectively measured) is not a direct correlate of anxiety. Thus, almost all procedures for assessing the effectiveness of these compounds in reducing anxiety have employed verbal self-reports of a subject's behavior (McReynolds 1968). One study by Kelly et al. (1969) has attempted to incorporate concomitant measures of the clinical, psychological, and physiological components of anxiety and the effects of chlordiazepoxide on such measures. Chlordiazepoxide was found to produce improvements in self-ratings and those of clinical observers on anxiety and depression assessments, to decrease the dizzy factor score on the Clyde Mood Scale, and to decrease resting forearm blood flow.

While it is not clear whether the anxiolytic effect of these compounds is distinctly different from their non-specific effects, several procedures have been utilized to selectively parcel out the sedative/hypnotic effects of these compounds as reflected in studies evaluating sleep (Kay et al. 1976).

ii) Electroencephalographic (EEG) Activity and Sleep

While procedures for assessing the direct effects of sedative/ hypnotics on human EEG are available, they have not, as yet, been systematically applied to characterize these compounds. Most studies have concentrated on subjective ratings of the relative amounts of various EEG waveforms such as alpha, delta, theta, and beta activity. In this regard Malpas et al. (1970) compared the EEG effects of nitrazepam with those of amylobarbitone sodium. Using a double-blind cross-over design, subjects received either 5 or 10 mg of nitrazepam, 100 or 200 mg of amylobarbitone, or placebo. Criteria for scoring EEG activity were established as follows.

0 - Epochs containing 50% or more alpha activity
1 - Epochs containing less than 50% of alpha but no paroxysmal features of sleep
2 - Epochs containing one paroxysmal feature of sleep
3 - Epochs containing delta activity more than 50% of the time.

The values were then tabulated as a function of time and then total scores calculated to determine the sleep-awake profile. These investigators also used subjective mood ratings and measured psychomotor performance. Approximately 18 hours after a single dose, mood and psychomotor performance had returned to normal, but

EEG changes were found to persist after the highest dose of nitrazepam. These effects were indicative of a drowsy state.

Procedures for assessing the effects of these compounds on sleep have been relatively well developed, refined, and validated in the clinic. In these types of studies, drugs are assessed with respect to three major criteria: the effectiveness of inducing and maintaining sleep, development of tolerance to the hypnotic effects, and effects upon individual sleep stages manifested by clinical signs and symptoms. Thus, by employing quantified EEG procedures, it is possible to replace verbal reports of how well a subject slept with an objective measure of the sleep stages during the night. Recently, Kay et al. (1976) reviewed the pharmacology of sleep. Barbiturates, benzodiazepines, nonbarbiturates, and alcohol have all been studied extensively using a variety of techniques for their effects on sleep. Few studies, however, have attempted to provide comparative information among several compounds. Hartmann (1968) compared the effects of pentobarbital, chlordiazepoxide, Ro 5-6901, and amitriptyline on sleep patterns in normal volunteers. All drugs except amitriptyline increased total sleep. REM sleep was markedly suppressed by amitriptyline and marginally suppressed by pentobarbital while chlordiazepoxide and Ro 5-6901 did not affect REM sleep.

2. CNS Depressant Physical Dependence Potential

a. Tolerance to Drug Effects

Procedures for determining the degree to which tolerance develops to the effects of these compounds have not been extensively utilized. Essentially, only the hypnotic effects of the barbiturates, benzodiazepines, and miscellaneous compounds have been the subject of tolerance assessment. These techniques are inherent in the procedures described in the previous section on electroencephalographic activity and sleep.

Tolerance to the hypnotic effects of barbiturates occurs very rapidly; in fact, blood levels upon awakening from a single dose are higher than when the subject originally fell asleep (Harvey 1980). The extent to which tolerance develops to the barbiturates depends, in part, upon the duration of action and frequency of use. Wikler (1976) demonstrated that the degree of tolerance to secobarbital or pentobarbital could be minimized by enforcing a once-a-day treatment with clinically acceptable hypnotic doses. When such controls over the subjects' behavior is absent, they may experience less satisfying sleep (due to the drug's effect on specific sleep stages) and as a result, increase their dosage. This practice may be responsible for the rapid development of tolerance.

Thus, while no systematic procedures are currently in use to compare the degrees of tolerance to the sedative effects of these compounds, a few points should be followed. First, the doses of the compounds to be compared should be optimized to produce qualitatively and quantitatively similar degrees of sedation. This may require using the pharmacokinetic profile of each drug in preparing the treatment

regimen. Secondly, the duration of treatment should be comparable to ensure similar degrees of exposure. And thirdly, objective measures of drug effect (e.g., latency to sleep and various sleep stages, duration of sleep, number of awakenings, etc.) should be obtained on a regular basis during control and drug phases.

b. Withdrawal from Chronic Drug Administration

Procedures for assessing the dependence potential of sedative/hypnotics in man have evolved over the past 30 years. The early studies of Isbell et al. (1950, 1955) demonstrated that chronic administration of intoxicating doses of barbiturates or alcohol produced a pronounced abstinence syndrome when treatment was discontinued. In addition, the withdrawal syndrome was significantly different from that observed following withdrawal from opiates.

While rating scales for opiate or opioid withdrawal are relatively well established (Himmelsbach 1941), there is no such uniformity of procedures for the evaluation of sedative/hypnotic dependence. The first signs to appear after barbiturate withdrawal include: anxiety, nervousness, tremors, weakness, anorexia, nausea, vomiting, and insomnia. Acute weight loss also accompanies these- signs. Unlike opiate withdrawal, the signs and symptoms of barbiturate withdrawal may increase in intensity to the extent that grand ma1 convulsions, hallucinations (both auditory and visual), and frank delirium occur. Hyperpyrexia followed by death has been reported (Fraser et al. 1953).

The first use of the EEG as a measure of barbiturate withdrawal was reported by Fraser et al. (1954, 1958). Abrupt termination of a dose of 0.2 g of pentobarbital per day for as long as six months was followed by no significant effects. About one third of the subjects that received 0.4 g for 3 months experienced paroxysmal EEG changes (e.g., random spikes, fast waves, slow waves) in lieu of other significant clinical signs of withdrawal. Minor signs of withdrawal and about 50% abnormal EEG's were characteristic of abrupt withdrawal from pentobarbital at a dose of 0.6 g for 1 to 2 months. Seizures, delirium, and all minor abstinence signs were evident in subjects upon withdrawal from high doses (0.9 to 2.2. g/day X several months) of pentobarbital.

Benzodiazepines have, for the most part, replaced barbiturates as the treatment of choice for sedation and hypnosis. Consequently, procedures for assessing their dependence potential have been reported. Hollister et al. (1961, 1963) demonstrated that the termination of high doses of chlordiazepoxide or diazepam in schizophrenics resulted in signs of withdrawal that resembled the barbiturate withdrawal syndrome. Studies demonstrating the relative dependence potential of various barbiturates have been reviewed by Woods et al. (1983). The lack of uniformity of experimental procedures between the various studies has made it impossible to distinguish between the various benzodiazepines, if indeed such a distinction exists.

3. CNS Depressant Abuse Liability

a. Drug Self-Administration

Procedures for measuring the self-administration of sedative/hypnotics by human subjects have been validated by experimental manipulation of the conditions surrounding drug availability including such factors as amount of work required to obtain drug and unit dose size (Bigelow et al. 1976a, 1976b; Pickens et al. 1977) and choice between different sedatives (Bigelow et al. 1976b; Griffiths et al. 1979, 1980).

One study by Johanson and Uhlenhuth (1978) used a paired preference procedure to assess the relative reinforcing efficacy of diazepam as compared to saline in normal subjects with no history of sedative abuse. Subjects did not choose any dose of diazepam over saline but did choose amphetamine over diazepam.

While some studies have assessed self-administration of these compounds in a treatment facility where patients merely ask for medication (Rothstein et al. 1976; Kryspin-Exner and Demal 1975), more recent reports were obtained in research settings employing more rigorous control over the drug delivery process. These studies typically use token economies (Bigelow et al. 1976a) in which subjects are required to perform work for a specific length of time in order to earn a specific number of tokens. These tokens can then be exchanged for drug. Surplus tokens are not carried over to the next day, but rather are cashed in for money to be paid to the subject upon discharge from the unit.

Most studies have been conducted with subjects that have current or past histories of sedative abuse. Bigelow et al. (1976b) studied the effects of varying the number of tokens required to purchase a single 30 mg dose of pentobarbital or a 10 mg dose of diazepam. Subjects were required to ride a stationary exercise bicycle for two minutes for each token. The number of tokens required to purchase the dose (drugs were available for 7hr/day) was randomly varied among 1, 3, 5, 8, and 10. Subjects generally worked for and subsequently consumed all doses of both drugs when the number of tokens required for purchase was 1 or 3. As the number of tokens for each dose was increased, however, the amount of drug earned correspondingly decreased. The results of this study provide a basic framework upon which to build a more complete program for assessing sedative self-administration by humans. In subsequent studies (Griffiths et al. 1979, 1980), it has been shown that subjects will generally prefer pentobarbital to diazepam over a fairly wide dose range.

b. Self-Report of Drug Effects

Subjective rating scales remain the primary means of assessing the effects of psychoactive compounds on mood and feeling states (Fraser and Jasinski 1977). The PCAG scale scores (Haertzen 1966) are particularly sensitive to feelings of lethargy, weakness, and loss of energy that characterize sedative/hypnotics. In order to obtain an

overall profile of drug effect, however, liking scores and the MBG scale scores are also calculated. Using this method, Fraser and Jasinksi (1977) demonstrated that pentobarbital and secobarbital produced dose-related increases in the above scale scores. Phenobarbital, while producing some increases in scores, was only one-fifth to one-seventh as potent as pentobarbital and secobarbital, and did not appreciably elevate MBG scale scores.

In a subsequent study, Jasinski et al (1981) compared the effects of various doses of pentobarbital with diazepam and chlordiazepoxide. In a double-blind crossover design, both diazepam and chlordiazepoxide were found to produce pentobarbital-like effects and euphoria. Diazepam was about ten times more potent than pentobarbital.

Two other procedures that have been used to characterize the mood effects are based upon a Mood Adjective Check List (MACL) for self-report of mood originally introduced by Nowlis and Nowlis (1956), and Magnitude Estimation (ME) introduced by Ekman (1967). Svensson et al. (1980) compared the efficiency of these two measures in evaluating the mood effects of diazepam and caffeine. The result of both scales indicated that diazepam decreased feelings of activation and extroversion and increased calmness. While the ME scale provided slightly better validity, it was harder for the subjects to complete.

c. Behavioral Toxicity

Numerous procedures for assessing the toxic effects of sedative/hypnotics on behavior have been developed, refined and validated. McNair (1973) reviewed the results of 101 studies that assessed the effects of antianxiety drugs on human performance. He grouped the 43 types of tests into four categories from high to low sensitivity. Among the highest were digit-symbol substitution test (DSST), driving accuracy, visual thresholds, and auditory flutter fusion. Among the low sensitivity tests were problem solving, visual and auditory vigilance, arithmetic, and learning nonsense syllables.

Studies that compare the psychomotor performance effects of various benzodiazepines and barbiturates have been reviewed recently by Johnson and Chernik (1982) with an emphasis on procedures designed to assess the "day-after" or hangover effect. Card sorting, tapping rate, symbol copying, and DSST were found to be among the most sensitive tests for assessing behavioral impairment after benzodiazepine administration. These effects were dose related, but inconsistencies with respect to plasma half-lives and duration of impairment were found (Johnson and Chernik 1982).

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D. Procedures for Assessing CNS Stimulants: Anorectics, Local Anesthetics, and Antidepressants

1. Characterization of CNS Stimulant Effects

a. Acute Drug Effects

i) Electroencephalographic (EEG) Activity and Sleep

The direct effects of CNS stimulants on EEG activity have been shown to be alerting or activating as determined by the qualitative techniques of visual inspection. The desynchronized pattern of EEG activity, characterized by a slight decrease in amplitude and an increase in predominant frequency, has been quantified by the use of voltage integration procedures (Goldstein et al. 1963). Although the use of power spectral analysis has not been employed extensively to assess the EEG effects of this class of compounds, a report by Gibbs and Maltby (1943) did describe a shift in the spectrum to higher frequencies following benzedrine.

ii) Appetite

Procedures for assessing the effects of stimulants on appetite have been developed for short-term, single dose experiments. Hoebel et al. (1975) utilized a procedure that tests a drug's effectiveness in reducing intake of a diet liquid meal product. Volunteers report to the laboratory having refrained from eating for 2 hours prior to lunchtime (12 noon). Using a double-blind cross-over design, subjects were given either placebo or 25 mg of phenylpropanolamine 30 minutes before lunch. Lunch consisted of a canned chocolate-flavored drink which was dispensed via a long straw from a graduated cylinder. The reservoir was hidden from the subject's view. Subjects were instructed to drink as much as they wished.. Upon completion of lunch they filled out questionnaires that related to the taste of the lunch, the reason for stopping, the amount that they consumed relative to the previous day, and the taste of the lunch relative to the previous day.

2. CNS Stimulant Physical Dependence Potential

a. Tolerance to Drug Effects

The assessment of tolerance to the effects of the CNS stimulants has been directed mainly at two of their pharmacologic effects: anorexia and mood elevation. Tolerance to the appetite-suppressant effects has been demonstrated to occur in numerous studies. It appears; however, that obesity has many complex components, at least one of which, the 'craving" for food, may interact with the evaluation of tolerance effects (Wooley and Wooley 1981).

The currently accepted criterion for the appetite suppressant effect is that weight is lost and not recovered. The fact that the rate of weight loss rapidly decreases over the course of treatment is taken as evidence of tolerance. Stunkard (1979) has suggested that these

criteria are not valid for assessing tolerance, since a deceleration in weight loss is common even in more drastic treatments of obesity such as jejunoileal bypass surgery. Additionally, the metabolic characteristics of the body change as a result of weight loss, and these changes should be taken into account when assessing tolerance. Food that has been ingested during a period of weight loss is more efficiently metabolized than when the caloric balance is in steady state (Keesey et al. 1976). A more appropriate determinant of whether tolerance has developed or not may be the degree of weight gain following cessation of drug treatment. Tolerance would be shown by a return to normal weight despite continued administration of the drug. Rebound hyperphagia and weight gain, upon withdrawal of the drug, would constitute a withdrawal reaction.

Tolerance to the mood elevating effects of CNS stimulants has been assessed and, in addition, is distinct, from the appetite-suppressant effects (Gunne 1977). Tolerance to the euphoric effects of amphetamine (as measured by a subjective questionnaire) was found to develop rather quickly over 14 days of daily treatment (Rosenberg et al. 1963). In addition, these authors demonstrated that there was no cross-tolerance to LSD. To date, no studies have been conducted to directly compare the degree of tolerance development to the subjective effects of CNS stimulants.

b. Withdrawal from Chronic Drug Administration

Only limited data are available on withdrawal from chronic CNS stimulant use, since experimental studies have rarely been undertaken, and virtually all reported observations have been made within the context of treatment programs. In addition., the difficulty in obtaining valid patient histories complicates determination of the exact profile of the CNS stimulant withdrawal syndrome. Amphetamine withdrawal has been characterized, however, by assessing affective states, sleep patterns, and MHPG excretion (Watson et al. 1972). Suprisingly. patients do riot seem to "crave" for amphetamine during this abstinence phase as patients withdrawing from opiates do for morphine.

3. CNS Stimulant Abuse Liability

a. Drug Self-Administration

Procedures for assessing self-administration of' i.v. cocaine have been reported by Fischman and Schuster (1982) with experienced cocaine users prepared with two indwelling Angiocath Teflon catheters, one for drug infusion and one for blood withdrawal. Subjects were instructed that each of two buttons would be associated with the same solution (drug or saline) throughout the study. On the first day, subjects were exposed to each solution and for the next 8 days were required to press the response button 10 times in order to receive an injection. Once a single response was made on a given button, the other one was deactivated. A total of 10 injections could be taken during a l-hour session with blood drawn prior to and after each injection followed by completion of the POMS and ARC1 questionnaires. After initial sampling on the

first day, subjects consistently chose cocaine over saline. Subjective ratings of drug effect correlated with the self-injection of cocaine. The most pronounced effects on subjective states, blood pressure, heart rate, and cocaine levels occurred after this initial injection.

b. Self-Report of Drug Effects

Studies assessing the subjective effects of CNS stimulants have been conducted using subjects with drug abuse histories (Martin et al. 1971; Jasinski et al. 1974; Fischman et al. 1976) and normal volunteers with no history of drug abuse (Johanson and Uhlenhuth 1980). In the former studies, subjects lived on the ward during their participation in the study. Martin et al. (1971) compared the subjective effects of several sympathomimetic amines with physiologic and behavioral effects. Amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate were given under double-blind conditions using a Latin square design. Subjects completed questionnaires every hour for 6 hours after drug administration. These scales consisted of the PCAG, MBG, BG, and a new amphetamine (A) scale which was constructed from significant items in the other scales. All compounds produced dose-related increases in MBG, BG. and A scale, as well as subject and observer liking. PCAG scale scores were also decreased, while the highest dose of all drugs increased LSD scale scores. These subjective responses correlated well with physiologic effects and allowed for valid estimates of relative potency measures.

Johanson and Uhlenhuth (1980) employed a procedure in which the subjects reported to the laboratory in the morning 3 times a week for each session. Subjects filled out a POMS form prior to each amphetamine or placebo ingestion and then again at 1, 3, and 6 hours post drug. The authors have used this procedure as a basis upon which to build a choice procedure for different drugs. Subjects associated certain colored capsules with drug effects, and during the latter part of the experiment they were allowed to request the capsule they preferred.

c. Behavioral Toxicity

Studies assessing the effects of CNS stimulants on psychomotor performance have used a number of strategies to detect increases or decreases in speed, error rate, and efficiency. In general, most CNS stimulants have been shown to enhance performance.

Early studies such as that by Seashore and Ivy (1953) and Somerville (1946) studied the effects of caffeine, amphetamine. and placebo on perception and motor skills in fatigued army soldiers. Performance was generally enhanced, but the differences observed between drug and placebo condition were small, probably because they used trained individuals that were already performing at peak levels. More recently Evans et al. (1976) studied the effects of various doses of dextroamphetamine on quantitative measures of psychomotor performance. Non-fatigued volunteers refrained from using any drugs for 18 hours prior to testing. Three measures of psychomotor

performance were used: the wobble board (Shipley and Harley 1971), the pursuit meter (Evans et al. 1973), and delayed auditory feedback (Hughes et al. 1963). There was some improvement in stability on the wobble board during the eyes closed condition as well as slight improvements in performance on the pursuit meter (but only at the 7 cycles/sec mode and not at 5 or 2 cycles/sec) that were dose related. No change in delayed auditory feedback performance was observed, however.

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E. Procedures for Assessing Cannabinoids

1. Characterization of Cannabinoid Effects

a. Acute Drug Effects

i) Analgesia

Clinical data on analgesic activity have generally been derived from studies assessing the effects of delta-9-THC or smoked marijuana on pain which have not yielded clear results. It appears, however, that delta-9-THC (5-20 mg) is effective in relieving the pain associated with' advanced stages of cancer (Noyes et al. 1976). While higher doses were effective in relieving pain, they were accompanied by significant side effects, including sedation and verbal impairment. In contrast, Hill et al. (1974) using experimental electrical stimulation were unable to detect analgesic activity after 12 mg of delta-9-THC.

While several of the newer synthetic cannabinoids are currently undergoing clinical evaluations as analgesics, it is clear that the most difficult problems associated with such assessments continue to involve the need for parceling out confounding side effects such as sedation and impaired verbal performances.

ii) Electroencephalographic (EEG) Activity and Sleep

Studies designed to assess the EEG effects of acute administration of cannabinoids have been conducted almost exclusively with delta-9-THC or marijuana via the oral or inhalation (smoked) route. Most of the past work was performed prior to the widespread use of computerized, power spectral analysis. In general, orally administered marijuana or THC has been reported to increase alpha activity and EEG synchronization (Hollister et al. 1970; Deliyannakis et al. 1970; Volavka et al. 1971, 1973; Tassinari et al. 1974). More recently, however, a study by Koukkou and Lehmann (19.76) utilizing spectral techniques to more accurately quantify the EEG effects of 200 mg/kg delta-9-THC showed that the predominant alpha frequency was decreased by THC. but the magnitude of change was related to the resting state and EEG baseline of each subject.

The effects of cannabis on sleep have been assessed using all-night EEG recordings in a laboratory setting (Barrett et al. 1974). Slow-wave sleep increases during the first four nights after smoking marijuana, though the amount of slow-wave sleep progressively decreased beyond that point until it was below normal levels. The suppression of slow-wave sleep persisted well into the post-drug period. These effects seem to be dose related in that higher doses actually overstimulate the subjects such that they sleep less. Pivik et al. (1972) compared the effects of delta-9-THC and synhexl on sleep patterns in normal subjects. Both compounds selectively increased stage 4 sleep while rapid-eye-movement or REM sleep was depressed. When a sleep deprivation procedure was employed,

however, subjects recovered from these effects much more rapidly when treated with synhexl than with delta-9-THC.

2. Cannabinoid Physical Dependence Potential

a. Tolerance to Drug Effects

Tolerance to the subjective and physiological effects of cannabis as compared to synhexyl was demonstrated by Williams et al. (1946). In this study measures were collected daily over a 39-day period, including rectal temperature, pulse, respiratory rate, blood pressure, body weight, caloric intake, EEG, sleep, and mood states. Pulse, caloric intake, and expressions of euphoria were all initially increased, but decreased after a few days of marijuana. A similar profile was noted for synhexyl. More recently, Fink et al. (1976) demonstrated tolerance to marijuana produced increases in pulse rate and alpha activity of the EEG as well as to the decremental effects of the drug upon short-term memory and reaction time. After low dose chronic administration of delta-9-THC, it is difficult to observe tolerance to subjective effects even though tolerance to the drug-induced tachycardia and dizziness is readily demonstrated (Hollister and Tinkleberg 1973). Such tolerance effects are clearly dose related, however, since they are most apparent after prolonged exposure to high doses.

b. Withdrawal from Chronic Drug Administration

Only limited data are available on procedures for assessing the signs and symptoms attendant upon cessation of chronic cannabinoid administration. Jones and Benowitz (1976), for example, gave subjects an oral 30 mg dose of delta-9-THC every 4 hours for 10 to 20 days. Autonomic signs of withdrawal included increased sweating, salivation, and tremors of the extremities. Milder signs included irritability, sleep disturbances, and anorexia, while nausea, vomiting, and diarrhea occurred in some subjects.

3. Cannabinoid Abuse Liability

a. Drug Self-Administration

Procedures for studying self-administration of cannabinoids have been established using basic operant procedures that employ marijuana cigarettes as the reinforcer (Mendelson et al. 1974, 1976). Subjects lived on a research ward during all three phases of the study: 5-day baseline, El-day marijuana smoking, 5-day post-marijuana. During their stay, subjects earned points by pressing a button on a hand-held portable manipulandum. Subjects could then "buy" a marijuana cigarette for 1800 points (the equivalent of 30 minutes of sustained button pressing) or save the points until the end of the study and exchange them for money (about 8.50 per 30 minutes). Once a subject decided to buy a marijuana cigarette, the points were immediately deducted from his running total and the cigarette was smoked at that time under staff supervision. Both "heavy" and "casual" users were studied. All subjects avidly worked for more points than were necessary to buy the number of cigarettes

they used, and as a result they earned a substantial amount of money as well. The procedure thus serves as' a basis for evaluation of other constituents of cannabis with respect to the maintenance of operant performance.

b. Self-Report of Drug Effects

Using the standardized ARCI, Isbell et al. (1967) demonstrated that subjects could not distinguish between marijuana and delta-9-THC. Jones and Benowitz (1976) administered the Profile of Mood States (POMS) questionnaire to subjects participating in a 30-day chronic marijuana study. Tolerance to the subjective effects (e.g., confusion, inertia, and vigor) of 210 mg/day of delta-9-THC was clearly evident within 3 days. In addition, using the Nurses' Observation Scale for Inpatient Evaluation (NOSIE-3O), tolerance to the decrease in social competence was also apparent by the 6th day.

Hollister and colleagues have systematically evaluated many of the constituents of marijuana, THC metabolites, and synthetic analogues of THC. In a summary of this work, Hollister (1974) showed that delta-8-THC differed from delta-9-THC in a quantitative fashion. Differences in relative potency were obtained with substitutions on the alkyl side chain. The metabolites 11-hydroxy-delta-9- and 11-hydroxy-delta-8-THC were both more potent than their respective parent compounds.

c. Behavioral Toxicity

Procedures for assessing the toxic consequences of cannabinoid administration have been developed for measures of both- verbal performances (e.g., "attention," "memory") and sensory-motor functions (e.g., reaction time, stimulus discrimination). Dornbush and Kokkevi (1976) assessed the acute effects of various doses of delta-9-THC or hashish (compared to placebo) upon digit spans, serial sevens, star tracing, and time estimation. The simple task (e.g., digit span) was unaffected by cannabinoid administration while performance on the more complicated tasks was impaired.

Numerous models of human memory assessment have been described (Delong and Levy 1974; Darley and Tinklenberg 1974) in which cannabinoids were shown to interfere with attention and decrease memory efficiency. Vachon and Sulkowski (1976) attempted to dissect the effects of marijuana on attention, memory, and psychomotor speed by means of numerous automated testing devices including the Continuous Performance Test (CPT) developed by Rosvold et al. (1956) and modified by Mirsky and Kornetsky (1964), and the Automated Digit Symbol Substitution Test (ADSST). A single dose of delta-9-THC (25 mg in a smoked cigarette) significantly decreased performance scores as a function of an increase in complex response times and the emmission of fewer responses.

Finally, the assessment of motor performance using an aviation instrument flight simulator involved subjects (licensed pilots) instructed to "fly" through each of four prespecified (and practiced) holding patterns (Blaine et al. 1976). Using

double-blind conditions, marijuana (0.09 mg delta-9-THC per kg) or placebo cigarettes were smoked during a lo-minute interval. Thirty minutes later the subjects began the simulations. There was a significant increase in the number of both major and minor errors, and an increased average deviation from the assigned flight sequence. This decrement in performance persisted for at least 2 hours after smoking and returned to control levels by 6 hours post drug.

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F. Procedures for Assessing Hallucinogens

1. Characterization of Hallucinogen Effects

a. Acute Drug Effects

i) Electroencephalographic (EEG) Activity

In general, LSD has been shown to increase the alpha frequency in patients with sensory defects (Korein and Musacchio 1968) and normal individuals (Shagass 1967). Reduction in the overall amplitude of the EEG has also been reported after LSD and mescaline (Monroe et al. 1957) and LSD-25 (Rodin and Luby 1966; Shagass 1967), while both frequency and power shifts have been quantified using spectral analysis after ditran and LSD administration (Itil and Fink 1966).

In a study using integrative techniques, Goldstein et al. (1963) demonstrated that a 1 microgram/kg dose of LSD decreased electrogenesis of the EEG of normal male volunteers, but not in chronic schizophrenic patients. The successive waves of the EEG were full-wave rectified and an oscillator was used to generate a train of pulses the frequency of which was directly proportional to the area under the rectified EEG. Thus, pulses per unit time were used to quantify the amount of energy contained in the corresponding epoch of EEG activity. Recordings from the occipital area were analyzed because of alpha rhythm prominence. After 10 minutes of control recording, the subjects were allowed to rest for 20 minutes. This cycle was repeated to obtain five lo-minute sessions at 10, 30, 60, 90, and 120 minutes. Drug or placebo was administered orally after the first control session.

Doses of LSD (0.001-0.002 mg/kg) were administered intravenously over a period of 5 minutes. Twenty-to 60-second epochs of EEG activity were sampled and subjected to computer analysis. Samples were taken before injection and 15 to 25 and 40 to 50 minutes post injection. LSD caused an increase in all frequencies, a decrease of slow activity, and an increase in beta activity.

2. Hallucinogen Physical Dependence Potential

a. Tolerance to Drug Effects

Physiologic measures of pupil diameter, patellar reflexes, blood pressure, heart rate, and body temperature are typically used for assessing the development of tolerance to the hallucinogens. Subjective effects are assessed using the 70 item LSD questionnaire (Isbell et al. 1956) and a clinical ordinal scale sensitive to expressions of anxiety at the low end, and perceptual distortions as well as hallucinations at the high end. While some exceptions have been found, chronic treatment with LSD leads to a rapidly developing tolerance to these effects (Isbell et al. 1956). Cross-tolerance in LSD-treated subjects to the acute effects of N,N-dimethyltryptamine (DMT) has also been found to occur for the above physiologic effects as well as subjective reports after drug administration (Rosenberg et al. 1964).

Wolbach et al. (1962) studied the effects of chronically administered mescaline and found tolerance to both the subjective effects and the mydriasis. In addition, marked cross-tolerance to the effects of LSD on subjective response, pupillary diameter, and blood pressure were found. The reverse situation was also observed (i.e., subjects tolerant to the effects of LSD were cross-tolerant to mescaline).

b. Withdrawal from Chronic Drug Administration

While the degree of tolerance that develops to the effects of these compounds is quite extensive, no signs of abstinence have been reported in subjects treated chronically with LSD.

3. Hallucinogen Abuse Liability

a. Drug Self-Administration

To date, no systematic studies have been undertaken to characterize the profile of hallucinogen self-administration in man. There are obvious difficulties in conducting such studies, which require rigorous control of the subject's environment during self-administration, including lighting conditions and visual and auditory stimuli as well as social contacts.

b. Self-Report of Drug Effects

Procedures for assessing the subjective effects of the hallucinogens have centered around the use of questionnaires that are completed at regular intervals after drug administration. Using the MMPI, Belleville (1956) found that LSD elevated the Psychasthenia, Schizophrenia, Paranoia, and Taylor Anxiety scales. Klee et al. (1961) found that the clinical grades of LSD reaction were dose related. These were found to range from expressions of anxiety and nervousness to perceptual distortion or hallucinations without recognition of the drug-related nature of these effects.

The LSD Significant Scale of the ARCI (Hill et al. 1963a) contains items that are related to expressions of euphoria and sedation, anxiety, restlessness and dysphoria, disruption of thought processes, paresthesia, perceptual changes, changes in self-image, and autonomic changes. The specific questions that relate to the above effects are outlined by Martin and Sloan (1977). Lower doses of LSD were found to produce expressions of euphoria, while higher doses were associated with nervousness and anxiety (Hill et al. 1963b).

Snyder et al. (1974) studied the stereospecific actions of DOET in man using the Lon Outpatient Mood Scale, Outpatient Symptom Check List, Hildreth Current Reaction Scales, and the Block Design and Digit Span subtests of the Wechsler Adult Intelligence Scale. Subjects were also evaluated using a modified clinical grade scale. All drugs and placebo were administered under double-blind conditions while the subjects resided in a quiet comfortable room. A variety of art objects as well as records were available. The (-)

or "R" isomer was found to be four times more potent than the (+) or "S" isomer. This study represents a novel approach to confirming the active chemical conformation of a hallucinogen at its receptor site.

C. Behavioral Toxicity

Procedures for assessing the effects of hallucinogens on psychomotor performance have mainly measured visual acuity and reaction time. Edwards and Cohen (1961) studied the effects of LSD on visual illusion, tactile sensibility, and reaction time in normal volunteers. Subjects were tested for their ability to detect colors while seated 10 feet from a translucent light filter (12.5 cm diameter) surrounded by a black panel. By randomly presenting different colors at various intensities using the Method of Constant Stimuli, the threshold for detection of- each color could be obtained. LSD had no effect on color detection, but size constancy (assessed by maneuvering two triangles until they appeared to be the same size) was affected, with the subjects becoming more susceptible to illusions of similar sizes. LSD also significantly elevated the difference threshold in a warmth detection discriminator procedure and increased visually determined reaction times. When a buzzer was used instead of light for reaction time determinations, no significant drug effects were observed.

Hartman and Hollister (1963) compared three hallucinogens (mescaline, LSD, psilocybin) for their effect on color perception using the Farnsworth-Munsell hue discriminator which consists of 85 colored buttons arranged in four banks of graded hues. The buttons are mixed thoroughly and the subjects are required to replace them in the correct sequence of graded hue. After-images were also determined by having the subjects look at a bright light for 5 seconds, close their eyes, and then name and pick out the colors that they perceived. All three compounds impaired the subjects' ability to distinguish the colors. LSD produced more disruptive effects in the red-yellow and yellow-orange range, while mescaline increased errors throughout a wider range. Psilocybin increased errors in all areas except green-blue. LSD and mescaline caused more colors to be evoked by flicker, but only psilocybin significantly increased the duration of after-image. Thus, the results of this study indicate that tests requiring subjective reports of color evoked artificially are more sensitive to hallucinogens than tests of color perception based upon hue discrimination procedures.

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6. Procedures for Assessing Dissociative Anesthetics

1. Characterization of Dissociative Anesthetic Effects

a. Acute Drug Effects

i) Anesthesia

The characteristics of the various stages of anesthesia following both inhalation and intravenous administration of dissociative anesthetics have been defined by Gillespie (1943) and remain in use today. Four stages are delineated in the progression from loss of consciousness through delirium and surgical anesthesia, to medullary depression and cardiovascular collapse. While early clinical studies showed that phencyclidine (PCP) readily induced and maintained anesthesia, the incidence of delirium, hallucinations, and disruptive reactions discouraged further use in surgical procedures (Johnstone et al. 1959; Luby et al. 1959; Domino 1968). Some of these effects are also seen with ketamine, but the incidence and severity are lower.

Stella et al. (1979) determined the relative potencies of ketamine with respect to a number of other anesthetics using standardized probit analysis. Drugs were administered via a large antecubital vein 20 seconds after releasing a sphygmomanometer cuff. A 10 ml volume was injected over a 15-second interval during which the subjects were asked to count out loud. When they stopped counting and did not respond to a request to open their eyes, they were considered sleeping. Using a total of 450 subjects, dose-respose relationships were obtained by considering the percentage of positive responses (i.e., asleep) in groups of subjects given different doses of each agent. In this manner, the UD30, UD50, and UD80 (unconscious dose 30%, 50%. and 80%, respectively) were determined. Ketamine was found to be about 4.4 times more potent than thiopentone and about equipotent with diazepam. The UD95 of each drug was calculated and is considered to be the clinically relevant dose.

ii) Analgesia

Sadove et al. (1971) determined the analgesic effects of ketamine both by an experimentally induced pain technique and by questioning individuals during recovery from surgery. Painful stimuli were produced using an earlobe algesimeter (Siker et al. 1966). While the earlobe contains undifferentiated bare nerve endings, subjects have easily distinguished between heat, cold prick, and touch (Sinclair et al. 1952). The current delivered to the earlobe is adjusted from 8 to 30 microamperes and after 3 determinations of control responses (time to release button), separate measures of pain threshold were obtained at 15-minute intervals after drug injection. Ketamine was compared with meperidine and saline and was found to increase the pain threshold to a level higher than meperidine, but its duration was shorter (about 75 minutes vs. 120 minutes for ketamine and meperidine, respectively). In the clinical double-blind study of post-operative pain, subjects were asked to rate their pain on a 0 to 3 scale ("none," "mild," "moderate," and

"severe"). Beginning with a pain scale score of 2, they were re-evaluated at 5-and lO-minute intervals after receiving 0.44 mg/kg of ketamine, i.m., or placebo. Ketamine significantly reduced the pain scores, but the duration of this analgesic effect was limited to 1 hour.

iii) Electroencephalographic (EEG) Activity

Procedures for assessing the EEG effects of dissociative anesthetics in man using visual inspection techniques have shown that doses of 2-3 mg of PCP produce slowing of the EEG that is most pronounced in the theta band. Higher doses produce more diffuse, slow activity mostly in the occipital, temporal, and parietal areas (Greifenstein et al. 1958). The EEG effects of ketamine have been shown to be similar in nature to PCP (Schwartz et al. 1974) using conventional EEG tracings and a single-channel cerebral function monitor (CFM) (Sully and Scott 1972) which graphs the mean amplitude of the EEG over a 2-50 Hz band on slowly moving paper. The CFM consistently detected changes 1O-15 seconds before the direct EEG when injections were given over both a 15-and 60-second interval. The differences in onset of effect were less for the second ketamine injection (same dose) given 10 minutes after the first.

Most recently, power spectral analysis has been used to quantify the frequency and voltage components of the EEG after PCP intoxication in one patient (Stockard et al. 1976). A prominent theta peak (5.75 Hz) persisted during the period when the patient was unconscious and unresponsive to stimulation. Intravenous administration of diazepam produced a shift to a lower predominant frequency accompanied by a return of spontaneous movements, though normal alpha frequencies (i.e., 8.5 Hz) were recovered only after 72 hours.

2. Dissociative Anesthetic Physical Dependence Potential

a. Tolerance to Drug Effects

Numerous case reports of tolerance to the anesthetic and analgesic doses of ketamine, particularly in pediatric medicine, have appeared stating the approximate percent increase in dose required to maintain adequate anesthesia (Cronin et al. 1972; Stevens and Hain 1981). No attempts to control for duration between treatments in these studies were reported, however, and no systematic quantitative studies of tolerance are available.

b. Withdrawal from Chronic Drug Administration

While drug-seeking behavior has been noted to occur, no signs of withdrawal were noted in individuals who reported smoking 100 mg or more of PCP daily for several months (Burns and Lerner 1981). To date, however, no quantitative methodology has been applied to determine the nature and extent of the abstinence syndrome following withdrawal from chronic administration of dissociative anesthetics.

3. Dissociative Anesthetic Abuse Liability

a. Drug Self-Administration

There are currently no accepted procedures for assessing the ability of PCP or its analogues to maintain self-injection performance in humans.

b. Self-Report of Drug Effects

Numerous studies of PCP have described verbal reports of subjective effects involving impairments of thought processes, changes in body image and sensory perception, and depersonalization concomitant with impaired attention and concentration (Burns and Lerner 1981). Occasionally delusions and hallucinations have been reported, as after-effects usually associated with the recovery following drug withdrawal. No reports are available describing the use of standardized psychological testing procedures (e.g., MMPI, ARCI).

c. Behavioral Toxicity

Morgenstern et al. (1962) administered a battery of seven tests to normal volunteers in order to study the effects of PCP on sensory processes. After swallowing a 7.5 mg tablet, the battery of tests (which took 10-12 minutes to complete) was repeated every 15 minutes for 2 hours. Phencyclidine produced a general impairment in sensory function as evidenced by the elevated thresholds on all seven tests. Two-point discrimination, aesthesiometry, and perimetry thresholds showed the greatest increase, while taste was the least affected. In addition, the PCP-induced sensory disturbances always occurred before any verbal reports of subjective changes in feelings or mood.

PCP's effects on reaction time, rotary pursuit, and weight discrimination have also been compared with LSD-25 and amobarbital sodium in normal volunteers (Rosenbaum et al. 1959). PCP and amobarbital were given i.v., while LSD was given orally. The tests were administered imediately after PCP and amobarbital, and 3 hours after LSD. A marked increase in reaction time was observed after PCP with a lesser increase observed after amobarbital. LSD did not affect reaction time. The ability to trace a rotating disc was also impaired by PCP, though amobarbital had little or no effect, while LSD actually improved performance on this task. PCP significantly disrupted performance on the weight discrimination tasks as well, though amobarbital and LSD had no such effect.

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