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Behavioral and Pharmacological Aspects of Opioid Dependence: Mixed Agonist-Antagonists*, †

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I. Introduction

ALTHOUGH drug dependence has been the subject of extensive research and discussion, precise scientific definition of this condition is a difficult undertaking. The distinctions among terms such as habituation, addiction, and dependence are ambiguous and often subjective. Their use has frequently resulted in more confusion than clarification. In response to this problem, the World Health Organization Expert Committee on Drug Dependence‡ has adopted the following definition of drug dependence:

> A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present.

Thus, drug dependence, characterized by compulsive drug self-administration, always includes a psychic and sometimes a physical component. Eddy et al. (20) have defined these two components of drug dependence as follows: Psychic dependence is a condition in which a drug produces "a feeling of satisfaction and a psychic drive that require periodic or continuous administration of the drug to produce pleasure or to avoid discomfort." Physical dependence is "... an adaptive state that manifests itself by intense physical disturbances when the administration of the drug is suspended .... These disturbances, i.e., the withdrawal or abstinence syndromes, are made up of specific arrays of symptoms and signs of psychic and physical nature that are characteristic for each drug type." Thus, drug dependence, be it pyschic, physical, or both, may be of several types and is classified into groups related to a prototypical dependence-producing compound(s). Among these are dependence of the alcohol-barbiturate, amphetamine, cannabis, cocaine, hallucinogen, khat, opiate, and volatile solvent types. We will use this definition of dependence and these concepts of physical and psychic dependence throughout this review. For our purposes, the concepts of physical and psychic dependence are most relevant as representing potentially independent classes of variables which can influence drug-seeking behavior.

Our review will concentrate on behavioral and pharmacological data that have been gathered by using animal models of drug dependence. Although many aspects of drug dependence can be directly observed (e.g. the expression of withdrawal symptoms in an opioid-dependent organism), the collection of statistical data necessary for precise definition of the variables controlling this condition is difficult outside the laboratory. This is particularly true of psychic dependence where subtle variables that are important in controlling this component of dependence (e.g. past behavioral history) may only become apparent when carefully controlled and quantifiable experiments can be done. Thus, major questions concerning drug dependence may only be answerable in the laboratory by using animal models. Animal models of drug dependence seek to analyze in a systemic and controlled way variables that are important in initiating

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‡ World Health Organization Technical Report Series, 1969, No. 407.

and maintaining dependence in animals with hope that animals can be useful in providing fundamental insights into the mechanisms controlling drug dependence in humans. As such, this model should be able to account for both the psychic and physical components of drug dependence in a meaningful and useful way.

The development of animal models of drug dependence has had two goals: 1) the development of a laboratory model that would help elucidate the physiological and behavioral mechanisms underlying dependence, and 2) the development of the methodology for predicting the dependence potential of novel compounds in humans. Significant progress has been made toward each of these goals. In the past it has been thought that the establishment of physical dependence was the sine qua non for drug seeking behavior. Addicts self-administered heroin in order to avoid the agonies of withdrawal. Thus, much initial research has been directed toward understanding the phenomenon of physical dependence and developing compounds with little or no capacity to produce physical dependence. Procedures for evaluating physical dependence potential have been utilized particularly in the search for analgesics with little or no dependence potential. The rhesus monkey has been the subject of experiments dealing with physical dependence for approximately 50 years and the similarities between the responses of rhesus monkeys and those of humans to the acute and chronic administration of narcotic analgesics have been well established (21, 130, 135). Standard procedures for studying physical dependence potential have been developed and refined. This has allowed the testing of an enormous number of analgesics for physical dependence capacity in monkeys, in programs initially developed at the University of Michigan, and more recently including the Medical College of Virginia. Direct comparisons between dependence data derived from these programs and that collected in humans at the Addiction Research Center in Lexington, Kentucky, support the value of this animal model in screening analgesics for physical dependence capacity. In spite of the synthesis and testing of many compounds, no real separation between analgesic potency and physical dependence capacity was realized until the serendipitous discovery of the analgesic properties of the narcotic antagonist nalorphine (92), a compound with low dependence potential. As a result there developed much interest in narcotic antagonists as a class of useful analgesics and several antagonist and mixed agonist-antagonist analgesics have been subsequently developed. Unfortunately, many of them have dysphoric and hallucinogenic effects that limit their therapeutic usefulness. Nevertheless, research has led to the development of many compounds that combine the therapeutically desirable agonist effects of morphine with fewer undesirable side effects. Compounds such as buprenorphine, butorphanol, and nalbuphine are among this fascinating group of compounds.

In recent years it has become apparent that substantial drug-seeking behavior can occur in the absence of physical dependence. It is this behavior that is thought to be the manifestation of psychic dependence. Unfortunately, the phenomenon of psychic dependence is less clearly observable than that of physical dependence. Obviously, effects such as "satisfaction" and "psychic drive" are difficult to describe and measure. Recently, however, the development of the discipline of behavioral pharmacology has made significant contributions to our understanding of the psychological mechanisms of dependence. The pioneering work of Weeks (139), Thompson and Schuster (134), and Deneau et al. (16), initiated the development of animal models for the study of intravenous self-administration of psychoactive compounds. This animal model has been applied to the prediction of dependence potential of compounds in humans as well as to questions concerning the behavioral mechanisms of dependence. It has become apparent that rhesus monkeys (and other species as well) will self-administer virtually all compounds that are abused by humans and fail to self-administer those with little or no abuse potential in humans (e.g., see Refs. 36, 81). This generalization is particularly strong for opioids (see Ref. 35), and appears to represent a measure of psychic dependence potential.

An important finding of this research has been that animals will self-administer psychoactive compounds even in the absence of physical dependence. However, self-administration of a drug is a nonspecific effect providing little unambiguous data as to drug class. That is, drugs of many different pharmacological classes will be self-administered but little is revealed by this demonstration about type of dependence potential (e.g. alcohol-barbiturate, opioid). The development of drug discrimination procedures (9, 101, 112) has made it possible to classify psychoactive compounds according to similarities in discriminative stimulus properties. Animals can be trained to emit a specific response after the injection of an active drug and another, different response after the injection of the vehicle. When tested with a novel compound, the extent to which responding occurs on the drug-appropriate lever reflects similarities in the discriminative stimulus properties of the training drug and the novel compound. The fact that the test is highly specific and arranges psychoactive compounds in groups that are consistent with what is known about the subjective effects of these compounds in humans has led to the hypothesis that drug discrimination procedures measure an effect that is analogous to subjective effects in humans (see, e.g. 64, 113). Thus, drug self-administration and discrimination procedures provide complementary data that can be used to assess and classify psychic dependence potential. For example, a compound that is self-administered and produces drug-appropriate responding in animals trained to discriminate morphine would be predicted to have psychic dependence potential of the opiate type.

Among the opioids, attention has recently been focused

on the class of compounds called benzomorphans, a group of morphine-like chemicals for which there is a low correlation between analgesic potency and physical dependence capacity (22, 135). Included in this class of compounds are many mixed agonist-antagonists. With few exceptions (phenazocine being a notable one) there has been good prediction from physical dependence studies in the rhesus monkey to physical dependence liability in humans. Thus, the benzomorphans would appear to represent an ideal class of therapeutic compounds—potent analgesics with low physical dependence liability. However, the recent application of the techniques of behavioral pharmacology has revealed behavioral effects of many of these compounds that would predict significant psychic dependence liability. Specifically, several of the benzomorphans maintain behavior that leads to their intravenous delivery in rhesus monkeys. Many also seem to possess other stimulus properties that are similar to those of morphine. Although this is by no means a property of all benzomorphans, the fact that some members of this group of compounds possess psychic dependence potential of the opiate type is a notable example of a situation in which physical dependence testing has been inadequate to predict dependence potential.

In consideration of these facts, our review of animal models of dependence will have several purposes. We will describe in some detail laboratory models used for the measurement of both physical and psychic dependence capacity of psychoactive compounds, especially as they have been applied to opioids. Since the literature for opioids in general is quite large, especially for physical dependence, we will restrict our detailed analysis to a group of compounds for which the physical dependence capacity is often low, the mixed agonist-antagonists, especially the benzomorphans. Particular emphasis will be placed upon intravenous self-administration and drug discrimination as measures of psychic dependence capacity by using opioids in general and benzomorphans in particular. For physical dependence and self-administration testing, we will for the most part limit ourselves to data collected with the rhesus monkey. For drug discrimination, since few data are available with rhesus monkeys as subjects, data from other species will be discussed with the caveat that species differences may exist. Finally, when data are available for these compounds in humans (generally research undertaken at the Addiction Research Center), these will be included in the discussion. Research with the benzomorphans provides a particularly intriguing look at central nervous system pharmacological research with a class of opioids for which the important pharmacological effects of psychic and physical dependence capacity appear to diverge.

II. Physical Dependence Testing

By far, the largest amount of testing for physical dependence capacity of opioids has been done in rhesus monkeys in the context of screening new analgesics. As stated above, the similarities between the responses of this species and those of humans to this class of compounds are quite striking. The procedures for evaluation of compounds for physical dependence capacity of the morphine type have been reported in detail elsewhere (116, 117, 135) and will be only briefly described here.

In the initial stages of testing, the effects of opioid analgesics are determined in monkeys that are physically dependent on morphine. Physical dependence is produced and maintained by injections of morphine sulfate (3.0 mg/kg, s.c) given every 6 hours for at least 30 days before testing begins. This dosing regimen has been reported to produce maximal physical dependence on morphine (117) and is the one used currently at both the University of Michigan and the Medical College of Virginia. Test compounds are administered, usually s.c., sometime after the last morphine injection and a trained observer scores the occurrence, intensity, and duration of withdrawal symptoms such as shivering, restlessness, irritability, abdominal cramps, vomiting, and diarrhea. Two basic tests are conducted: the single dose suppression test (SDS) and the precipitated withdrawal test (PPT). The SDS test determines the ability of a drug to suppress the signs of abstinence in dependent animals that have not received morphine for approximately 15 hours, i.e. are in withdrawal. This procedure is based upon the well-established principle that most drugs that suppress the various signs of morphine abstinence are capable of producing morphine-like physical dependence themselves during chronic administration (clonidine is a recently discovered exception to this rule; 32, 138). On the other hand, compounds suspected of having morphine antagonist properties are tested for their ability to precipitate the abstinence syndrome in morphine-dependent monkeys. The PPT withdrawal test is initiated with an injection given approximately 2½ hours after the last injection of morphine and the effects are compared to those of a standard antagonist such as naloxone or nalorphine. This test is based upon the generalization that narcotic antagonists precipitate an acute abstinence syndrome in morphine-dependent organisms. A third test to evaluate the primary dependence capacity (PDC) of a compound, is conducted if the SDS and PPT tests so indicate, and if drug supplies are adequate. For this test, animals receive the test drug s.c. every 6 hours for 30 to 45 days and are then abruptly withdrawn from the drug and observed for signs of an abstinence syndrome. In addition, compounds can be tested for morphine-like physical dependence capacity by conducting of a PPT withdrawal test with a narcotic antagonist. PDC tests should be evaluated with the understanding that they may underestimate or even fail to detect the physical dependence capacity of short-acting drugs, since blood levels adequate to produce physical dependence may not be maintained between injections (67).

The results of screening most new opioid analgesics for physical dependence capacity have been included for

many years in the annual report of the Committee on Problems of Drug Dependence, and a detailed treatment of the results is beyond the scope of this review. Control studies with "traditional" opioids have been conducted and the results are for the most part consistent with the generalities outlined above. Thus, heroin, codeine, and methadone can suppress withdrawal in the SDS test and can produce primary physical dependence. Drugs such as nalorphine and naloxone elicit abstinence symptoms when tested in the PPT withdrawal test, and have little or no liability for primary physical dependence of the morphine type.

Many benzomorphans have been evaluated by these procedures, and the data available for 10 of these compounds are presented in table 1. The chemical structures are presented in figure 1. Although this group of compounds was selected because of the relatively large amount of data available from the behavioral pharmacology laboratory concerning their psychic dependence

TABLE 1

Effects of selected benzomorphans in tests for physical dependence capacity using rhesus monkeys.

Compound	Results	References
1. NIH 8241 (UM 624)	Suppresses withdrawal	135
2. Pentazocine	Precipitates withdrawal; low primary dependence capacity	129, 136, 153
3. α-(−) Etazocine (NIH 8178, UM 600)	Precipitates withdrawal; no primary dependence capacity	15, 135
4. Cyclazocine	Precipitates withdrawal; does not suppress withdrawal; some primary dependence capacity (not morphine-type)	135
5. NIH 8240 (UM 623, GPA-1657)	Precipitates withdrawal; no primary dependence capacity; suppresses withdrawal; has primary dependence capacity in humans	135
6. Ketocyclazocine	Does not precipitate withdrawal; Does not suppress withdrawal; no primary dependence capacity	93, 128
7. Ethylketocyclazocine	Does not precipitate withdrawal; does not suppress withdrawal	93, 128, 147
8. NIH 8735 (UM 909)	Does not precipitate withdrawal; does not suppress withdrawal; some primary dependence capacity (not morphine type)	127, 137, 147
9. NIH 8737 (UM 911)	Does not precipitate withdrawal; does not suppress withdrawal; some primary dependence capacity (not morphine type)	127, 137, 147
10. NIH 9102 (UM 1072)	Does not precipitate withdrawal; does not suppress withdrawal; some primary dependence capacity (withdrawal precipitated by naloxone)	2, 147

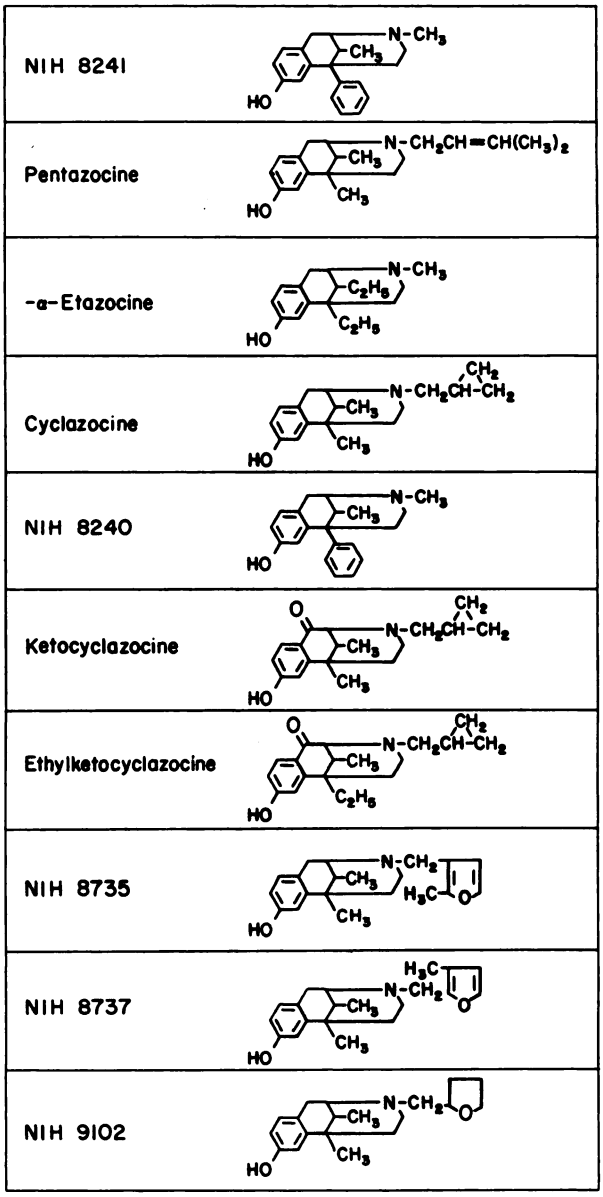

FIG. 1. Chemical structures of compounds in table 1.

potential, it is evident that the experimental results in table 1 are consistent with the notion that benzomorphan analgesics have a relatively low potential for producing physical dependence. Of these 10 compounds, only one (NIH 8241) suppresses morphine withdrawal symptoms. Pentazocine can suppress abstinence symptoms in minimally dependent animals, but precipitates abstinence in animals with a high degree of physical dependence (153). The other benzomorphans either precipitate withdrawal, a characteristic of opiate antagonists, or neither suppress nor precipitate the syndrome. It is noteworthy that several of these compounds (pentazocine, cyclazocine, NIH 8735, NIH 8737, and NIH 9102) showed evidence of producing some type of physical dependence when tested in primary dependence tests, although the abstinence symptoms were not typically morphine-like. In one case (NIH 9102) withdrawal could be precipitated with a

naloxone injection. In addition, in another case (NIH 8240), the rhesus monkey was a poor predictor of the results in humans. Although this compound precipitates abstinence and has no primary dependence capacity in rhesus monkeys, in humans it both suppresses abstinence and produces primary physical dependence of the morphine type (77). Interestingly, it is the optical isomer of NIH 8241 that suppresses morphine withdrawal in rhesus monkeys.

Because of these data, and the availability of a significant body of data pertinent to prediction of the psychic dependence potential of these compounds, they represent a useful group of compounds for comparing predictions of animal models of physical and psychic dependence. Physical dependence testing in rhesus monkeys would lead to the prediction that only one of these compounds, NIH 8241, has any dependence potential of the morphine type. The remainder of this review will describe animal models for predicting psychic dependence potential and present the data available for these compounds that have been tested by these methods.

III. Psychic Dependence Testing

A. Assessment of the Reinforcing Properties of Opioids

Over the past 15 to 20 years, procedures based on conditioning principles used by experimental psychologists and behavioral pharmacologists have been developed to analyze the behavioral aspects of drug dependence in animals. For the analysis of drug-seeking behavior, conditions are arranged so that a behavioral response by the animal is followed by a drug injection. If the behavior that leads to the drug injection increases in frequency to a greater extent than found with the drug vehicle, then the drug is defined as a positive reinforcer. Research with a large number of psychoactive compounds by using this paradigm has led to the conclusion that laboratory animals, in particular rhesus monkeys, will self-administer most of the drugs that are self-administered for nonmedical purposes by humans (36, 85, 109). Thus, this animal model would appear to have predictive value in the evaluation of the dependence potential of a wide variety of drug classes.

In self-administration studies, the largest number of compounds has been tested by the intravenous route of administration. This route has the virtue of a rapid onset of effect and accurate control of dose. The general methodology may be outlined as follows. An animal is surgically prepared with a chronic, indwelling intravenous catheter and fitted with an apparatus for catheter protection and restraint. A harness with an attached restraint arm is the system most often used, although primate restraint chairs and protective vests are also used. The restraint arm is attached to the cubicle where the animal lives 24 hours a day. The catheter is threaded through the restraint arm and connected to an automatic infusion pump. Drug injections are made contingent upon some behavioral response under schedules of drug delivery that are controlled by electronic programming apparatus. In this way, the behavioral aspects of opioid dependence can be analyzed within the context of operant conditioning principles, with the goal of determining a drug's reinforcing efficacy, that is, the extent to which it will be self-administered. The results from investigations of the self-administration of opioids by laboratory animals have been reviewed extensively elsewhere (110, 111, 115). In the present context, we can summarize these data by stating that both drug-experienced and drug-naive rhesus monkeys will self-administer a wide variety of opioid agonists including morphine, methadone, codeine, and heroin. On the other hand, narcotic antagonists such as nalorphine, naloxone, and levallorphan fail to maintain self-administration in rhesus monkeys. In short, there is an excellent correspondence between those opioids that are self-administered by monkeys and those with dependence potential in humans. Several self-administration procedures have been used to evaluate opioids. They may be classed under the general headings: unlimited access procedures, limited access substitution procedures, and procedures that measure relative reinforcing efficacy.

Although many of the earliest self-administration experiments were unlimited access experiments, this procedure has not been widely used with opioids (see Ref. 7 for a review of this literature). In experiments with unlimited access, animals are prepared with intravenous catheters and given access to a drug or the drug vehicle for 23 or 24 hours a day. The behavioral requirement is usually minimal: a single lever press results in a drug injection. Usually drug access is continued for periods of up to 30 days with food intake, response rate, and general observations of the animal's condition recorded daily. If an animal fails to self-administer a drug above vehicle rates, the dose may be changed or programmed, noncontingent infusions administered in an attempt to "prime" the animal. Although these experiments have typically involved experimentally naive subjects in order to ascertain whether self-administration will be initiated, it is also possible to use animals that are experienced in drug self-administration in this procedure (154).

The data provided by unlimited access experiments are of value for several reasons, particularly with regard to drug toxicity. When a drug is self-administered, they allow evaluation of the effects of long-term, high level, continuous exposure to the compound, and characteristic toxicities usually emerge. For example, under conditions of unlimited access to opioids, physical dependence readily develops (16). Unlimited access to psychomotor stimulants in monkeys results in cyclical patterns of self-administration with periods of high intake alternating with periods of low intake (17, 82). Toxicities such as extreme psychomotor stimulation, often resulting in convulsions and death, are frequently observed. It should be noted that a similiar pattern of intake and toxicity has

been observed in human stimulant abusers (89). Since the behavioral task is simple, this procedure provides the least quantitative information about the psychic dependence potential of a drug, although when considered in conjunction with other self-administration procedures, unlimited access can provide valuable behavioral information concerning the self-administration of a compound under conditions of minimal response cost. In addition, the important question of whether a drug-naive organism will initiate self-administration can be answered. Thus, unlimited access is a valuable component of the assessment of the dependence potential of a compound.

Morphine, methadone, and codeine have been tested under conditions of unlimited access (16, 111) and the general results are similar among these compounds. Self-administration of these compounds varies diurnally, with intake being highest during the daylight hours and lower at night. There is a gradual increase in daily intake of the opioid during the initial period of drug availability, stabilizing at some level and remaining at that level for extended periods. Several variables may contribute to this negatively accelerated acquisition curve, including the development of tolerance and/or physical dependence as well as learning of the behavioral response. When saline is substituted for each of these drugs after an extended period of access, a temporary increase in drug-seeking behavior (extinction burst) followed by a gradual decline in responding over a period of several days, is usually observed. In an analogous fashion, typical opioid abstinence signs initially increase in severity, then gradually decline.

Of the benzomorphans listed in table 1, only pentazocine has been studied under conditions of unlimited access (24, 50, 149). Drug-naive rhesus monkeys readily initiated self-administration of pentazocine under these conditions at doses of 0.5 to 2.0 mg/kg per injection. Lower unit doses were not as reliably self-administered. Total daily intake of pentazocine increased slightly as unit dose was increased, ranging between 45 and 101 mg/kg per day. When saline was substituted for pentazocine after periods of self-administration of between 1 and 3 weeks, marked withdrawal signs were noted and included irritability, anorexia, and prostration. Thus, although pentazocine does not suppress morphine withdrawal in highly dependent rhesus monkeys, and has low dependence capacity in primary dependence tests, unlimited access, self-administration tests provided clear evidence of physical dependence to pentazocine. It is likely that unlimited access, self-administration procedures maximize the probability of physical dependence development to a drug that is a positive reinforcer by virtue of the continuous high blood levels that may be maintained by the animal (8).

To allow the relatively rapid evaluation of self-administration of several doses of a compound in drug-experienced animals, limited access substitution procedures have been developed (6, 3, 152). Usually an animal is trained to respond each day in an experimental session that lasts 2 to 3 hours for a base-line drug that is a known positive reinforcer, often cocaine or codeine. When responding is stable for the base-line drug, the test drug vehicle is substituted for the base-line drug for a period of five to seven sessions and the operant level of responding is determined. Animals are then briefly returned to base-line conditions followed by a 5- to 7-day substitution period with a dose of the test drug. This process is repeated with several unit doses of the unknown drug until the experimenter is assured of having tested an adequate dose range. Rates of responding for the test drug are compared to rates of responding for vehicle and for the base-line drug. Dose-response relationships are usually of an "inverted U" shape. At doses higher than that which maintains maximal responding, response rates are usually inversely related to dose. That is, higher doses maintain lower rates of responding. A drug that maintains responding above vehicle levels in several animals is considered to be a positive reinforcer.

This basic substitution procedure has the virtue of providing complete self-administration dose-response relationships in a relatively short period of time and allows testing of a larger number of animals. However, a minimum 1½- to 2-month period is still required for a dose-response determination. In addition, base-line drug, i.e. drug history, has been found to be a determinant of rate of responding for some compounds, making it desirable to test new drugs in animals maintained on different base-line drugs (8).

Recently, in the context of screening many opioid analgesics for dependence potential, more rapid limited access substitution procedures have been developed (4, 145, 146). In these procedures, animals are trained to respond in two experimental sessions per day with vehicle made available during every third or fourth session. After the animals have had repeated experience with vehicle substitution, rates of responding decline rapidly when vehicle is substituted. When responding for vehicle occurs at low rates, a unit dose of the test compound is substituted for one or two consecutive sessions and rates of responding are compared to vehicle rates. Thus, two or three doses of an unknown compound can be evaluated within a 1-week period. In the procedure used by Aigner and Balster (4), animals were trained to respond under a multiple schedule, with a brief period of food availability preceding and following the period of drug access within the same experimental session. This procedure has the virtue of assuring the testing of an adequate dose range. Altered responding for food in the period following drug availability is an indication that active drug doses have been achieved. Although they are rapid, both of these procedures suffer from the limitation that only a single data point is obtained for each unit dose in each animal making the testing of more animals or redetermination of drug effects in the same animal desirable. In

addition, as with other substitution procedures, base-line drug may be an important determinant of the reinforcing properties of an unknown compound. This is particularly true when these procedures are used for testing opioid agonists and antagonists because of the complex interactions possible among this group of compounds. For example, in the procedure used by Woods (6), animals were maintained on codeine as a base-line drug. Although the physical dependence capacity of codeine may be low in this situation, exposure to opioids is known to alter the response of an organism to antagonists or mixed agonist-antagonists. Compounds with antagonist properties may precipitate withdrawal in these animals and thereby suppress responding. Thus, to the extent that physical dependence is present, the reinforcing properties of antagonists and mixed agonist-antagonists may be underestimated by this procedure. In general, these rapid screening substitution procedures should only be relied upon for initial qualitative answers about reinforcing properties of test drugs.

A substantial amount of testing of opioids for reinforcing properties has been done with some form of the limited access substitution procedures outlined above. Correspondence between the available opioid self-administration data in monkeys using substitution procedures and subjective effects testing in former heroin addicts has recently been reviewed (35). Their conclusions for this class of compounds can be summarized by stating that 29 of 33 drugs showed exact correspondence between humans and monkeys. Of the remaining four, three were self-administered by monkeys but were not judged to be morphine-like by humans. It should be kept in mind that testing humans for morphine-like subjective effects is undoubtedly a more specific test than self-administration, perhaps more analagous to drug-discrimination testing in animals discussed below. That is, humans and monkeys will self-administer many drugs that do not have morphine-like subjective effects, e.g. amphetamine or cocaine. In any case the overlap between drugs that are morphine-like in humans and those that are self-administered by monkeys is striking.

Self-administration results for the benzomorphans in table 1 are summarized in table 2. All have been tested in a limited access substitution procedure. The only compound among that group that suppressed morphine withdrawal (NIH 8241) was readily self-administered under a FR 10 schedule of drug delivery (fixed ratio 10:10 responses per injection) by monkeys maintained on either cocaine or codeine under base-line conditions (2). Both experimental results suggest a high level of dependence capacity for this compound. A second group of compounds (pentazocine, α-(−)etazocine, cyclazocine, and NIH 8240) precipitated withdrawal in physically dependent monkeys, typically an antagonist effect. When tested in substitution self-administration tests, all but cyclazocine were self-administered. This result is somewhat surprising since, because of experiences with

TABLE 2

Self-administration results with selected benzomorphans in limited access substitution procedures.*

Compound	Result	References
1. NIH 8241 (UM 624)	+	2
2. Pentazocine	±	1, 4, 59
3. α-(−)Etazocine (NIH 8178, UM 600)	+	1
4. Cyclazocine	−	4, 61
5. NIH 8240 (UM 623, GPA 1657)	+	2, 145, 146
6. Ketocyclazocine	−	146, 147
7. Ethylketocyclazocine	−	146, 147
8. NIH 8735 (UM 909)	+	146, 147
9. NIH 8737 (UM 911)	±	146, 147
10. NIH 9102 (UM 1072)	±	146, 145

* + = self-administered above saline levels; − = self-administered at or below saline levels; ± = equivocal.

nalorphine (92) and naloxone, these drugs were thought to have a low dependence potential. The data for pentazocine are equivocal. As stated above, pentazocine will precipitate abstinence in animals that are highly dependent on morphine. In self-administration studies, Hoffmeister and Schlichting (59) found pentazocine to be a positive reinforcer in rhesus monkeys maintained on cocaine or codeine under base-line conditions. Aigner and Balster (4), by using a rapid substitution procedure, found that three of the four animals they tested self-administered pentazocine at higher than saline levels. However, Aceto et al. (1) reported that only two of four animals self-administered pentazocine. This result did not appear to be a function of base-line drug since the drug was a positive reinforcer for one animal maintained on codeine and one maintained on cocaine. Thus, pentazocine appears to have intermediate dependence capacity in monkeys, a prediction that is generally borne out in humans (114). α-(−)Etazocine was self-administered by rhesus monkeys maintained on either cocaine or codeine under base-line conditions (1). Another benzomorphan that precipitated withdrawal is cyclazocine. Despite the finding that cyclazocine has some capacity to produce a non-morphine-like primary physical dependence (135), it has no apparent psychic dependence capacity based on tests in monkeys (4, 61) or humans (43, 96). NIH 8240, the *l*-isomer of NIH 8241, had no apparent physical dependence capacity in monkeys, yet is readily self-administered in both the 6-day substitution procedure of Aceto et al. (2) and in the rapid substitution procedure used by Woods (145, 146). When NIH 8240 was tested in humans, it suppressed withdrawal, produced primary physical dependence, and was identified as having morphine-like subjective effects (77, 135). In this case, physical dependence testing in the rhesus monkey apparently failed to detect a compound with significant dependence potential of the morphine type.

The remainder of the compounds in table 1 (ketocy-

clazocine, ethylketocyclazocine, NIH 8735, NIH 8737, and NIH 9102) neither precipitate nor suppress morphine withdrawal in physically dependent rhesus monkeys. Thus, in that preparation they act as neither opioid agonists nor as antagonists. There is apparently some capacity for production of primary physical dependence for NIH 8735, 8737, and 9102, though the symptoms of withdrawal are not morphine-like. The reinforcing effects of all of these compounds have been determined in a rapid substitution procedure with codeine as the baseline drug (146, 147). Neither ketocyclazocine nor ethylketocyclazocine supported self-administration responding above saline levels at any dose tested. NIH 8735 maintained responding above saline levels in all four animals tested, though the maximal average response rate was low. For NIH 9102, two of three animals tested responded above saline levels, though rates of responding were low relative to those maintained by codeine. The situation was similar for NIH 8737. For these latter two compounds the self-administration results could be termed, as with pentazocine, equivocal.

Thus, limited access substitution procedures have been useful in detecting reinforcing effects of opioid analgesic compounds. In several cases, compounds that have a spectrum of action that would not indicate physical dependence liability in morphine dependent monkeys would be predicted to have the potential to produce psychic dependence based on the results of these self-administration tests.

Limited access substitution procedures have the virtue of providing a relatively rapid answer to the qualitative question of whether a drug will be self-administered over a given dose range. However, several variables besides reinforcing effects (e.g. direct effects of a drug that may interfere with responding) can alter the rate of responding for a drug under these conditions. Most, if not all, drugs that have positive reinforcing effects that tend to increase the rate of behavior that led to their administration also have effects that decrease the rate of responding after their administration, regardless of the reinforcing event. Thus, interpretation of the results is limited by the fact that, under these conditions, response rate is not exclusively a measure of the reinforcing efficacy of a drug. For example, the relatively low rates of responding maintained by a compound such as NIH 8735 may be the result of relatively low reinforcing efficacy, response rate suppression by the drug, or a combination of these two. In addition, under conditions in which there is little alternative to drug self-administration these procedures might be suspected of producing false positive results, especially with marginally reinforcing drugs. These issues have received extensive theoretical treatment elsewhere (see e.g. 38, 80, 85).

Several procedures have been developed that allow comparison of the reinforcing efficacy of the drug under study to that of a standard drug or some other reinforcer, such as food. The important methodological variables in these paradigms seem to be: 1) to allow sufficient time between injections for any rate-disrupting effects of a drug to dissipate and/or 2) to allow the animal to choose between the test drug and some alternative reinforcer. These procedures have been developed by using psychomotor stimulants and can be divided into three categories: discrete trial choice, concurrent schedules of drug access, and progressive-ratio procedures. In the case of discrete trial choice, two variations of the basic procedure have been developed. The switching choice was initially developed by Findley et al. (25) and modified by Griffiths et al. (40, 41) and Aigner and Balster (3). A second discrete trial procedure has been developed by Johanson and Schuster (83). In each of these procedures the animal is allowed to choose between a test drug and some other reinforcer (usually another drug or food). Once one option has been chosen, the other is not available again until another choice trial is instituted. They differ from each other principally in the mechanics of how a choice is made, with the basic proposition being to allow the animal to choose between alternative reinforcers, the availability of which is signaled by different colored lights. On the other hand, in the concurrent access procedure of Iglauer and Woods (66) and Llewellyn et al. (94), relative reinforcing efficacy was determined by giving animals simultaneous access to a series of doses of cocaine, presented in pairs. Drug doses were available on two separate levers on identical schedules of reinforcement, and a 5-minute time-out period followed each injection of cocaine to allow rate-disrupting effects of cocaine to dissipate. This procedure differs from discrete trial choice in that responding on the lever associated with one drug solution does not alter the availability of the other drug solution. In other words, a choice is not irreversible as it is in the discrete trial procedures.

The progressive ratio procedure differs from discrete trial and concurrent access procedures in several ways. Only one drug solution is available to the animal at a time. Responding is initially established for a drug under some ratio schedule of drug delivery, i.e. a schedule that requires *N* responses per drug injection. Once responding is stable, the number of responses required for an injection is systematically increased until the response cost gets so high that responding drops below some criterion level. The ratio value at which responding drops below criterion is called the breaking point and is thought to reflect the relative reinforcing efficacy of the drug. That is, a larger breaking point implies greater reinforcing efficacy. The use of this technique to rank order drugs in terms of reinforcing efficacy is based on early studies in experimental psychology that used other reinforcers to show that breaking point varies as a function of several variables, including magnitude of reinforcement (54, 55).

The potential of each of these procedures for evaluating the relative reinforcing efficacy of drugs has been demonstrated in several experiments, principally with psychomotor stimulants. When animals were given a

choice between two doses of cocaine, the higher dose of the pair was usually preferred (83). Similarly, under conditions of concurrent access to different doses of cocaine, responding occurred principally, often exclusively, on the drug lever associated with the highest dose of cocaine (66). Thus, although higher drug doses often maintain lower rates of responding in limited access substitution procedures, the higher dose was preferred when the animal was given a choice. In between-drug comparisons made with cocaine and methylphenidate in a discrete trial procedure, the drug that was in the highest dose was preferred (83). When food was the alternative to cocaine, the choice frequency depended upon drug dose (150). At low doses of cocaine, food was usually selected but as the dose of cocaine was increased, cocaine came to be preferred. In the extreme case, a high dose of cocaine (300 μg/kg per injection) was selected to the exclusion of food for periods of 7 to 8 days (3). With the food-drug choice procedure it is hoped that comparisons between drugs can be made by assessing the reinforcing efficacy of each relative to food.

Initial studies with the progressive-ratio procedure have, again, been done largely with psychomotor stimulants. Yanagita (153) showed that breaking point was a direct function of unit dose of cocaine. In another study, Griffiths et al. (37) found that for unit doses of cocaine less than 0.4 mg/kg per injection, breaking point was a direct function of dose. However, in an earlier study, Griffiths et al. (39) reported that for doses of cocaine higher than 0.4 mg/kg per injection, the breaking point did not change. The suggestion that at high doses cocaine may have effects that limit its reinforcing efficacy is interesting, though several procedural variables, such as the duration of the time-out period between injections, could account for these results.

Although a limited amount of data are available, the correspondence of results across species and procedures used in comparing the relative reinforcing efficacy of different drugs is encouraging. Johanson and Schuster (84) found that rhesus monkeys given a choice between cocaine and diethylpropion usually preferred cocaine. Similarly, when Griffiths et al. (37) compared cocaine and diethylpropion in baboons by using a breaking point procedure, cocaine had a higher breaking point.

Application of these procedures to opioids as positive reinforcers has not been extensive. It has been shown that the frequency of heroin self-administration in a food-drug discrete trial choice procedure can be altered by both pharmacological and behavioral manipulations (23, 40, 151). However, there is only one report of the use of a discrete trial choice procedure to compare the relative reinforcing efficacy of several opioids (5; see below). In addition, concurrent access schedules have not, to our knowledge, been used in the evaluation of opioids. Hoffmeister (58) compared heroin, codeine, *d*-propoxyphene, and pentazocine by using a progressive-ratio procedure in the rhesus monkey. Heroin maintained a higher breaking point than did the other three drugs, supporting the notion that heroin is highly reinforcing among opiates. The breaking points of codeine, *d*-propoxyphene, and pentazocine reached the same maximum although further increases in dose of pentazocine and *d*-proproxyphene reduced the breaking point again to saline levels. The suggestion that these compounds may have aversive properties is consistent with the general finding that their reinforcing effects in humans are limited because of unpleasant side effects at high doses (77).

Benzomorphans have rarely been tested with procedures designed to evaluate relative reinforcing efficacy. The findings of Hoffmeister (58) with pentazocine by using a breaking point procedure have been described. When comparing opioids in a switching choice procedure that allowed rhesus monkeys to choose between an intravenous drug injection and a food pellet, Balster et al. (5) were able to rank order several opioids, including two benzomorphans, as to relative reinforcing efficacy. In this experiment morphine appeared to be a more efficacious reinforcer than pentazocine which, in turn, was selected more frequently than was cyclazocine. These findings bear a striking similarity to the results from clinical experience and human testing.

It should be noted that it is impossible to distinguish between a compound that is neutral and one that has aversive stimulus properties according to the self-administration procedures outlined above. Both types of compounds would be predicted to maintain little or no responding. In this case, dependence potential might only be a significant concern under conditions of excessive medical use since neither type of compound would be predicted to have significant psychic dependence potential (except to the extent that relief of pain might produce psychic dependence). An animal model that would distinguish between these two types of compound would be useful in the screening of opioid analgesics (or other psychoactive compounds for that matter) since those with aversive psychic effects might be expected to be of less therapeutic usefulness than neutral compounds. For example, the clinical usefulness of cyclazocine and nalorphine as analgesics has been limited by their unpleasant subjective effects with consequent poor patient compliance.

In the behavioral literature, if a response terminates a stimulus and the frequency of that response subsequently increases, that stimulus is defined as a negative reinforcer. For example, when the contingencies are arranged appropriately, an animal will make a response to escape or avoid the delivery of an electric shock. Under these conditions, electric shock is functioning as a negative reinforcer. Recently, paradigms have been developed for using monkeys to study drugs as negative reinforcers. Although this is a new area of research, several opioids as well as representatives of other classes of compounds have been tested by using the paradigm.

In order to demonstrate that a psychoactive compound

functions as a negative reinforcer, it is necessary to show that an animal will engage in a behavioral response to escape or avoid exposure to the drug or stimuli associated with the drug. Two procedures have been used to demonstrate this effect: escape and avoidance-escape. In a simple drug escape procedure, animals are trained to make a behavioral response to escape a continuous drug infusion. An appropriate response terminates the infusion for some period of time but it is impossible to avoid exposure to the drug. On the other hand, in an avoidance-escape procedure, an external stimulus (e.g. a light) precedes the onset of an infusion. A response in the presence of this stimulus will avoid a drug infusion for a predetermined period of time. In the absence of an avoidance response, an escape response can be made to terminate the infusion once it has begun.

Several investigators have studied the negative reinforcing properties of drugs in this context. For example, since narcotic antagonists can precipitate withdrawal in dependent organisms, these compounds might be expected to function as negative reinforcers in morphine-dependent monkeys. This has been shown to be the case for both naloxone (18, 19, 33) and nalorphine (33, 87). Negative reinforcement has also been demonstrated with another class of compounds, the antipsychotic drugs. In the experiment of Kandel and Schuster (87), after the monkeys had been withdrawn from morphine and were no longer dependent, escape responding was maintained by the antipsychotic compound perphenazine. (Saline infusions failed to maintain escape responding.) Similarly, perphenazine and another antipsychotic compound haloperidol, have been shown to generate and maintain avoidance-escape responding in drug-naive rhesus monkeys (56, 57). Thus, the ability of certain compounds to function as negative reinforcers has been demonstrated in both morphine-dependent and drug-naive rhesus monkeys.

Experience with opioids as negative reinforcers is limited. Hoffmeister and Wuttke (60) studied morphine antagonists and mixed agonist-antagonists in drug-naive rhesus monkeys. Nalorphine and cyclazocine maintained avoidance-escape responding while naloxone, cocaine, codeine, pentazocine, and propiramfumarate did not. Thus, cyclazocine and nalorphine can function as negative reinforcers in drug naive monkeys. Although conclusions must be tentative because of the limited amount of research, the results of these studies with drugs as negative reinforcers are consistent with what is known about the subjective effects of these compounds in humans. That is, antipsychotic compounds as well as cyclazocine and nalorphine have aversive subjective effects in humans and will maintain escape or avoidance-escape responding in monkeys. On the other hand, those that are neutral or positive (saline, cocaine) fail to maintain avoidance-escape responding. These data support the conclusion that drugs that have aversive subjective effects in humans can function as negative reinforcers in monkeys. This is an area of research that clearly merits further development.

In summary, self-administration data with benzomorphans are sufficient to allow several conclusions that are relevant to discussion of animal models of dependence. Unlimited access and limited access substitution procedures have both proven useful in providing qualitative data relevant to the reinforcing efficacy of opioids. Although there are very few studies involving quantitative evaluation of the relative reinforcing efficacy of opioids, research has shown that procedures developed for use with stimulants may be effectively applied to this class of compounds (40, 41, 151).

It is clear that results from self-administration procedures with monkeys are remarkably consistent with what is known about opioid subjective effects in humans. Drugs that are identified by humans as being morphine-like are self-administered by monkeys. Thus, self-administration in monkeys appears to measure an important component of psychic dependence potential. Secondly, self-administration testing is clearly a critically important component in the overall evaluation of the dependence potential of narcotics. Although pentazocine, α-(−)etazocine, NIH 8240, and cyclazocine all precipitated withdrawal in morphine-dependent rhesus monkeys, typically a narcotic antagonist effect, all of these compounds except cyclazocine were self-administered. Pentazocine, which has little or no physical dependence potential with the usual tests, clearly produced physical dependence in rhesus monkeys allowed to self-administer the drug under conditions of unlimited access. Moreover, several compounds that produced physical dependence, albeit not of the morphine type, were only equivocal reinforcers in rhesus monkeys (NIH 8737, NIH 9102). In a recent study, Young et al. (156) concluded that there exists a strong positive correlation between the potency of a compound in suppressing the morphine withdrawal syndrome and its potency in maintaining drug-reinforced responding. In spite of this correlation, the data with benzomorphans suggest that a lack of potency in suppressing the morphine withdrawal syndrome is not well correlated with a lack of potency in maintaining drug-reinforced responding. Thus, self-administration testing is an important component if an animal model of opioid dependence. Further development of procedures designed to assess the relative reinforcing efficacy of compounds in this class is clearly warranted.

B. Assessment of the Discriminative Stimulus Properties of Opioids

For many years psychotropic drugs have been characterized and classified in humans by using methods designed to measure their subjective effects. Morphine and related narcotic analgesics produce a spectrum of subjective effects that can be reliably discriminated from other psychoactive drugs by experienced narcotic users. Several methods have been utilized to evaluate subjective

effects of opioids in humans (42, 71). Former heroin addicts are administered a compound and, at selected time intervals after administration, are asked to complete questionnaires designed to detect and classify subjective effects. The single-dose opiate questionnaire asks the subject whether he can feel the drug, to identify the drug, to describe the symptoms, and to rate the degree of liking. In addition, multiple-scale questionnaires of the Addiction Research Center Inventory (ARCI) allow classification of the drug effects according to similarities with the morphine-benzedrine group (MBG), the pentobarbital, chlorpromazine, alcohol group (PCAG) and the LSD group. These questionnaires are sensitive to pharmacological manipulations such as dose and drug class. For instance, when approximately 6 mg of morphine is administered intravenously, about 50% of the subjects correctly identify the compound. Approximately 90% of the subjects correctly identify 20 mg of morphine. Further, even within the analgesic class, compounds that are mixed agonists-antagonists (e.g. cyclazocine) can be readily discriminated from morphine by former heroin addicts (43). It was felt until recently that measurement of drug-induced changes in the subjective state was only possible with humans, since only this species has the necessary verbal skills to describe how a drug made them "feel." In the past two decades, however, behavioral methods have been developed that allow animals to form discriminations between various centrally acting drugs. What makes this area of research so exciting is the striking concordance of data derived from the classification of drugs by humans based on their subjective effects to those shown by animals categorizing drugs on the basis of their similarities as discriminative stimuli. This has led many researchers in this field to make the working assumption that the component of drug action responsible for the discrimination between various classes of psychotropic drugs by animals is analogous to the component of action responsible for the differences in the subjective effects of these drugs in humans. To the extent that the subjective effects of a drug play a role in its dependence potential, the development of procedures that measure this property in animals is of importance.

In many experiments in behavioral pharmacology, animals are trained to engage in some standard behavior through the use of operant conditioning procedures. In these procedures behavior is brought under environmental control by the delivery of certain stimuli (e.g. food to a food-deprived animal) or the termination of certain stimuli (e.g. electric shocks) contingent upon the animal's engaging in the behavior being trained. In addition, environmental stimuli are often used to signal when the behavior will or will not be followed by the reinforcing event. Stimuli uniquely associated with the availability of the reinforcer are called discriminative stimuli. In a well-trained animal (under the appropriate conditions), the behavior comes under such precise control that it appears as though the discriminative stimulus is eliciting the behavior in a reflexive manner. After this type of stimulus control is established, it is possible to systematically alter the discriminative stimulus (e.g. the intensity or wavelength of a light) and determine how this alters the probability of the occurrence of the conditioned behavior. To the extent that the altered discriminative stimulus continues to control the behavior we say that discriminative control generalizes from the training stimulus to the "test" stimulus. In more common terms we can say that the animal is indicating how similar the two stimuli are. This basic procedure can be used to establish drugs as discriminative stimuli and to test other drugs in terms of the similarities in their stimulus properties.

One of the important conceptual issues to address initially is that considering drugs as stimuli seems to stretch our usual definition of stimulus events. We generally think of stimuli as operating through receptors of one of the external sensory modalities. However, we can use the term "drug stimuli" in a purely functional sense which does not depend upon the knowledge of the receptors involved nor understanding of the mechanisms of transduction of stimulus energy into neural activity. For instance, with olfactory and gustatory stimuli the stimulus event is operationally defined as a procedure that places the chemical in physical proximity to the appropriate receptor. In the present context, this stimulus event is defined as the administration of a drug. Lack of knowledge about the anatomical location or neurochemical system subserving transduction in no way alters the functional relationships between the stimulus event and behavior. It should also be noted that lack of information about mechanisms of transduction is not peculiar to drug stimuli as shown by the interest in the stimulus properties of x-rays for which the receptors and transduction mechanisms are also unknown (30, 100, 126). Further, data are beginning to be collected on the relationships between drug discrimination and receptor mechanisms (48).

There are several problems that are unique to the use of drugs as discriminative stimuli. For example, control of the onset and termination of drug stimuli are only imprecisely under the control of the experimenter. Further, the fact that most drugs are long-acting prevents the rapid alternation of stimulus conditions that is possible when studying stimulus control via traditional sensory modalities. (For a more complete discussion of the problems peculiar to the use of drugs as discriminative stimuli see Ref. 112.) Nevertheless, a wide variety of procedures have shown that behavior can be brought under the discriminative control of drug states. Several examples of these methods will serve to illustrate the generality of the findings.

Although many methods have been used to study the discriminative stimulus properties of drugs (13, 14, 101, 102, 112), the most common method currently used is a two lever food-reinforced operant procedure. For train-

ing, an animal is given an injection of a drug or vehicle solution and placed into an experimental chamber that has two response levers. Responding on one of these levers is reinforced on some schedule of reinforcement after drug injections and responding on the other lever is reinforced on the identical schedule after vehicle injections. Over a period of several weeks the animal acquires the discrimination such that responding occurs almost exclusively on the lever that is appropriate to the animal's pretreatment injection. After the discrimination has been acquired, brief test sessions are instituted on a regular basis to quantitatively and qualitatively assess the stimulus properties of the training compound or various test compounds. Thus, if the dose of the training drug is reduced in test sessions, a greater proportion of responding occurs on the vehicle lever. The proportion of responding that occurs on the drug-appropriate lever after injections of a novel drug is thought to reflect the extent to which the discriminative stimulus properties of the drug are similar to those of the training drug. If the novel drug results in drug lever responding that is comparable to that seen with the training drug, the discriminative stimulus properties of the training drug are said to generalize to the test drug. Alternatively, the test drug may be said to substitute for the training drug. This method has proven to be quite sensitive to the discriminative stimulus properties of opioids.

Other procedures have also proven useful for investigating the discriminative stimulus properties of opioids. Holtzman and his colleagues have developed a method that involves a discrete-trial avoidance-escape paradigm in which an animal (rats and monkeys have been studied) could prevent the onset of or terminate an electric shock by pressing one of two choice levers (105, 106, 122, 123). The animals were trained to press one lever after receiving drug (morphine or cyclazocine) and the other lever after saline administration. Procedurally, this method differed in several ways from the food-reinforced procedure outlined above. In the session a light was illuminated for 5 seconds before the onset of electric shock delivered to the feet of the animal through the grid floor on which they stood. Three response levers were present in the chamber. Depression of the "observing response" lever followed by depression of the correct choice lever terminated the light (an avoidance response) or both the light and the shock (escape response) if the animal took more than 5 seconds to complete this sequence. Thus, each session consisted of several (20) discrete trials in which responding was maintained by avoidance of or escape from electric shock. On days when morphine was given, one of the choice levers was correct and, on days when saline was given, the other choice lever was correct. As with food-maintained responding, the morphine-saline discrimination was acquired over a period of several weeks, and test sessions were instituted. The discriminative stimulus properties of opioids have been extensively investigated by using this paradigm.

There are two ways in which discriminative stimuli may be varied for generalization testing: quantitatively and qualitatively. When using a drug as the discriminative stimulus, quantitative generalization tests are accomplished by varying the dose of the drug. When this is done in animals trained with 3.0 mg/kg of morphine as one of the discriminative stimuli, lowering the dose results in dose-related decrements in responding on the morphine appropriate lever with a concomitant increase in responding on the saline appropriate lever (122, 123). Doses higher than that used in training often produce an even higher frequency of drug lever responding until levels of drug are reached which are behaviorally disruptive. This relationship between dose of morphine and response choice is highly similar to that observed when exteroceptive discriminative stimuli are varied along a quantitative dimension.

When conducting generalization studies in which the discriminative stimulus is varied qualitatively, the situation is more complex. With an auditory discriminative stimulus, the qualitative dimension to be manipulated is the unidimensional continuum of frequency. For a visual stimulus the continuum is wavelength. When using drugs as discriminative stimuli, however, we do not know the relevant changes in physical structure of the drug which might show a lawful relationship to behavior. This deficit is not unique to drugs, however, as the same problem exists in relationship to olfactory stimuli. Nevertheless, it is possible to do generalization tests from training drugs to test drugs with different structures and hence more or less similar pharmacological properties. For example, after approximately 8 to 10 weeks of training in the Holtzman experiments, most animals responded almost exclusively on the correct lever on test days when given either the usual dose of morphine or saline. Subsequently, a variety of psychotropic drugs were investigated to determine which produced "morphine-like" discriminative effects (i.e. animals would, at some dose, respond on the morphine appropriate choice lever as with the training dose of morphine). The results of many of these experiments are outlined below. This series of experiments has convincingly demonstrated that generalization tests in animals can be used to classify drugs in the opiate class as well as those with mixed opiate agonist-antagonist activity.

The discriminative control exerted by morphine meets several criteria that justify classifying it as a specific narcotic effect: 1) narcotics tested show distinct ranking in potencies which correlates highly with their potencies in producing morphine-like subjective effects in man; 2) the stimulus control exerted is stereospecific with only the analgesically active isomer exerting morphine-like effects; 3) naloxone or naltrexone administration produces a pronounced shift in the dose-response curve relating dosage of morphine to its discriminative control; 4) tolerance to the discriminative effects of morphine develops after repeated administration as does cross-

TABLE 3

*Relationship between morphine-like subjective effects in humans and morphine-like discriminative stimulus effects in laboratory animals.**

Compound	Species				
	Human	Rat	Pigeon	Squirrel monkey	Rhesus monkey†
Alphaprodine	+ (68)	+ (123)	N.R.	N.R.	N.R.
Codeine	+ (86)	+ (123)	+ (46)	N.R.	+ (49)
Etonitazene	+ (28)	+ (123)	N.R.	N.R.	+ (12)
Etorphine	+ (72)	N.R.	N.R.	N.R.	+ (12)
Fentanyl	+ (34)	+ (123)	N.R.	+ (105)	+ (12)
Heroin	+ (95)	+ (123)	N.R.	N.R.	N.R.
Levorphanol	+ (69)	+ (144)	+ (15)	+ (105, 132)	+ (12)
Meperidine	+ (78)	+ (53)	− (46)	+ (105)	+ (49)
Methadone	+ (98)	+ (31, 53)	N.R.	+ (105)	N.R.
Oxymorphone	+ (26)	+ (91)	N.R.	+ (105)	N.R.
Phenazocine	+ (27)	+ (123)	N.R.	N.R.	N.R.
Profadol	+ (77)	+ (122, 124)	N.R.	+ (107)	N.R.
d-Propoxyphene	+ (79)	+ (123)	N.R.	N.R.	N.R.
Butorphanol	± (73)	+ (123)	N.R.	− (65, 107)	N.R.
Nalbuphine	± (74)	+ (124); − (123, 124)	N.R.	− (65, 107)	N.R.
Pentazocine	± (73, 76)	+ (122, 124); − (53)	+ (148); − (46)	− (65, 107)	− (49)
Cyclazocine	− (43, 96)	− (53, 122, 124)	− (46)	− (65, 107)	− (12)
Dextrorphan	− (69)	− (123, 144)	− (46, 70)	− (105, 132)	− (12)
Levallorphan	− (75)	− (123)	N.R.	− (107)	N.R.
Nalorphine	− (43, 76)	− (53, 123)	− (46)	− (107)	N.R.
Naloxone	− (75)	− (91)	N.R.	− (105)	N.R.
Naltrexone	− (99)	− (91)	N.R.	N.R.	N.R.
Oxilorphan	− (78)	− (123)	N.R.	− (65)	N.R.
SKF 10,047	− (88)	− (103)	− (46)	− (131)	− (12, 49)

* Animals trained in a two-choice operant task to discriminate morphine from saline. + = Morphine like; − = not morphine-like; ± = equivocal; N.R. = not reported.

† Since no data are available for rhesus monkeys trained to discriminate morphine, these generalization results are for monkeys trained to discriminate etorphine or codeine from saline.

tolerance to methadone; and 5) non-narcotic drugs usually failed to produce morphine-like discriminative control at any dose (122, 123).

The classification of the discriminative stimulus properties of other opioids derived from the animal experiments is in striking concordance with that based upon the subjective effects of these drugs in humans. Table 3 presents data derived from several experiments involving animals trained to discriminate morphine (etorphine or codeine for rhesus monkeys) from saline. These data are compared to data available for subjective effects testing in humans. As can be seen, with the exception of meperidine in pigeons, there is a perfect correspondence between morphine-like subjective effects in humans and morphine-like discriminative stimulus properties in animals, where these comparisons are possible. Moreover, drugs that are clearly not morphine-like in humans in all cases failed to produce morphine-like responding in animals. For drugs that have some morphine-like subjective effects in humans, but are clearly distinguishable from morphine (equivocal) the results are, perhaps predictably, inconsistent. Butorphanol, nalbuphine, and pentazocine—all mixed agonist-antagonists—have in some instances produced morphine-like responding in animals and failed to in others. It should also be noted that occasionally distinctions are hazy. For example, cyclazocine produces some morphine lever responding at intermediate doses while higher and lower doses result in saline lever responding and therefore might be termed equivocal in animals (see below). Nevertheless, the correlation between morphine-like subjective effects in humans and morphine-like discriminative stimulus properties in animals is clearly a substantial one.

The effects of several benzomorphans have been investigated by using the drug discrimination paradigm. Among the compounds that are self-administered by rhesus monkeys, pentazocine has been most thoroughly studied in drug discrimination procedures. Several studies have shown that pentazocine can function as a discriminative stimulus and that pentazocine and morphine have similar discriminative stimulus properties. Kuhn et al. (90) trained rats to discriminate pentazocine (10.0 mg/kg) from saline. As with morphine, the discriminative stimulus effects of pentazocine could be antagonized by naloxone. When morphine injections were given to these animals, the frequency of responding on the pentazocine lever increased as dose of morphine was increased. It should be noted, however, that Hirschhorn (51) found only partial generalization to morphine in rats trained to discriminate this same dose of pentazocine from saline. White and Holtzman (141) trained squirrel monkeys to discriminate pentazocine (3.0 mg/kg) from saline. As was found by Kuhn et al. (90), the pentazocine discriminative stimulus generalized to morphine and could be blocked by a narcotic antagonist, in this case naltrexone. In addition, levorphanol and cyclazocine produced pen-

tazocine-appropriate responding whereas ketocyclazocine and ethylketocyclazocine only partially substituted for pentazocine.

Testing has been more extensive in animals that have been trained to discriminate morphine or other morphine-like agonists from saline and tested with pentazocine. The results of these studies are complex and appear to depend upon variables such as dose of the training drug and species (see Table 3). For example, pentazocine produced stimulus control of responding that was comparable to that seen with a low (1.5 mg/kg) or moderate (5.6 mg/kg) dose of morphine (122, 124). Similar results were found when the training drug was fentanyl (13). However, Hirschhorn and Rosecrans (53) found only partial generalization to pentazocine when the training dose of morphine was high (7.5 mg/kg). Pentazocine only partially substituted for morphine in the pigeon (46) and failed to produce etorphine-like responding in the rhesus monkey (49) or morphine-like responding in the squirrel monkey (107). Thus, although morphine substituted for pentazocine in squirrel monkeys (141) pentazocine did not substitute for morphine in this species. Although the reason(s) for this asymmetrical generalization are unclear, experiments with rats suggest that training dose may play a role. That is, it is possible that pentazocine would engender more drug lever responding in primates if a lower dose of agonist were used for discrimination training. These results make it clear that experiments that involve one-way generalization tests and single-dose training conditions must be interpreted with caution.

Pentazocine has also been tested in several species trained to discriminate a mixed agonist-antagonist opioid from saline. Rats trained to discriminate a low dose of cyclazocine (0.3 mg/kg) from saline generalized completely when tested with pentazocine, whereas only partial generalization was seen in animals trained to discriminate a high dose of cyclazocine (1.0 mg/kg) from saline (133). In addition, in squirrel monkeys trained to discriminate cyclazocine (0.1 mg/kg) from saline, partial generalization to pentazocine was found (106). Pentazocine also partially substitutes for the mixed agonist-antagonist nalorphine in rats (53). When pentazocine was tested in animals trained to discriminate ethylketocyclazocine from saline, no generalization was found in rhesus monkeys (44) whereas complete generalization was found in pigeons (148). Although there are apparent species differences, the studies of the discriminative stimulus properties of pentazocine are generally consistent with its mixed agonist-antagonist classification. It is important to note that in humans, pentazocine has morphine-like subjective effects at low to moderate doses but that high doses of pentazocine are distinctly different from morphine (29, 76). Thus, consistent with the animal literature, dose is an important determinant of the qualitative nature of subjective effects of pentazocine in humans.

Characterization of the discriminative stimulus properties of other benzomorphans that are positive reinforcers has not been extensive. NIH 8735 and NIH 9102 have been tested in rhesus monkeys trained to discriminate ethylketocyclazocine (44), and in pigeons trained to discriminate morphine or ethylketocyclazocine (148) from saline. Both compounds appeared to have stimulus properties that were similar to those of morphine in the pigeon and ethylketocyclazocine in both the pigeon and the rhesus monkey. It is important to note that these reinforcing compounds (NIH 8735 and 9102) substituted completely for ethylketocyclazocine, a compound that is not self-administered by rhesus monkeys. Thus, in this case, the self-administration and drug discrimination paradigms are apparently measuring different stimulus properties of drugs. The remaining compounds in table 2 that are self-administered by rhesus monkeys have not been studied by using the drug discrimination paradigm in animals. α-(−)Etazocine, NIH 8240, and NIH 8241 have been tested in humans and found to have morphine-like subjective effects (71,135). NIH 8737 does not appear to have been tested in animal drug discrimination or in human subjective effects tests.

The group of compounds in table 2 that are not self-administered by rhesus monkeys (cyclazocine, ketocyclazocine, and ethylketocyclazocine) have been studied by using drug discrimination procedures, though the animal data are, as with pentazocine, somewhat ambiguous. Stimulus control of behavior by cyclazocine has been studied in rats (51, 133) and squirrel monkeys (106, 107) and generalization tests have been conducted using several opioid compounds. Stimulus control is readily established with cyclazocine and the results of generalization testing are consistent with the finding in humans that cyclazocine and morphine have distinctive stimulus effects (see table 3). However, several experiments suggest a morphine-like component to the discriminative stimulus properties of cyclazocine that appears to vary somewhat with species and training dose of cyclazocine. In rats trained to discriminate 1.0 mg/kg cyclazocine from saline, the cyclazocine discriminative stimulus failed to generalize to morphine (133). However, when a lower dose of cyclazocine (0.3 or 0.5 mg/kg) was used for training, some cyclazocine lever responding was seen with morphine (51, 133). Further evidence for an agonistic component to the discriminative stimulus properties of cyclazocine is provided by testing cyclazocine discrimination in the presence of narcotic antagonists. The discriminative effects of cyclazocine in the squirrel monkey can be antagonized by naloxone, although the dose of antagonist is at least 10 times as large as that required to antagonize the stimulus properties of morphine (105, 106). In addition, naloxone and naltrexone antagonized the discriminative stimulus effects of cyclazocine in rats, again at considerably higher doses than those required to block the discriminative effects of morphine (51, 133). Testing of other opioids in animals trained to discrimi-

nate cyclazocine from saline is consistent with the concept of a mixed agonist-antagonist profile for the discriminative effects of cyclazocine. Ketocyclazocine and SKF-10,047 both substituted for cyclazocine in the rat (133) and squirrel monkey (106). In addition, the cyclazocine discriminative stimulus generalized completely to both ethylketocyclazocine and pentazocine at the lower but not the higher training dose (133).

Cyclazocine has been extensively tested in animals trained to discriminate opiate agonists, antagonists, and mixed agonist-antagonists from saline. Squirrel monkeys (107), rats (52), and pigeons (46) trained to discriminate morphine from saline failed to show morphine-like responding after injections of cyclazocine. On the other hand, when Shannon and Holtzman (122) administered cyclazocine to rats trained to discriminate morphine from saline, they found an intermediate level of morphine-appropriate responding. Perhaps more surprising is the fact that intermediate doses of cyclazocine substituted completely for fentanyl in rats trained to discriminate fentanyl from saline (13). The discrepant results may be accounted for, at least in part, by differences in the dose of the opioid used for training. Shannon and Holtzman (124) found partial generalization to cyclazocine in rats trained to discriminate a low dose of morphine (1.75 mg/kg) from saline, and no generalization when the morphine training dose was 5.6 mg/kg. Indeed, the training dose of morphine in the Shannon and Holtzman (122) study (partial generalization) was 3 mg/kg whereas the Hirschhorn (52) study (no generalization) the training dose was 10 mg/kg morphine. In addition, although intermediate doses of cyclazocine resulted in fentanyl-appropriate responding, the dose-response relationship was biphasic with increased saline-lever responding at higher doses of cyclazocine. Thus, for cyclazocine the relative intensity of morphine-like subjective effects may, as with other agonist properties, vary with drug dose. Cyclazocine engendered some drug-appropriate responding in pigeons trained to discriminate naltrexone from saline, while pigeons trained to discriminate ethylketocyclazocine from saline responded predominantly on the saline lever following cyclazocine injections (148). In contrast, in rhesus monkeys trained to discriminate ethylketocyclazocine from saline, cyclazocine produced principally drug-appropriate responding (44).

Thus, animal data for cyclazocine suggest a mixed agonist-antagonist profile for the discriminative stimulus properties of this compound. These data are consistent with what is known about the pharmacological properties of cyclazocine in other preparations as well as its subjective effects in humans. Although cyclazocine is clearly distinctive from morphine, especially at high doses, low doses of cyclazocine possess morphine-like effects and are identified as being "dope" in experienced drug users (43, 96). Recently, it has been reported that rats can be trained in a three-lever drug discrimination to discriminate between morphine, cyclazocine, and saline (140, 142), and that there is little or no cross-generalization between these drugs in this situation. These findings clearly support the notion that cyclazocine and morphine have distinctive stimulus properties. Pentazocine produced both morphine- and cyclazocine-appropriate responding in these animals, results that are consistent with its mixed agonist-antagonist discriminative stimulus properties demonstrated in other experiments. Ketocyclazocine and ethylketocyclazocine engendered predominantly cyclazocine lever responding with little or no morphine lever responding. Although the three-drug discrimination task requires lengthy training, it appears to be a useful procedure for studying the discriminative stimulus properties of opioids. It has the potential for avoiding some of the ambiguity of the partial generalization often found in two-lever drug discrimination paradigm and clearly merits further research.

Ketocyclazocine and ethylketocyclazocine are the two remaining compounds from table 2 that have been tested in the drug discrimination paradigm. The available data suggest that these compounds have similar discriminative stimulus properties. In both rhesus monkeys (44) and pigeons (148) trained to discriminate ethylketocyclazocine from saline, ketocyclazocine resulted in drug lever responding. As described previously, both ethylketocyclazocine and ketocyclazocine produced drug lever responding in rats trained to discriminate cyclazocine from saline (133). Similar generalization results were found for ketocyclazocine in squirrel monkeys trained to discriminate cyclazocine from saline (106). However, in contrast to cyclazocine, neither of the compounds appears to have morphine-like discriminative effects. Morphine failed to generalize to ketocyclazocine in the rat (123) or squirrel monkey (cited in Ref. 48). Further, ethylketocyclazocine failed to substitute for etorphine or codeine in rhesus monkeys trained to discriminate these morphine-like agonists from saline (12, 49) or for fentanyl in rats (118). It should be noted, however, that naloxone antagonized the discriminative stimulus properties of ethylketocyclazocine (47, 118) and the cyclazocine-like discriminative properties of ketocyclazocine in cyclazocine-trained squirrel monkeys could be partially antagonized by naloxone (106). The demonstration of discriminative stimulus properties that are naloxone-antagonizable but not morphine-like is fascinating and should be investigated further. Such a compound might be expected to be clinically useful. Moreover, in pigeons trained to discriminate morphine from saline, ketocyclazocine and ethylketocyclazocine each resulted in morphine lever responding and, as with rats, the ethylketocyclazocine discriminative stimulus could be antagonized by naltrexone (46). In addition, both morphine and ketocyclazocine produced drug lever responding in pigeons trained to discriminate ethylketocyclazocine from saline (148). Based on these data, the pigeon appears to be a unique species in terms of the discriminative stimulus

properties of these opioids, and may provide valuable information relevant to the receptor mechanisms of these drug effects.

Although the data for the discriminative stimulus properties of benzomorphans appear to be somewhat ambiguous, several generalizations can be made. A significant portion of the data are consistent with the three-receptor model for opiate action postulated by Martin et al. (97). According to this hypothesis, the different pharmacological syndromes produced by morphine and related drugs are due to their agonist actions at three distinct opioid receptors, termed mu, kappa, and sigma. Morphine is the prototypical mu receptor agonist while ketocyclazocine and SKF-10,047 are prototypical agonists for the kappa and sigma receptors, respectively. The drug discrimination literature for opioids has been recently reviewed in this context by Herling and Woods (48). Thus, while mu agonists such as heroin or codeine substitute completely for morphine, kappa and sigma agonists such as cyclazocine, ketocyclazocine, or ethylketocyclazocine usually fail to or only partially substitute in animals trained to discriminate morphine or other mu agonists. Similarly, drugs thought to act via kappa receptors usually substitute for other kappa agonists used as training drugs (e.g. ethylketocyclazocine, cyclazocine) while morphine and codeine do not. The prototypical sigma agonist, SKF-10,047 (also a benzomorphan) does not substitute for mu agonists (morphine, etorphine, or codeine) in any species tested but does substitute for cyclazocine which is thought to have sigma agonist action. However, caution must be exercised in applying this receptor model. There are clearly species differences in the effects of these drugs. Most notably, in the pigeon the morphine discriminative stimulus generalized to kappa agonists, and morphine, as well as other mu agonists, substituted for the kappa agonist ethylketocyclazocine. In addition, morphine has been found to generalize to cyclazocine and pentazocine in the rat, but these drugs do not substitute for mu agonists in other species. The data from primate species are perhaps most consistent with the three-receptor hypothesis, with the exception that the kappa agonist ethylketocyclazocine generalized to SKF-10,047, a sigma agonist, in rhesus monkeys (44). Experimentation has, however, been limited in primate species. Further testing with these species will be important in elucidating receptor mechanisms underlying the stimulus properties of the various agonist and mixed agonist-antagonist opioids.

Training dose has also been found to be an important determinant of the discriminative stimulus properties of opioid compounds. For example, training dose clearly influences the extent to which pentazocine and cyclazocine substitute for morphine in rats and, coversely, the extent to which cyclazocine generalizes to morphine (133). These data suggest, perhaps, that different components of the discriminative stimulus properties of drugs that have multiple receptor actions may vary in intensity with dose. Also, it is possible that differences in training dose may explain, at least in part, the observed species differences in drug discrimination. It would be difficult to ensure training doses of cyclazocine that had similar intensities of kappa agonist effects across species. In any case, these data are consistent with subjective effects testing in humans where morphine-like effects are clearly dependent upon dose.

Recent developments in the study of the discriminative stimulus properties of opioids have revealed stimulus properties that may be particularly relevant to the dependence potential of this group of compounds. Cyclazocine and SKF-10,047 produce drug lever responding in rats and squirrel monkeys trained to discriminate phencyclidine (PCP) from saline (62, 63, 120, 121) and in pigeons trained to discriminate ketamine from saline (45, 48). The discrimination is symmetrical, since animals trained to discriminate cyclazocine or SKF-10,047 from saline generalize the discriminative stimulus to PCP and ketamine (119, 133). These effects appear to be stereospecific in that *d*-SKF-10,047 and *d*-cyclazocine result in responding comparable to that seen with PCP in both rats and squirrel monkeys, while the *l*-isomers do not (10, 11, 63). Moreover, in rhesus monkeys trained to discriminate ketamine from saline, *d,l*-SKF-10,047, *d*-SKF-10,047, and dextrorphan resulted in drug lever responding while neither *l*-SKF-10,047 nor cyclazocine substituted for ketamine (48, 155). It has also recently been found that rhesus monkeys will self-administer the *d*- but not the *l*-isomers of cyclazocine and SKF-10,047 in a limited access substitution procedure (125). The possibility that some of these compounds, particularly those with sigma agonist properties, may have stimulus properties in common with the group of drugs known as the arylcyclohexylamines (phencyclidine, ketamine, etc.) is intriguing. Although, in general, sigma agonists of the opioid class are not generally thought of as drugs of abuse, these data suggest that there may be some common neurochemical mechanism of action through which sigma agonists and phencyclidine-like drugs exert their subjective effects, perhaps via the putative phencyclidine receptor (157). Be that as it may, these effects suggest that the *d*-isomers of the sigma agonists have PCP like dependence potential (104).

IV. Conclusions

Because of ethical limitations on experimentation with human subjects, the development of animal models that accurately predict dependence potential of psychotropic compounds is of paramount importance. In the past it was widely believed that physical dependence potential was a necessary component of abuse potential. However, recent research has shown that many compounds have significant abuse potential but little or no capacity to produce physical dependence. Thus, psychic dependence potential has been recognized to play a major role in the abuse potential of psychoactive compounds.

Animal research over the past 20 years has established methodologies that are useful in the evaluation of psychic dependence potential. Self-administration techniques allow the determination of whether a compound will maintain self-administration behavior in animals, that is, whether it has reinforcing efficacy. Reinforcing efficacy in animals has proven to be highly correlated with dependence potential in humans. In addition, procedures have been developed that allow estimation of the relative reinforcing efficacy of a compound, an important determinant of dependence potential in an environment in which alternatives to drug dependence are available. However, self-administration tests are relatively nonspecific in that compounds of many different pharmacological classes may be self-administered. Based on self-administration data alone it is difficult to describe psychic dependence potential as being of the opioid class, for example. The drug discrimination paradigm, on the other hand, has proven useful for classifying compounds according to similarities in discriminative stimulus properties. Data collected by this procedure strongly suggest that animals trained to discriminate a psychoactive compound respond after an injection of a novel compound in a manner that is consistent with what is known about the subjective effects of psychoactive drugs in humans. Thus, drug discrimination procedures can be used in conjunction with self-administration experimentation to classify psychic dependence potential as being of some specific type. A compound that is self-administered and has discriminative stimulus properties that are like those of morphine can be said to exhibit a dependence potential of the morphine type.

Application of these techniques to the opioids has revealed several findings of interest. Self-administration experiments with opioids, particularly the benzomorphans, have shown that several compounds with little or no physical dependence capacity of the morphine type will be readily self-administered by animals. The implication is that these compounds have significant potential for abuse in spite of low physical dependence capacity. That is, they have psychic dependence capacity. In addition, drug discrimination experiments have shown that many of these compounds will substitute for morphine or other morphine-like agonists and, recently, for phencyclidine. The implication of these findings is that several of these novel compounds have psychic dependence potential without producing morphine-like physical dependence. It is clear from the data that conditions such as species and training dose can influence the outcome of these experiments and the interpretation of results from a single experiment should be done with caution. This is not, perhaps, a surprising finding particularly among the opioids where so many compounds have a combination of agonist and antagonist actions. Further experimentation with the rhesus monkey in drug discrimination would be of value since the largest part of physical dependence and self-administration testing has been done in this species. It is clear from the available data, however, that procedures designed to evaluate psychic dependence potential should play a major role in the evaluation of the dependence potential of psychoactive compounds.

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