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Reinforcing Effects of Stimulants in Humans: Sensitivity of Progressive-Ratio Schedules

William W. Stoops, Ph.D.

Department of Behavioral Science, University of Kentucky College of Medicine, Lexington, KY

Abstract

Drug self-administration methodologies have been developed for use in humans to model naturalistic stimulant drug-taking behaviors. These methodologies use a number of schedules of reinforcement, including progressive-ratio schedules. As the name implies, in a progressive-ratio schedule, the response requirement for each subsequent delivery of drug increases and the primary outcome variable is often the break point (i.e., the last ratio completed to receive a drug delivery). These schedules have been used in a number of human laboratory studies evaluating the reinforcing effects of stimulants. The results of these studies demonstrate that progressive-ratio schedules are sensitive to manipulation of a pharmacological variable, dose, as well as to non-pharmacological variables contributing to stimulant drug effects. In addition, findings with progressive-ratio schedules are largely concordant with clinical findings, suggesting that drug self-administration under these schedules has predictive validity in terms of drug abuse and dependence. Future research is necessary, however, to understand better how pharmacological factors like route of administration, onset of effects and pretreatment influence the reinforcing effects of stimulants under progressive-ratio schedules.

Keywords

progressive-ratio; stimulant; humans; drug reinforcement

Introduction

Drug abuse and dependence are characterized by persistent drug-taking behavior, even if negative consequences result from that behavior (American Psychiatric Association, 2000). Drug self-administration methods have been developed for use in humans and in nonhuman animals to determine whether drugs maintain responding (i.e., function as positive reinforcers), thus indicating a potential for abuse by humans (Foltin & Fischman, 1991; Gardner, 2000). These methods are also used to determine which variables influence drug-taking behavior in hopes of better understanding drug abuse and dependence processes (Henningfield, Lukas, & Bigelow, 1986; Spiga & Roache, 1997). To be considered a positive reinforcer under a self-administration paradigm, a drug must be self-administered more often than placebo or vehicle in a situation where drug taking is optional (Henningfield, Cohen, & Heishman, 1991). In addition, drug-taking behavior must be responsive to behavioral and pharmacological manipulations and be maintained over time (Henningfield et al., 1991).

Address correspondence to: William W. Stoops, Ph.D. University of Kentucky College of Medicine Department of Behavioral Science 140 College of Medicine Office Building Lexington, KY 40536-0086 william.stoops@uky.edu phone: +1 (859) 257-5388 facsimile: +1 (859) 257-7684.

A self-administration experiment involves the administration of a compound (e.g., drug or placebo) contingent upon a response on a specific schedule of reinforcement (e.g., 1 lever press or the first lever press after 1 minute). For example, in a seminal study, 0.5 mg/kg intravenous (IV) cocaine was available to drug naïve rats on a one response fixed-ratio (FR 1) schedule (Pickens & Thompson, 1968). Under this schedule, stable levels of responding were observed when cocaine administration was paired with each response. However, when saline was substituted for cocaine or when only the stimulus-light paired with cocaine administration was presented, responding ceased, indicating that administration of cocaine was maintaining responding and functioning as a positive reinforcer (Pickens & Thompson, 1968).

Self-administration methods have been modified to measure the reinforcing effects of drugs in humans. Drugs like cocaine, amphetamine and pentobarbital maintain responding in humans (e.g., Fischman & Schuster, 1982; Johanson & Uhlenhuth, 1980; McLeod & Griffiths, 1983). For example, in one seminal study, doses of IV cocaine (0, 16 and 32 mg) were available on an FR 10 schedule (Fischman & Schuster, 1982). Under this schedule, cocaine dose-dependently increased responding relative to placebo, indicating that cocaine functioned as a positive reinforcer.

Various schedules of reinforcement have been used in drug self-administration studies (reviewed in Young & Herling, 1986; Haney & Spealman, 2008). Drugs of abuse, particularly stimulant drugs, maintain responding under many different schedules of reinforcement. These schedules include fixed and variable ratio schedules as well as fixed and variable interval schedules. More complex schedules of reinforcement such as second order schedules have also been used to examine the reinforcing effects of drugs. Each of these types of schedule yields important data regarding drug self-administration, which, when considered together demonstrate that drug-taking behavior is an operant that is influenced not only by pharmacological factors, but also by non-pharmacological variables (Young & Herling, 1986).

Another schedule of reinforcement that has been used to assess drug reinforcement is the progressive-ratio schedule. The progressive-ratio schedule was initially used to examine the reinforcing effects of sweetened milk solutions in rats (Hodos, 1961) and as the name implies, the schedule begins with one response requirement for the initial presentation of a reinforcer and then requires an escalating number of responses for each subsequent presentation of that reinforcer. This escalation of responses generally occurs within a single session, but some studies have increased the ratio across different sessions (for a review see Richardson & Roberts, 1996). Often, the primary outcome variable of experiments using progressive-ratio schedules is the “break point,” defined as the final ratio completed by an organism, indicating “the maximum effort that an animal will expend in order to receive a particular drug infusion” (Richardson & Roberts, 1996, p4). The results from studies with nonhuman animals have demonstrated that progressive-ratio schedules are sensitive to the reinforcing effects of drugs in a dose-related manner across a number of classes and can be used with a number of species (Stafford, LeSage, & Glowa, 1998). It has been suggested that progressive-ratio schedules assess the relative reinforcing efficacy of drugs because they provide a single outcome (i.e., the break point) that can be compared across drugs without relying on response rates (Comer, Ashworth, Foltin, Johanson, Zacny & Walsh, 2008; Stafford et al., 1998).

As described above, the progressive-ratio schedule can be used as a measure of the reinforcing efficacy of drugs and is sensitive to numerous manipulations, both pharmacological and non-pharmacological, in nonhuman animals. A considerable portion of my work has examined the reinforcing effects of stimulant drugs in humans, particularly

because the reinforcing effects of stimulants in humans are most predictive of their abuse potential (Foltin & Fischman, 1991). By inference, then, factors that alter the reinforcing effects of stimulants in the laboratory should also alter naturalistic use of stimulants and vice versa. It is for these reasons that the present, invited review was completed as a means for demonstrating the sensitivity and utility of progressive-ratio schedules in humans and to apply these results to clinical or naturalistic findings. Although progressive-ratio schedules have been used to investigate other drug classes (i.e., opioids, sedatives and alcohol) in humans, the focus of this review is stimulant drugs. Where appropriate, illustrative examples from these other studies are included.

While the intent of this review is to demonstrate the sensitivity and predictive validity of progressive-ratio schedules to measure stimulant self-administration in humans, other measures of drug reinforcement in humans have also proven valuable. A rich literature exists demonstrating that stimulant drugs maintain responding on other schedules of reinforcement or are chosen over placebo or money by humans (e.g., Fischman & Schuster, 1980; Hart, Ward, Haney, Foltin & Fischman, 2001; Higgins, Bickel & Hughes, 1994). Moreover, the reinforcing effects of stimulant drugs as measured by other means are sensitive to pharmacological and non-pharmacological manipulations (e.g., Hart, Haney, Vosburg, Rubin & Foltin, 2008; Roehrs, Johanson, Meixner, Turner & Roth, 2004; Silverman, Kirby & Griffiths, 1994). Progressive-ratio schedules were selected for review, however, because they constitute a significant theme of my work, which resulted in receipt of the Wyeth Young Psychopharmacologist Award for 2008.

References were obtained from a computerized PubMed search that combined the terms progressive-ratio, stimulant and humans. The citation lists of original research articles were also used to identify additional references that the computerized literature search may have missed. This review included only placebo-controlled, laboratory studies that used humans as subjects. As mentioned above, to be considered a reinforcer, a drug must maintain responding to a greater degree than vehicle or placebo. Without a placebo condition, this comparison cannot be made.

Progressive-Ratio Schedule Methodologies with Humans

Progressive-ratio schedules have been used to measure drug reinforcement in humans for over two and a half decades. In the seminal experiment, five sedative drug abusers sampled doses of pentobarbital (0, 200, 400 and 600 mg) and were then allowed to self-administer these doses on a progressive-ratio schedule (McLeod & Griffiths, 1983). Subjects completed the ratio requirements by button pressing or timed bicycle riding. Regardless of how the ratios were completed, availability of pentobarbital increased break point in a dose-related fashion. Since the initial experiment, studies have demonstrated that other types of operant responding (e.g., pulling Lindsley plungers, pressing a key on a computer key board, clicking a computer mouse, etc.) are valid ways of completing progressive-ratio response requirements (Sigmon, Tidey, Badger & Higgins, 2003; Stoops, Fillmore, Glaser & Rush, 2004; Stoops, Vansickel, Lile & Rush, 2007a).

Another important aspect of the study by McLeod and Griffiths was that ratio requirements increased across sessions as opposed to within sessions. For example, after subject ZA had sampled a pentobarbital dose, he was required to ride the bicycle for 15 minutes to earn that dose again on the next day that it was available. He was then required to ride the bike 30 minutes to earn that dose on the next day after that and so on. More recent studies have commonly escalated the ratio within a session (Haney, Foltin & Fischman, 1998; Rush, Essman, Simpson & Baker, 2001) and demonstrated the validity of increasing responses in this manner. These studies also suggest that the nature of the increase of ratio requirements

(e.g., arithmetical or exponential) can vary from study to study yet still be sensitive to the reinforcing effects of drugs.

While it is apparent that variability in the manner of increase of ratio requirements across studies does not diminish the sensitivity of progressive-ratio schedules to the reinforcing effects of drugs, optimal ratio values for testing specific hypotheses have yet to be determined. One drawback to the use of schedules in which response costs are increased multiplicatively, as described below in the study by Stoops and colleagues (2004), is that initial response costs are low (e.g., 50 responses) and later costs can be quite high (e.g., 6400 responses). At low initial response costs, responding has been observed for placebo, and high response costs at the end may discourage maximal drug-taking behavior (see Figure 1). An empirical comparison of various types of increases in ratios remains to be conducted, however, to determine how the nature of ratio increases changes responding in humans. Moreover, whether certain individual differences (e.g., drug dependence status) differentially modify responding remains to be fully tested (see discussion of individual differences below).

The nature of ratio increases also raises statistical considerations. The main concern is which data to analyze. If analyzing break point, particularly on a schedule in which ratios increase multiplicatively, assumptions about homogeneity of variance within Analysis of Variance may be violated. That is, the increase in responses from one ratio to the next (i.e., 50 responses at the beginning of a schedule and 3200 responses at the end of a schedule) varies greatly and may obscure significant effects. Data transformations (e.g., square root transformations of the breakpoint) can correct for this issue. However, presenting data as a square root transformation graphically complicates interpretation of results.

Violations of homogeneity of variance assumptions can also be avoided if data are analyzed as the number of ratios completed (or number of drug doses earned), although this manner of analysis is less traditional than use of the hallmark characteristic of progressive-ratio schedules: break point data. Number of ratios completed can also be presented graphically in a manner that is easy to interpret. Regardless of the manner in which data are analyzed (i.e., using break point, square root transformations of break point or number of ratios completed), results are generally consistent, although analyzing number of ratios completed may be slightly less sensitive to significant effects than using actual break point or square root transformation data.

The manner in which drug is made available for self-administration has also been varied across studies. That is, some studies have allowed subjects to sample a dose of drug and then self-administer that exact dose a number of times (e.g., Haney et al., 1998), whereas other studies have allowed subjects to sample a dose of drug and then self-administer portions of that dose up to the fully sampled amount (e.g., Rush et al., 2001). In the study by Haney and colleagues, subjects sampled doses of IV cocaine (0, 8, 16 and 32 mg/70 kg). They were then required to complete responses on a progressive-ratio schedule (starting at 600 responses and increasing by 400 responses for each subsequent dose up to 2200 responses) to receive those doses again. In the study by Rush and colleagues, subjects sampled doses of oral *d*-amphetamine (0, 10 and 20 mg). They were then required to complete responses on a progressive-ratio schedule (starting at 50 responses and doubling for each subsequent dose up to 6400 responses) to receive 1/8 (or 12.5%) of the previously sampled dose. Regardless of how dose was presented (either the full or divided dose), the stimulant drugs under study maintained break points higher than those maintained by placebo. A direct comparison of full or divided dose presentation remains to be tested empirically to determine whether one is superior to the other.

The results of the studies described above serve to demonstrate that across methodological variations, progressive-ratio schedules are sensitive to the reinforcing effects of drugs in humans. These findings point to the flexibility of progressive-ratio schedules to measure drug reinforcement. Important practical and ethical concerns differentiate the implementation of these schedules from the way they are used with nonhuman animals. For example, in humans, only a limited number of drug administrations are available within a session, whereas with nonhuman animals, the number of drug administrations is less restricted. In addition, the way drug is delivered in a number of studies (i.e., by divided dosing) is different from methods with nonhuman animals. Irrespective of these differences, data from progressive-ratio schedules with humans and nonhuman animals are strikingly concordant in their ability to demonstrate the reinforcing effects of drugs that have potential for abuse and dependence, as well as which variables influence drug-taking behavior (Griffiths, Bigelow & Henningfield, 1980; Stafford et al., 1998).

Stimulants Investigated Using Progressive-Ratio Schedules

The reinforcing effects of a range of stimulant-type drugs have been investigated using progressive-ratio schedules. These include caffeine, cocaine, *d*-amphetamine, nicotine, methylphenidate and modafinil (Griffiths, Bigelow, & Liebson, 1989; Haney et al., 1998; Rush et al., 2001; Rusted, Mackee, Williams, & Willner, 1998; Shahan, Bickel, Madden, & Badger, 1999; Shahan, Bickel, Badger, & Giordano, 2001; Stoops et al., 2004; Stoops, Lile, Fillmore, Glaser & Rush, 2005a; 2005b). Caffeine, cocaine, *d*-amphetamine and methylphenidate clearly maintain responding under progressive-ratio schedules in humans and increase break points relative to placebo levels (Griffiths, et al., 1989; Haney et al., 1998; Rush et al., 2001; Stoops et al., 2004).

In one study, for example, subjects sampled caffeinated coffee, decaffeinated coffee, caffeine capsules or placebo capsules and in subsequent sessions were allowed to self-administer the sampled drug at hourly intervals by riding a bicycle (Griffiths et al., 1989). The response requirement for self-administration increased across days (i.e. 0.5, 1, 2, 4, 8, 16, 32 and 50 [for two subjects only] minutes of riding per cup of coffee or capsule). When low levels of work were required, subjects tended to self-administer both caffeine and placebo at similar rates. As work requirements increased, subjects tended to work only for active drug (caffeinated coffee or caffeine capsules), indicating that caffeine was maintaining responding. Importantly, as work requirements increased to the highest levels, all responding ceased, demonstrating that subjects reached their breakpoint for caffeine at 32 or 50 minutes of bicycle riding.

In another study, subjects sampled doses of oral *d*-amphetamine (8, 16 and 24 mg), methylphenidate (16, 32 and 48 mg) or placebo and were then allowed to self-administer the previously sampled drug (in divided doses as described for Rush et al., 2001 above) in subsequent sessions (Stoops et al., 2004). The response requirement for self-administration increased within session (i.e., 50, 100, 200, 400, 800, 1600, 3200 and 6400 responses on a computer keyboard per capsule). Figure 1 represents break point for human subjects responding for oral *d*-amphetamine or methylphenidate. Intermediate doses of *d*-amphetamine and methylphenidate produced break points higher than placebo, indicating that these drugs function as reinforcers. Taken together, studies with progressive-ratio schedules in humans indicate that stimulant drugs maintain responding, concordant with naturalistic reports of abuse of these drugs (Novak, Kroutil, Williams & Van Brunt, 2007; Substance Abuse and Mental Health Services Administration, 2007).

The reinforcing effects of nicotine (assessed using regular and de-nicotinized cigarettes as the placebo) are more variable under progressive-ratio schedules (Rusted et al., 1998;

Shahan et al., 1999; 2001). Nicotine containing cigarettes have been shown to maintain greater levels of responding and increase break point relative to de-nicotinized cigarettes when subjects are offered the choice between both types of cigarettes within a session (Shahan et al., 1999; 2001), but not when only one of the two options is available within a session (Rusted et al., 1998; Shahan et al., 1999; 2001), suggesting that subjects rely on within-session comparisons between the sampled cigarettes to make decisions about drug taking. Importantly, the reinforcing effects of nicotine can be difficult to demonstrate in laboratory studies across schedules of reinforcement, which is consistent with the notion that non-pharmacological factors heavily influence cigarette smoking behavior and contribute to the considerable abuse potential of nicotine (Dar and Frenk, 2004; Harakeh, Engels, Van Baaren & Scholte, 2007)

As with nicotine, the reinforcing effects of modafinil are dependent upon experimental conditions (Stoops et al., 2005b). That is, under conditions in which subjects must complete a performance task, modafinil maintains responding and dose-dependently increases break point under a progressive-ratio schedule relative to placebo (Stoops et al., 2005b). This effect is not observed when subjects must complete a relaxation task (Stoops et al., 2005b). Importantly, naturalistic self-administration (in the form of abuse or dependence) of modafinil is not common (Myrick, Malcolm, Taylor & La Rowe, 2004). The influence of environmental variables on the reinforcing effects of drugs under progressive-ratio schedules is discussed further below.

The results of the studies described above are strikingly concordant with clinical findings in that widely abused drugs generally maintain progressive-ratio responding, whereas drugs with limited abuse potential only function as reinforcers under specific experimental conditions. A strength often identified for data obtained using progressive-ratio schedules is that relative reinforcing efficacy of drugs can be determined without relying on rate of responses (Griffiths, Brady & Bradford 1979; Stafford et al., 1998). From some of the studies described above, it can be inferred that *d*-amphetamine and methylphenidate are equally efficacious positive reinforcers, although methylphenidate is roughly half as potent as *d*-amphetamine (Rush et al., 2001; Stoops et al., 2004). It is difficult to compare the relative reinforcing efficacy of drugs across extant studies (e.g., compare nicotine and cocaine) due to methodological variations unique to these studies.

Pharmacological Variables that Influence Progressive-Ratio Responding

One of the most important pharmacological variables manipulated in studies that have used progressive-ratio schedules with humans is drug dose. Cocaine, *d*-amphetamine, methylphenidate and modafinil, have been shown to dose-dependently change break point on progressive-ratio schedules (Haney et al., 1998; Rush et al., 2001; Stoops et al., 2005a; 2005b). Within the limited dose ranges that can safely be administered to human subjects participating in laboratory-based research, these studies have generally demonstrated monotonic increasing dose-response functions (Fischman & Johanson, 1998). These findings are consistent with those of other human drug self-administration methodologies (e.g., Haney, Hart & Foltin, 2006; Hart et al., 2008). One study conducted in our laboratory examining the reinforcing effects of *d*-amphetamine and methylphenidate resulted in a bitonic dose-response curve for both drugs (see Figure 1; Stoops et al., 2004). With dose-dependent increases, or bitonic dose-response curves, observed for break point for active drug, the results of these studies demonstrate that drug dose influences drug-taking behavior under progressive-ratio schedules in humans.

Interestingly, studies in our laboratory have demonstrated both bitonic and monotonic increasing dose response curves for methylphenidate self-administration under progressive-

ratio schedules (Stoops et al., 2004; Stoops et al., 2005a; see Figures 1 and 2). Moreover, the highest break point observed for methylphenidate in the earlier study was higher than that for similar doses in the more recent one. The reason for the discrepancies observed between these two studies is not known, but could be due to population differences (i.e., stimulant abusing versus relatively drug-naïve subjects) or experimental design (i.e., the absence or presence of behavioral demands following drug administration).

Route of administration and in turn, rate of onset of effects, is another important pharmacological variable known to influence the behavioral effects of drugs (Griffiths et al., 1980). All studies that have used progressive-ratio schedules with stimulants in humans have employed only one route of administration within a study (i.e. IV, smoking or oral) (e.g., Haney et al., 1998; Shahan et al., 1999; 2001; Stoops et al., 2004). Future work should thus determine whether route of administration influences the reinforcing effects of stimulants under progressive-ratio schedules in humans. The results of one study indicate that the reinforcing effects of heroin do not differ as a function of route of administration, however (Comer et al., 1999).

A final pharmacological variable that has been manipulated in human subjects using progressive-ratio schedules is pretreatment with agents that theoretically should attenuate or enhance the effects of the drug in question. The results of two studies have failed to demonstrate that the reinforcing effects of stimulants measured by progressive-ratio schedules are sensitive to the administration of pretreatment agents (Haney et al., 1998; Stoops et al., 2007a). In the first study, subjects sampled doses of IV cocaine (0, 8, 16 and 32 mg/70 kg) and were then allowed to self-administer these doses (or take money, see discussion of alternative reinforcers below) during maintenance on placebo or the dopamine agonist, pergolide (Haney et al., 1998). Although cocaine maintained responding on the progressive-ratio schedule, chronic pergolide dosing failed to alter the reinforcing effects of cocaine. In the second study, subjects sampled doses of oral *d*-amphetamine (0, 8 or 16 mg) and were then allowed to self-administer these doses following acute pretreatment with placebo or 15 mg oral *d*-amphetamine (Stoops et al., 2007a). Although *d*-amphetamine maintained responding on the progressive-ratio schedule, *d*-amphetamine pretreatment failed to alter drug self-administration.

These findings suggest that progressive-ratio schedules are sensitive to manipulation of dose, perhaps the most important pharmacological variable in terms of abuse potential. More work is necessary to understand the sensitivity of progressive-ratio schedules to manipulation of route of administration and pretreatment. It should be noted, however, that in humans, the reinforcing effects of stimulant drugs are notoriously difficult to alter with pharmacological pretreatment regardless of schedule of reinforcement (Haney et al., 2006; Haney & Spealman, 2008). Moreover, the robust reinforcing effects of stimulant drugs and the relative lack of effect when combined with pretreatment may mirror the lack of clinical efficacy for a number of medications tested for cocaine or methamphetamine dependence (see Vocci & Ling, 2005).

Non-pharmacological Variables that Influence Progressive-Ratio Responding

Several studies have evaluated the influence of non-pharmacological variables on the reinforcing effects of stimulants when measured using progressive-ratio schedules of reinforcement. Although the examination of the effects of such non-pharmacological variables is not extensive, the results of the extant studies demonstrate the sensitivity of these schedules. In one study, IV cocaine doses (0, 8, 16 and 32 mg) were available on a progressive-ratio schedule in which subjects had to make a choice between drug and money

(\$5) prior to completing a ratio for the chosen option (Haney et al., 1998). Ratios increased only for the chosen option. That is, if a subject chose to administer a cocaine dose, the ratio for the subsequent cocaine dose would be increased by 400 responses, but the response requirement for the monetary option would not increase. Break points were higher for cocaine and lower for money at the 16 and 32 mg IV cocaine doses than placebo and 8 mg IV cocaine doses (although statistical significance is not denoted in the report), consistent with other studies (using FR1 choice procedures, e.g., Higgins et al., 1994; Donny, Bigelow & Walsh, 2003; 2004), indicating that availability of an alternative reinforcer can diminish drug self-administration on progressive-ratio schedules of reinforcement. This finding is also concordant with clinical literature demonstrating that the use of voucher-based reinforcement techniques, in which non-drug alternative incentives are made available to cocaine dependent patients, are effective at decreasing cocaine use (reviewed in Higgins, Alessi & Dantona, 2002).

Studies in our laboratory have focused on other non-pharmacological variables that influence naturalistic drug-taking behavior. For example, illicit use of prescription stimulant drugs is becoming increasingly prevalent on college campuses, with students often report using them as a study aid (Arria, Caldeira, O'Grady, Vincent, Johnson & Wish, 2008; McCabe, Teter & Boyd 2006). A series of experiments from our laboratory sought to model the influence of behavioral demands following drug administration on the reinforcing effects of the prescription stimulants methylphenidate and modafinil (Stoops et al., 2005a; 2005b). The results of those studies demonstrate that break points for methylphenidate and modafinil were above placebo levels when subjects were required to complete a three-hour performance task after drug administration, but not when they were required to complete a three-hour relaxation task (Figure 2). These findings mirror those of the common reports that stimulants are taken to enhance performance of one kind or another.

Progressive-ratio schedules of reinforcement are also sensitive to the influence of individual differences on stimulant-taking behavior (Stoops, Lile, Robbins, Martin, Rush & Kelly, 2007b). In that study, 10 high sensation seekers (scoring in the upper quartile of the normal distribution of scores on the Zuckerman-Kuhlman Personality Questionnaire [ZKPQ]) and 10 low sensation seekers (scoring in the lower quartile of the normal distribution of scores on the ZKPQ) sampled doses of oral *d*-amphetamine (0, 8 and 16 mg). In subsequent sessions, subjects were offered the opportunity to self-administer these drug doses on an 8-trial modified progressive-ratio schedule similar to that described above in the study by Stoops et al. (2004). In high sensation seekers, break points for active drug (1 or 2 mg unit doses per ratio completed for a maximum of 8 or 16 mg) were significantly higher than in low sensation seekers, which mirrors clinical findings that individuals high in sensation seeking are more likely to abuse stimulant drugs (Herman-Stahl, Krebs, Kroutil & Heller, 2007).

Non-pharmacological variables, including the availability of an alternative reinforcer, behavioral demands following drug administration and personality, influence drug self-administration under progressive-ratio schedules of reinforcement. Perhaps of most interest is that the findings for each of these variables are consistent with clinical data suggesting that stimulant self-administration with this schedule has predictive validity in terms of naturalistic stimulant-taking behavior.

Progressive-Ratio Schedules and Choice Procedures: Oral *d*-Amphetamine

The findings and issues described above raise the question of how results obtained using progressive-ratio schedules compare to those from studies using other self-administration methodologies in humans. Moreover, advantages or disadvantages of progressive-ratio

schedules relative to these other methodologies are of concern. A direct comparison between stimulant self-administration using progressive-ratio and other self-administration methodology remains to be published, but findings from different studies using various models of stimulant self-administration in humans shed some light on these issues. A full comparison of stimulant drug self-administration across methodologies is beyond the scope of this invited review so oral *d*-amphetamine was chosen for review here because it is the stimulant drug that has been studied most widely using progressive-ratio schedules and has been tested fairly extensively in choice procedures.

As described above, oral *d*-amphetamine maintains responding on progressive-ratio schedules (Rush et al., 2001; Stoops et al., 2004). These reinforcing effects are sensitive to dose manipulations and individual differences, but not necessarily acute pharmacological pretreatment (Rush et al., 2001; Stoops et al., 2004; 2007a; 2007b). Data from choice procedures demonstrate that *d*-amphetamine functions as a reinforcer across a range of doses similar to those tested using progressive-ratio schedules (i.e., 5 to 15 mg) (Johanson & Uhlenthuth, 1980; Johanson, Kilgore & Uhlenthuth, 1983; Mitchell, Laurent & de Wit, 1996). The reinforcing effects of oral *d*-amphetamine are sensitive to manipulation of perception of task performance as well as behavioral demands following drug administration (Comer, Haney, Foltin & Fischman, 1996; Silverman et al., 1994). Importantly, the reinforcing effects of *d*-amphetamine do not vary as a function of individual differences (i.e., in depressed or overweight subjects) in choice procedures. Moreover, the reinforcing effects of *d*-amphetamine are not sensitive to manipulation of expectancies about drug effect (de Wit, Uhlenthuth & Johanson, 1987; Mitchell et al., 1996). Whether the reinforcing effects of *d*-amphetamine are sensitive to dose or pharmacological pretreatment has not been widely tested using choice procedures. For instance, most studies have only tested a single dose of *d*-amphetamine against placebo, although the results of one study indicate that a high dose of *d*-amphetamine is chosen over placebo while a low dose is not (de Wit et al., 1987).

Comparing the results from progressive-ratio and choice studies, it is apparent that *d*-amphetamine functions as a reinforcer in both models. In addition, these models are sensitive to manipulation of non-pharmacological variables. Choice procedures have often only tested a single active dose of *d*-amphetamine against placebo, limiting conclusions that can be made about sensitivity to dose manipulations. Testing a single active dose is likely due to the nature of choice paradigms and the relatively long-lasting effects of *d*-amphetamine.

With choice paradigms using *d*-amphetamine, subjects sample placebo and the active dose at least once each, with multiple sessions following in which subjects choose between the sampled doses. This design requires a number of sessions (up to 9 in some studies) to compare the effects of a single dose against placebo. With progressive-ratio schedules, only two sessions are required to determine the reinforcing effects of each oral *d*-amphetamine dose and a dose response curve can be determined in the number of sessions necessary to test a single dose using choice procedures. Thus, while the progressive-ratio schedule and choice procedures are sensitive to the reinforcing effects of oral *d*-amphetamine, the use of progressive-ratio schedules may be more efficient in determining whether oral drugs with relatively long effects like *d*-amphetamine maintain responding. This efficiency allows for the testing of a range of doses in a single experiment that places no more demands on subjects than those in a typical choice study in which a single active dose is tested. Of course, with drugs that have short half-lives, like cocaine, choice or progressive-ratio procedures can determine a dose-response curve in many fewer sessions (e.g., Haney et al., 1998; Hart et al., 2008).

Discussion and Conclusions

The studies reviewed above demonstrate five important points. First, the use of progressive-ratio schedules of drug reinforcement represents a valid and flexible method for measuring drug reinforcement in humans. Second, stimulant drugs with demonstrated abuse potential maintain responding in humans using this class of schedules. Third, progressive-ratio schedules are sensitive to manipulation of dose but further work is necessary to understand the influence of other pharmacological variables on stimulant-taking behavior under this schedule. Fourth, progressive-ratio schedules are sensitive to a number of non-pharmacological variables known to influence drug-taking behavior. Fifth, by comparing the results of studies testing *d*-amphetamine in progressive-ratio and choice methodologies, it is apparent that progressive-ratio schedules may be a more efficient way to determine the ability of oral drugs with relatively long-lasting effects to maintain responding.

Regardless of the schedule of reinforcement used, drug self-administration measures produce results concordant with naturalistic findings. In fact, using drug self-administration measures may have more predictive validity than the use of subject-rated measures alone, perhaps the most common tools used to study drugs in humans. For example, when Haney and colleagues (1998) pretreated subjects with pergolide, cocaine self-administration did not decrease, but subject-ratings indicative of abuse potential were attenuated. Pergolide has since proven ineffective as a medication for cocaine dependence, consistent with negative self-administration results (Focchi, Leite, Andrade & Scivoletto, 2005; Malcolm, Kajdasz, Herron, Anton & Brady, 2000). In another study described above, break points were higher for methylphenidate when subjects were instructed they would have to complete a performance task than when they knew they would have to complete a relaxation task, although subject ratings of drug liking were equivalent across conditions (Stoops et al., 2005a). Again, the self-administration results are more consistent with naturalistic reports of stimulant use when performance enhancement is important (Arria & Wish, 2006; Arria et al., 2008). Fortunately, subject-rated and reinforcing effects of drugs are not mutually exclusive and can be measured simultaneously. Subjects' ratings can be valuable for understanding what may motivate drug-taking behavior, particularly in initial studies of abuse liability. The use of multiple indices to determine the effects of drugs is a cornerstone of human behavioral pharmacology (Griffiths, Bigelow & Ator, 2003).

Drug self-administration methodologies, including those using progressive-ratio schedules, are not without their limitations. First, in these studies, subjects typically sample a drug on one day and then are given opportunities to self-administer or choose the drug on ensuing days. Each dose condition generally requires at least two experimental sessions to assess the reinforcing effects of that condition (e.g., Evans & Griffiths, 1992; Hart et al., 2001; Rush et al., 2001), although this is not always the case for drugs with short half-lives like cocaine (e.g., Haney et al., 1998). This increased number of sessions presents ethical and practical issues (Fischman & Johanson, 1998). For instance, numerous drug self-administration sessions can result in increased drug exposure or greater subject attrition.

For stimulant drugs, self-administration methodologies may also be insensitive to pharmacological pretreatment, which may be seen as a limitation. Only a few studies have been able to decrease stimulant self-administration following pretreatment with a putative pharmacotherapy using other schedules of reinforcement (Foltin & Fischman, 1994; Haney et al., 2006; Hart et al., 2008). Importantly, these results are largely concordant with clinical findings of efficacy for the medications tested in managing cocaine dependence (Dackis, Kampman, Lynch, Pettinatti & O'Brien, 2005; Montoya et al., 2004; Shoptaw et al., 2003). The results of one study described above (Stoops et al., 2007a) may be discordant with clinical findings suggesting *d*-amphetamine is effective in managing stimulant dependence

(see Grabowski, Shearer, Miller & Negus, 2004), however, the use of acute dosing likely contributed to the lack of effect. Chronic *d*-amphetamine treatment is apparently necessary to decrease stimulant use (Grabowski et al., 2001). One consideration is that the high number of responses required at the end of progressive-ratio schedules may result in limited levels of drug-taking, which may be difficult to attenuate with pharmacological pretreatment (Stoops et al., 2007a). Manipulation of ratio requirements so that ratios at the end of the sequence do not produce response fatigue might enhance drug-taking behavior and allow for attenuation by pharmacological pretreatment. Thus, insensitivity to pharmacological pretreatment can be seen as a limitation, but may actually be reflective of a lack of clinical efficacy of tested agents (see also Haney & Spealman, 2008) or due to response fatigue. More work in this area is clearly warranted.

In closing, progressive-ratio schedules are sensitive to the reinforcing effects of stimulant drugs in humans, particularly to manipulations of non-pharmacological variables contributing to these effects. Future research should determine further the sensitivity of these schedules to pharmacological manipulations, including route of administration and pharmacological pretreatment. These future studies would contribute to the evidence reviewed above demonstrating the predictive validity of data gathered using progressive-ratio schedules in humans. That is, findings with progressive-ratio schedules are largely concordant with clinical findings in terms of non-pharmacological variables that influence drug taking. If pharmacological variables, in addition to dose, known to influence drug taking also modulate the reinforcing effects of stimulants under progressive-ratio schedules, these schedules could be used as tools for investigating putative pharmacotherapies for stimulant abuse and dependence. Moreover, it is likely that non-pharmacological and pharmacological variables interact to result in stimulant-taking behavior. Future research should test these variables in concert and model both behavioral and pharmacological treatments for stimulant abuse and dependence.

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Figure 1.

Dose-response function for methylphenidate and *d*-amphetamine for break point (N=10) on the modified progressive-ratio procedure.. X-axis: total dose (mg). Filled symbols denote a significant difference from placebo response. Brackets indicate one S.E.M. Redrawn from Journal of Psychopharmacology, 18, Stoops, Glaser, Fillmore & Rush. Reinforcing, subject-rated, performance and physiological effects of methylphenidate and *d*-amphetamine in stimulant abusing humans. Pages 534–543. Copyright (2004), with permission from Sage Publications.

Figure 2.

Dose-response function for methylphenidate (left panel) and modafinil (right panel) for break point on the modified progressive-ratio procedure as a function of condition. X-axis: total dose (mg). Brackets indicate one SEM. Unidirectional brackets were used for clarity. Left panel: Reprinted from *Psychopharmacology*, 177, Stoops, Lile, Fillmore, Glaser & Rush. Reinforcing effects of methylphenidate: influence of dose and behavioral demands following drug administration. Pages 349–355. Copyright (2005), with permission from Springer. Right panel: Reprinted from *Psychopharmacology*, 182, Stoops, Lile, Fillmore, Glaser & Rush. Reinforcing effects of modafinil: influence of dose and behavioral demands following drug administration. Pages 186–193. Copyright (2005), with permission from Springer.